Exploratory study of the association in the United Kingdom between hypertension and inorganic arsenic (iAs) intake from rice and rice products

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Abstract Hypertension risks 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 a lack of epidemiological evidence demonstrating an association of hypertension risks with iAs intake from rice, especially in areas where there is little exposure from drinking water but a growing demand for rice intake. To address this, we conducted an individual-level cross-sectional analysis to quantify the extent to which daily iAs intake from rice and rice products (E-iAs\textsubscript{ing,rice}) modifies the association between hypertension risks and previously well-established risk factors. The analysis was based on secondary dietary, socio-demographic and health status data of 598 participants recorded in the UK National Diet and Nutrition Survey 2014–2016. E-iAs\textsubscript{ing,rice} and five blood pressure endpoints were derived with potential associations explored through generalized linear models. According to the results, a negative but not significant relationship was found between hypertension risks and E-iAs\textsubscript{ing,rice} after adjusting for major risk factors, notably age, gender, diabetes and obesity, with relatively higher risks being observed for male, middle-aged, overweight, alcohol consumer or Asian or Asian British, Black or Black British and mixed ethnic groups. Though inconclusive and mainly limited by potential incomplete adjustment for major confounders and intrinsic disadvantages of a cross-sectional design, this study was the first quantifying the individual level dose–response relationship between E-iAs\textsubscript{ing,rice} and hypertension risks and is consistent with previous studies on the limited associations of hypertension with low-level arsenic exposure from drinking water. Larger scale cohort studies are indicated to quantify the association but in any event it is likely to be weak.

Keywords Inorganic arsenic · Rice · Hypertension · Cross-sectional analysis · Exposure science

Introduction

Arsenic (As), which originates from either geological or anthropogenic sources (Polya and Lawson 2016), is reported to be ubiquitously present in the environment (Bundschuh et al. 2012; Huda et al. 2014). Arsenic has been widely recognized as a human carcinogen for over 50 years (Currie 1947; Frost 1969; Hueper 1967;
Polya and Middleton (2017), and it is especially the case for inorganic arsenic (iAs), which is predominant or important in soil, water, air and some foodstuffs (Bae et al. 2017; Currier et al. 2014; Diane et al. 2013; Molin et al. 2015; Yañez et al. 2015). According to the US Department of Health And Human Services et al. (2007), people may be exposed via various pathways, notably inhalation, dermal contact, ingestion and through parenteral routes. Ingestion of iAs through drinking water is a particularly important exposure route, especially for people living in certain geographic regions, such as parts of the Indian subcontinent, south-east and east Asia (Chakraborti et al. 2018; McCarty et al. 2011; Polya and Middleton 2017; Xia and Liu 2004).

Based upon a substantial literature of research on medicinal, epidemiological, experimental toxicology and in vitro mechanistic aspects of iAs, iAs exposure from drinking water can be closely causally connected with the risk of cardiovascular disease (CVD) (Tsuji et al. 2014). For example, individuals who were in direct contact with high level well water iAs in Bangladesh were reported to suffer increased risk of mortality from both ischemic heart disease and cerebrovascular disease (Chen et al. 2011). In addition, a huge amount of empirical evidence supports the impacts of drinking water iAs on the risk of hypertension, specifically both higher diastolic blood pressure and systolic blood pressure (Hall et al. 2017; Hossain et al. 2017; Kunrath et al. 2013). Similar positive associations with exposure to iAs through drinking water were also observed for the risk of CVD markers (Wu et al. 2012) and stroke (Rahman et al. 2014).

Particularly, in areas where there is little or no iAs exposure from drinking water, iAs exposure is, more importantly, from everyday foods (European Food Safety Authority 2009; Meharg and Zhao 2012; Mondal and Polya 2008; Schoof et al. 1999). Because of the joint impact of its physiology along with flooded paddy field geochemistry, rice, in many cases, contains substantially more As than other major staples (Meharg et al. 2008), and is therefore particularly regarded as an important source of iAs exposure (Food and Agriculture Organization of the United Nations 2008). This is especially the case for areas, notably Bangladesh, India, South-East Asia, southern China and parts of South America (Meharg and Zhao 2012), where the majority of residents exposed with high As from drinking water and mainly consume rice—as opposed to other staples—in everyday meals. In regions, 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. 2017) where there is little exposure from drinking water, rice is not regarded as the daily staple for the majority of the population but nevertheless, its role in iAs exposure cannot be ignored particularly for sub-populations taking rice at a relatively high rate (Awata et al. 2017; Cleland et al. 2009; Mantha et al. 2017). It has been reported that rice consumption is increasing in the UK due to the changes of ethnic distribution and food diversification (Schenker 2012). Although the intake of rice has become the main iAs exposure pathway for more than three billion individuals around the world, to the best of our knowledge, little epidemiological evidence exists to demonstrate CVD risks arising from iAs exposure from rice and rice products (Torres-Escribano et al. 2008).

Hypertension, a common form of CVD, is not only the leading cause of morbidity and mortality in the world with a global prevalence of approximately 40% (Hall et al. 2017; World Health Organization 2011), but also, more seriously, recognized as a major risk factor for some other CVD types (Kannel 1996; Sowers et al. 2001; Wang et al. 2011), including stroke (Hu and Balakrishnan 2005) and ischemic heart disease (Collins and MacMahon 1994; Stamler et al. 1993). Considering a number of factors, such as age, obesity, gender, smoking status, alcohol consumption and sodium intake (Biino et al. 2013; He et al. 2018; NHLBI Obesity Education Initiative Expert Panel on the Identification Evaluation and Treatment of Obesity in Adults (US) 1998), that are widely known to be important indicators of hypertension, the effect of iAs intake from rice and rice products is likely to be less important. However, given the large number of people exposed to iAs, and the high prevalence of morbidity and mortality due to hypertension worldwide, even a small association might result in hundreds of thousands of additional hypertension cases (Ferguson et al. 2018; Gao et al. 2018; Li et al. 2015; World Health Organization 2011). It is, therefore, of importance to quantify the contribution of rice and rice products on iAs intake and assess its relation with hypertension risk.

In this study, we conducted an individual level cross-sectional analysis to quantify the extent to which
daily iAs intake from rice and rice products (E-iAs\textsubscript{ing,\text{rice}}) modifies the association between hypertension risks and previously well-established risk factors. In addition to general hypertension (abnormally high arterial blood pressure), four other blood pressure parameters, viz. mean values of diastolic blood pressure (DBP), systolic blood pressure (SBP), arterial pressure [AP, defined as $1/3 \times (SBP + 2 \times DBP)$] and pulse pressure (meanPulse, valid pulse readings), which are associated with an increased risk of vascular disease have also been included as indicators of hypertension risks (Chen et al. 2007; Lelong et al. 2019; Rahman 2002; US Department of Health And Human Services et al. 2007).

The objectives of the study were to (1) quantify the importance of E-iAs\textsubscript{ing,\text{rice}} and other confounders to the variability of hypertension risks; (2) model the relationships between E-iAs\textsubscript{ing,\text{rice}} and hypertension risks; (3) test the effects modification of several well-established risk factors on the association between E-iAs\textsubscript{ing,\text{rice}} and hypertension risks, identifying vulnerable subgroups. We further discussed our exploratory findings, and in the light of these, made recommendations for future work.

**Methods**

We explored the extent to which E-iAs\textsubscript{ing,\text{rice}} modifies the association between hypertension risks and previously well-established risk factors using a repeated cross-sectional design within the National Diet and Nutrition Survey Rolling Programme from April 2014 through August 2015 for Year 7 and April 2015 through August 2016 for Year 8 (NDNS RP 7–8) (MRC Elsie Widdowson Laboratory and NatCen Social Research 2019).

Details of the parent survey NDNS RP 7–8 may be found elsewhere (MRC Elsie Widdowson Laboratory and NatCen Social Research 2019). In summary, NDNS RP 7–8 is a national population-based survey of food consumption and nutritional status of people aged 1.5 years and older living in private households in the UK. Information is gathered on demographic, socio-economic, behaviour, dietary and health status through door-to-door recruitment, in-person interviews, along with comprehensive data collection, physical measurements and a food diary. The present study used secondary data from the most recent data cycles (from April 2014 through August 2015 for Year 7 and April 2015 through August 2016 for Year 8) because these two surveys provide the latest source of high-quality nationally representative data on the types and quantities of different rice and rice products consumed by individuals and their health status.

Because our present study only used publicly available and anonymized data from NDNS RP 7–8, we required no further ethical approval for our study, noting that the authors of the NDNS RP 7–8 study had themselves obtained ethical approval for their study from the Cambridge South NRES Committee (Ref. No. 13/EE/0016).

**Study population**

We firstly extracted secondary data related to all the participants in NDNS RP 7–8 ($N = 2723$). NDNS RP 7–8 was carried out in all four countries of the UK and was designed to be representative of the UK population, selecting participants using a cross-sectional, multistage and random sampling design. Also, their fieldwork was conducted throughout the year (from April 2014 through August 2015 for Year 7 and April 2015 through August 2016 for Year 8) in order to take into account the potential seasonal variations in food consumption. Details about the recruitment of participants can be found in MRC Elsie Widdowson Laboratory and NatCen Social Research (2019). During the study period, a representative sample of 2723 participants aged 1.5 and older was recruited.

As the dietary pattern, some socio-demographic characteristics, general health condition and blood pressure status of children, pregnant and breastfeeding women may change and may be different from the general population (Attorp et al. 2014; MRC Elsie Widdowson Laboratory and NatCen Social Research 2019; Yoder et al. 2009), and this study excluded participants based on the following criteria: (1) women who were pregnant and breastfeeding ($N = 0$); (2) people younger than 16 ($N = 1074$); and (3) participants with missing data ($N = 1051$), in relation to SBP (681), DBP (681), AP (681), general hypertension (681), meanPulse (524), qual7 (qualifications gained) (49), ethgrp5 (ethnic group) (8), eqv3 (equalized household income) (243), cigsta3 (cigarette smoking status) (8), dnoft (frequency of alcohol consumption in past 12 months) (9), bmival (valid BMI) (149), whgval (waist-hip ratio groups) (543),
Table 1 Description of variables included in the present study

| Variable number | Variable name/code | Description | Variable type |
|-----------------|-------------------|-------------|---------------|
| 1               | Age               | Age of respondent 16 + year (16–34; 35–49; 50–64; 65 + years) | Categorical |
| 2               | AP                | Mean arterial pressure (mmHg) | Continuous |
| 3               | bmival            | Valid BMI group (underweight; normal; overweight; obese) | Categorical |
| 4               | cigsta3           | Cigarette smoking status (Current cigarette smoker; ex-regular cigarette smoker; never regular cigarette smoker) | Categorical |
| 5               | DBP add 10        | Omron valid mean diastolic blood pressure (DBP) incremented by 10 mmHg is added if anti-hypertension medication is taken (mmHg) | Continuous |
| 6               | Diabetes.combined | Whether respondent is diabetic (Yes; no) | Categorical |
| 7               | dnoft             | Frequency of alcohol consumption in past 12 months (5 or 7 days a week; 3 or 4 days a week; once or twice a week; once or twice a month; once every couple of months; once or twice a year; not at all in the last 12 months/non-drinker) | Categorical |
| 8               | E-iAsing,grain    | Daily inorganic arsenic (iAs) intake from grain and grain-based products (µg/person/day) | Continuous |
| 9               | E-iAsing,rice     | Daily iAs intake from rice and rice products (µg/person/day) | Continuous |
| 10              | E-iAsing,water    | Daily iAs intake from drinking water (µg/person/day) | Continuous |
| 11              | EnergyDkJ         | Intake of total energy per day (KJ) for diet only (grouped into quartiles based on the distributions of energy intake level in the study population) | Categorical |
| 12              | eqv3              | Equivalized household income (£) [Lowest tertile (≤ 17,500); middle tertile (> 17,500 ≤ 32,216); highest tertile (> 32,500)] | Categorical |
| 13              | ethgrp5           | Ethnic group, 5 groups (White; mixed ethnic group; Black or Black British; Asian or Asian British; any other group) | Categorical |
| 14              | FatgD             | Intake of fat per day (g) for diet only (grouped into quartiles based on the distributions of fat intake level in the study population) | Categorical |
| 15              | FolateugplussuppsD| Intake of folate (µg) per day for both diets and supplements (grouped into quartiles based on the distributions of folate intake level in the study population) | Categorical |
| 16              | General hypertension | Whether participants were diagnosed as general hypertension (Yes; no) | Categorical |
| 17              | GlucosegD         | Intake of glucose per day (g) for diet only (grouped into quartiles based on the distributions of glucose intake level in the study population) | Categorical |
| 18              | HessCon           | Whether have any physical/mental health condition/illnesses for 12 months or more (Yes; no) | Categorical |
| 19              | meanPulse         | Mean value of the three valid pulse pressure readings (mmHg) | Continuous |
| 20              | MN                | Daily intake of several micro-nutrients (Participants with 0–3 nutrients ≥ the mean intake of the accordingly nutrients; participants with 4–7 nutrients ≥ the mean intake of the accordingly nutrients; Participants with 8–11 nutrients ≥ the mean intake of the accordingly nutrients; participants with 12–15 nutrients ≥ the mean intake of the accordingly nutrients; participants with 16–18 nutrients ≥ the mean intake of the accordingly nutrients) | Categorical |
| 21              | NumChild          | Number of Children aged between 0 and 15 (Have no child; have 1–2 children; have 3–4 children; have 5–6 children) | Categorical |
| 22              | ProteingD         | Intake of protein per day (g) for diet only (grouped into quartiles based on the distributions of protein intake level in the study population) | Categorical |
| 23              | qual7             | Qualifications gained (Degree or equivalent; Higher education, below degree level and GCE, A level or equivalent; GCSE grades A–G or equivalent/commercial qualifications/apprenticeship; Foreign or other qualifications and no qualifications and still in FT education) | Categorical |
Diabetes.combined (whether respondent is diabetic) (768) and SalHowC (how often salt added during cooking) (24). After such exclusions, the final population size used in the present study was 598.

Data collection

NDNS RP 7–8 dataset was collected from 2-stage interviewer visits to each household covering face-to-face interviews, self-completion questionnaires, a food diary and physical measurements. Details about the related interviews, questionnaires, dietary record and physical measurements can be found elsewhere (MRC Elsie Widdowson Laboratory and NatCen Social Research 2019). A brief description of variables included in the present study is illustrated in Table 1, with a detailed description being summarized and provided in Table S1 (For some characteristics, individuals were regrouped due to the small number of subjects in some categories).

Daily iAs intake from rice and rice products (μg/person/day), E-iAs_{ing,rice}

Daily iAs intake from rice and rice products (μg/person/day), E-iAs_{ing,rice}, was estimated using the NDNS RP 7–8 reported consumption level by Eqs. (1) and (2) followed (Awata et al. 2017):

\[ E-iAs_{ing,rice} = \sum_i RC_i \times C_{rice,i} \times (1 - LOSS_{cooking}) \]  

(1)

\[ RC_i = \frac{\sum^n_i DRC_i}{n} \]  

(2)

where RC$_i$ is the average daily consumption (kg/day) of rice and rice product, $i$, during the food diary (ready-to-eat), $C_{rice,i}$ is the iAs concentration (μg/kg) of the rice and rice product, $i$ (ready-to-eat or raw), LOSS$_{cooking}$ is the estimated proportion of iAs lost from rice and rice products upon cooking, $n$ length of the food diary [3 days ($n = 3$) or 4 days ($n = 4$)], DRC$_i$ consumption rate (kg/day) of rice and rice product, $i$, in each day during the food diary.

Food commodity consumption was calculated for all food diary periods, and the average consumption
value was used for average daily commodity consumption level of each survey participant. Values for $C_{\text{rice}}$ were estimated from those reported by European Food Safety Authority (2014). LOSS$_{\text{cooking}}$ was estimated as 5% across all not ready-to-eat foods based upon the study of Mwale et al. (2018) and as 0% for ready-to-eat foods.

Blood pressure endpoints

Several blood pressure endpoints, including SBP, DBP, meanPulse, SBP add 10, DBP add 10, AP and general hypertension, all of which are associated with an increased risk of vascular ill-health (US Department of Health And Human Services et al. 2007) were included as our target outcomes.

Mean values of three valid SBP, DBP and pulse pressure readings were used to represent SBP, DBP and meanPulse level, respectively. Given that people taking anti-hypertension medications have controlled and likely artificially low blood pressure (Banda et al. 2010; Zamora-Kapoor et al. 2018), we addressed this by adding a constant 10 mmHg to the SBP and DBP for participants with such medications as SBP add 10 and DBP add 10 (cf. Mordukhovich et al. 2012). AP is defined as the average pressure in a patient’s arteries during one cardiac cycle, calculated as (SBP add 10 + 2 × DBP add 10)/3 (Chen et al. 2007; Lelong et al. 2019). General hypertension is defined as a SBP ≥ 140 mmHg, or a DBP ≥ 90 mmHg and/or under regular treatment with anti-hypertension medications (Among the total 2723 NDNS RP 7–8 participants, 245 of them were identified as taking anti-hypertension medications at the time of the interview) (Rahman 2002).

Considering the final population size used in the present study (598), except for DBP add 10 and meanPulse, the statistical power of the findings for all the other blood pressure endpoints was higher than 0.8 (data not shown).

Definition of confounders

Variables which are well recognized as important predictors of either hypertension risks or As intake should be considered when testing the association between E-iAs$_{\text{ing,rice}}$ and hypertension risks (Banda et al. 2010; Biino et al. 2013; Chen et al. 2007; Jarrah et al. 2018; Kim and Lee 2019; Lelong et al. 2019; Mohtasham-Amiri et al. 2018; Re 2009).

In general, confounding information in the present study (Sex (gender), age (age of respondent 16 + years old), ethgrp5, region (country people live), HessCon (whether have any physical/mental health condition/illnesses for 12 months or more), NumChild (number of Children aged between 0 and 15), qual7, Diabetes.combined, WrkStat (economic status), Quarter (fieldwork quarter), surveyyr (NDNS RP 7–8 survey year), eqv3, cigsta3, dnoft, bmival, whgval, SalHowC, MN (daily intake of several micronutrients including potassium, calcium, magnesium, iron, copper, zinc, retinol, vitamin A, vitamin D, Vitamin e, thiamin, riboflavin, niacin equivalent, vitamin B6, vitamin B12, vitamin, iodine, selenium), EnergyDkJ (intake of total energy per day (KJ) for diet only), ProteinD (intake of protein per day (g) for diet only), FatgD (intake of fat per day (g) for diet only), GlucosegD (intake of glucose per day (g) for diet only), SodiummgD (intake of sodium per day (mg) for diet only) and FolateugplussuppsD (intake of folate (µg) per day for both diets and supplements), E-iAs$_{\text{ing,water}}$ (daily iAs intake from drinking water) as well as E-iAs$_{\text{ing,grain}}$ (daily iAs intake from grain and grain-based products) was collected by NDNS RP 7–8 trained staffs and nurses during the two stages interviews coupled with a series of questionnaires, physical measurements and a food diary.

Some demographic, behavioural and socio-economic risk factors, such as Sex, age, ethgrp5, region, HessCon, NumChild, qual7, Diabetes.combined, WrkStat, Quarter, surveyyr and eqv3, were obtained during detailed background interview. cigsta3 and dnoft were included through smoking and drinking self-completion questionnaires.

Trained staff measured participants’ height and weight and then calculated BMI during the first stage interview based on the protocols from MRC Elsie Widdowson Laboratory and NatCen Social Research (2019). Standard international cut-off points were used for bmival, grouping participants into underweight (< 18.5 kg/m$^2$), healthy weight (18.5–24.9 kg/m$^2$), and overweight (≥ 25.0 kg/m$^2$) categories (NHLBI Obesity Education Initiative Expert Panel on the Identification Evaluation and Treatment of Obesity in Adults (US) 1998).

It has been proposed that the distribution of body fat is an important indicator of increased risk of CVD (He
et al. 2018). In the NDNS, nurses measured the waist and hip circumference and such data have been used for our calculation of whgval (both subcutaneous and intra-abdominal) in the present study. The whgval has been classified as normal weight, overweight and obesity, using the cut-off points as 0.8 for women and < 0.9 for men, 0.8–0.84 for women and 0.9–0.99 for men and > 0.85 for women and > 1 for men according to DGSP regulation (Dt. Gesellschaft für Sportmedizin und Prävention e.V. (DGSP) 2007).

In addition, confounding information such as SalHowC, MN and EnergyDkJ, ProteingD, FatgD, GlucosegD, SodiummgD as well as FolateugplussuppsD was all derived from the food diary. Among these, EnergyDkJ, ProteingD, FatgD, GlucosegD, SodiummgD and FolateugplussuppsD were divided into four quartiles based on their distribution in the population. For MN, a score of 0 or 1 was assigned to participants with less than (<) or greater than or equal to (≥) the mean daily intake level of each nutrient, respectively, with a composite measure then created by summing the individual score to indicate the intake level of these micro-nutrients (cf. El-Masri et al. 2018).

Moreover, drinking water and grain and grain-based products have been regarded as two important exposure pathways for iAs in the UK and some other European countries (European Food Safety Authority 2014), and this study, therefore, included E-iAsing,water (µg/person/day) and E-iAsing,grain (µg/person/day) as confounders with their calculation following Eqs. (3), (4) for E-iAsing,water and Eqs. (5), (6) for E-iAsing,grain:

\[
E\text{-}i\text{As}_{\text{ing,water}} = C_{\text{water}} \times WC
\]  

(3)

\[
WC = \frac{\sum_{i=1}^{n} DWC}{n}
\]  

(4)

\[
E\text{-}i\text{As}_{\text{ing,grain}} = \sum_{i} C_{\text{grain},i} \times GC_{i}
\]  

(5)

\[
GC_{i} = \frac{\sum_{i=1}^{n} DGC_{i}}{n}
\]  

(6)

where \( C_{\text{water}} \): iAs concentration (µg/L) in drinking water, \( WC \): average daily intake (L/day) of drinking water during the food diary, \( n \): length of the food diary [3 days (\( n = 3 \)) or 4 days (\( n = 4 \)), DWC: consumption (L/day) of drinking water in each day during the food diary, \( C_{\text{grain},i} \): iAs concentration (µg/kg) of the grain and grain-based product, \( i \), \( GC_{i} \): average daily consumption (kg/day) of grain and grain-based product, \( i \), during the food diary, \( DGC_{i} \): consumption rate (kg/day) of grain and grain-based product, \( i \), in each day during the food diary. Similar to E-iAsing,rice, consumption rates for drinking water and grain and grain-based products were calculated for all food diary periods, and the average daily consumption values were used for average consumption level of each survey participant. Values for \( C_{\text{grain},i} \) and \( C_{\text{water}} \) were estimated from those reported by European Food Safety Authority (2014).

Statistical analysis

In this study, we explored, for the UK population from April 2014 through August 2015 and April 2015 through August 2016, the extent to which E-iAsing,rice modifies the association between hypertension risks (several blood pressure endpoints, including DBP add 10, SBP add 10, AP, meanPulse and general hypertension) and previously well-established risk factors categorically and continuously, utilizing a series of generalized linear models. In addition, the influence of an appropriate range of socio-economic, demographic and lifestyle as confounders is explored through minimizing objective model comparison criteria, notably Akaike’s Information Criterion (AIC) (Bozdogan 1987).

Statistical analysis was conducted through R statistical software [version 3.4.3 (R Foundation for Statistical Computing)].

Before the main analysis, we compared participants’ (over 16 (\( N = 1649 \))) iAs intake level and some demographic and lifestyle characteristics for those included and those excluded from the present study (see previous exclusion criteria), with significance of differences being computed by Fisher’s exact test, Mann–Whitney U Test and Student’s \( t \) test as appropriate. Participants included and participants excluded from this study were found to have similar levels of E-iAsing,rice, NumChild, gender and ethnicity distribution, health condition, bmiwal and whgval. However, participants were more likely to be middle-aged, in employment, have higher household income or live in England compared to other UK countries (Table S2).

For the main analysis, E-iAsing,rice was either categorized in quartiles based on its weighted
distributions in the study population or was used as a continuous measure.

Descriptive analysis was firstly conducted comparing participants by E-iAsing,rice quartiles and by the status of general hypertension in terms of sociodemographic and lifestyle characteristics and some established or suspected risk factors of hypertension. The results were reported as means [standard deviations (SD)] for continuous variables (E-iAsing,rice, E-iAsing,water and E-iAsing,grain) or as frequencies (percentages %) for categorical ones (surveyyr, Quarter, Sex, age, ethgrp5, qual7, cigsta3 and eqv3, dnoft, HessCon, NumChild, Diabetes.combined, WrkStat, MN, EnergyDkJ, ProteingD, FatgD, GlucosegD, SodiummgD, FolateugplussuppsD, bmival, region, SalHowC and whgval). The significance of differences across intake quartiles or general hypertension status was determined from $\chi^2$ tests and Wilcoxon rank-sum tests with Tukey post hoc tests, and the $p$ values for trend were computed via analysis of variance (ANOVA) test with type II error.

Then, we quantified the individual and interactive contributions of E-iAsing,rice and all the potential confounders to the variability of hypertension risks (DBP add 10, SBP add 10, AP, meanPulse and general hypertension, respectively) through generalized linear model (GLM) (contributions (%) = 100 $\times$ (null deviance–residual deviance)/null deviance) (Bjorndal et al. 2013). Among this, the importance of two-way interactive effects was calculated based on the relative excess risk for interaction (RERI) according to Chen et al. (Chen et al. 2011) [see Eq. (7)], with a value over zero indicating the presence of synergy effects:

$$\text{RERI} = e^{b_1+b_2+b_3} - e^b_1 - e^b_2 + 1. \quad (7)$$

where $b_1$: the continuous coefficient of E-iAsing,rice, $b_2$: the coefficient of each potential confounder, $b_3$: the interactive term coefficient.

The resultant $p$ values were computed using ANOVA test with type II error with the values for interaction obtained by adding a cross-product term between continuous iAs intake and different confounders to the main model.

We finally analysed the extent to which E-iAsing,rice modifies the association between hypertension risks (DBP add 10, SBP add 10, AP, meanPulse and general hypertension) and previously well-established risk factors by GLMs. Separate independent models were used for the changes of DBP add 10, SBP add 10, AP, meanPulse and the odds ratio of general hypertension to assess their associations with E-iAsing,rice, respectively.

To firstly get a general understanding of whether E-iAsing,rice could significantly modify the association between hypertension risks and previously well-established risk factors, we obtained a best-fitted model of hypertension risks without E-iAsing,rice but including some important previously known risks factors and then tested whether or not adding this intake factor as a confounder made that model better.

To further evaluate the associations between E-iAsing,rice and hypertension risks at various intake levels, both categorical and continuous intake variables were used in the crude and multivariable adjusted models. For categorical analysis, the odds ratios for general hypertension (binary variable) and the corresponding 95% confidence intervals (CIs) were calculated by using logistic regression to compare participants in quartiles of E-iAsing,rice. Similarly, SBP add 10, DBP add 10, AP and meanPulse (continuous variables) and the corresponding 95% CIs for different intake quartiles were estimated and compared between each of the higher 3 quartiles with the bottom one by multiple linear regression models. For continuous analysis, E-iAsing,rice was used as a continuous measure to evaluate the changes of each blood pressure endpoint for an increase of 1 $\mu$g/person/day E-iAsing,rice, respectively. In addition, we examined the assumption of nonlinear relationships by including higher order polynomial terms for E-iAsing,rice in the best-fitted linear models. To allow a more flexible dose–response association, we also estimated DBP add 10, SBP add 10, AP, meanPulse and the odds ratio of general hypertension by dividing E-iAsing,rice Into 15 groups based on its distributions in the study population. The differences of the hypertension risks across four quartiles or 15 groups of iAs intake were obtained from Wald tests for E-iAsing,rice coefficients, and the $p$ values for linear and nonlinear trends were computed by ANOVA test with type II error where E-iAsing,rice is a continuous measure.

The main covariate of interest was determined a priori based on biological and behavioural plausibility (such as Sex, age, ethgrp5, cigsta3 and dnoft, HessCon, Diabetes.combined, MN, SalHowC, EnergyDkJ, ProteingD, FatgD, GlucosegD, SodiummgD, FolateugplussuppsD, bmival and whgval), and some
socio-economic information (surveyr, Quarter, region, qual7, eqv3, NumChild, WrkStat) as well as other important exposure pathways (E-iAs\textsubscript{ing,water} or E-iAs\textsubscript{ing,grain}) if they had a \( p \) value less than 0.2 in the univariate models. For better modelling their relationships, we also checked the existence of multicollinearity problems. Given the sample size, the number of variables included (Burnham and Anderson 2002) as well as the best and most parsimonious fit, models were derived from the full set of data and reduced by model selection using AIC with the stepwise selection allowed in both directions.

Vulnerability to As toxicity differs widely from person to person, and hypertension risks may be higher in certain susceptible subgroups. However, most of such variability in susceptibility to date remains unexplained (Steinmaus et al. 2015). To identify the most vulnerable subgroups and provide better suggestions for lowering the adverse effects of iAs intake, we performed subgroup analysis to evaluate effect modifications in adjusted models for subgroups defined by Sex, age, ethgrp5, bmival, cigsta3, dnoft, Diabetes.-combined and region. Forest plots have been applied to show the changes of hypertension risks for an increase of 1 \( \mu g/\text{person/day} \) E-iAs\textsubscript{ing,rice} by participants’ characteristics. In the forest plot, boxes represent the SBP add 10, DBP add 10, AP, meanPulse and the odds ratio of general hypertension, with horizontal lines indicating their 95% CIs. \( p \) values for the interaction were obtained by adding a cross-product term between E-iAs\textsubscript{ing,rice} and the corresponding characteristic in the multivariable model, computed by the ANOVA test with type II error to account for the complex design.

For the assessment of the consistency of the findings, a sensitivity analysis has also been conducted. Specifically, we excluded people taking anti-hypertension medications, identifying whether the estimated associations in the main analysis would be substantially different after such exclusion.

Results

Characteristics of E-iAs\textsubscript{ing,rice}, hypertension risks and all the potential confounders

In this study, the mean values of SBP add 10 and DBP add 10 (127 (SD = 19) and 75 (SD = 12) mmHg) were lower than the minimum values defining general hypertension (140 and 90 mmHg, respectively) with about 30% participants being classified as having general hypertension. In addition, the mean level of AP and meanPulse was 92 (SD = 14) and 69 (SD = 11) mmHg, respectively.

For the E-iAs\textsubscript{ing,rice}, ranging from 0 to 41.8 \( \mu g/\text{person/day} \), participants included in this study consumed a mean level of 2.81 \( \mu g \) iAs each day with its SD being 4.73 \( \mu g/\text{person/day} \).

There were significant associations between E-iAs\textsubscript{ing,rice}, hypertension risks and some of the potential confounders (Tables 2, 3). Participants who have general hypertension tended to be older, overweight, less healthy, have less children or have become diabetics. Also, a larger proportion of participants who have no jobs or were current or ex-regular cigarette smokers could be found in the hypertension group. In addition, there were significant associations between E-iAs\textsubscript{ing,rice} and Sex, age, ethgrp5, nutrient intake, qual7 and E-iAs\textsubscript{ing,water} with people taking higher level iAs from rice and rice products being generally younger, not White or having a higher education level.

Importance of different factors to the hypertension risks

Whatever the relationship between E-iAs\textsubscript{ing,rice} and hypertension risks, it is likely to be of lesser importance than a number of factors that are widely known to be important indicators, such as age, obesity, gender, smoking status, alcohol consumption and sodium intake (Biino et al. 2013; He et al. 2018; NHLBI Obesity Education Initiative Expert Panel on the Identification Evaluation and Treatment of Obesity in Adults (US) 1998). Thus, the relationship between E-iAs\textsubscript{ing,rice} and hypertension risks can only be reasonably determined after first quantifying the importance of these factors.

To quantify the contributions of factors shown to influence hypertension risks and attempt to account for their importance, GLM was performed in our analysis. According to Table 4, similar results could be observed for SBP add 10, DBP add 10, AP and general hypertension. Specifically, age was the most important contributor for the variability of those blood pressure endpoints, accounting for over 20% of the observed variations. Meanwhile, whgval and bmival,
### Table 2  Characteristics of population satisfying inclusion criteria by hypertension status in the NDNS RP 7–8. Data from NDNS RP 7–8 (MRC Elsie Widdowson Laboratory and NatCen Social Research 2019) with exclusions as detailed in the text ($N = 598$)

| Variable | General hypertension | $p$ value* |
|----------|-----------------------|------------|
|          | Yes ($N = 178$)   | No ($N = 420$) |           |
| E-iA$_{\text{ing,rice}}$ (µg/person/day) | 2.17 (3.65) | 3.08 (5.11) | 0.015 |
| E-iA$_{\text{ing,water}}$ (µg/person/day) | 0.74 (0.70) | 1.02 (1.10) | <0.001 |
| E-iA$_{\text{ing,grain}}$ (µg/person/day) | 2.69 (1.32) | 2.89 (1.47) | 0.100 |
| Sex | | | |
| Male | 80 (44.94) | 171 (40.71) | 0.365 |
| Female | 98 (55.06) | 249 (59.29) |  |
| surveyyr | | | |
| 2014/15 | 90 (50.56) | 203 (48.33) | 0.655 |
| 2015/16 | 88 (49.44) | 217 (51.67) |  |
| HessCon | | | |
| With any physical/mental health condition/illnesses for 12 months or more | 98 (55.06) | 119 (28.33) | <0.001 |
| Without any physical/mental health condition/illnesses for 12 months or more | 80 (44.94) | 301 (71.67) |  |
| Diabetes.$\text{combined}$ | | | |
| Without diabetes | 149 (83.71) | 402 (95.71) | <0.001 |
| Diabetic | 29 (16.29) | 18 (4.29) |  |
| NumChild | | | |
| Have no child | 152 (85.39) | 259 (61.67) | <0.001 |
| Have 1–2 child | 23 (12.92) | 143 (34.05) |  |
| Have 3–4 child | 3 (1.69) | 18 (4.29) |  |
| Age | | | |
| 16–34 years | 4 (2.25) | 151 (35.95) | <0.001 |
| 35–49 years | 32 (17.98) | 130 (30.95) |  |
| 50–64 years | 71 (39.89) | 91 (21.67) |  |
| 65 + year | 71 (39.89) | 48 (11.43) |  |
| Quarter | | | |
| Season 1 | 29 (16.29) | 98 (23.33) | 0.217 |
| Season 2 | 45 (25.28) | 106 (25.24) |  |
| Season 3 | 52 (29.21) | 101 (24.05) |  |
| Season 4 | 52 (29.21) | 115 (27.38) |  |
| WrkStat | | | |
| In full- or part-time employment | 75 (42.13) | 259 (61.67) | <0.001 |
| Full-time student or not working | 103 (57.87) | 161 (38.33) |  |
| ethgrp5 | | | |
| White | 167 (93.82) | 383 (91.19) | 0.641 |
| Mixed | 1 (0.56) | 7 (1.67) |  |
| Black or Black British | 2 (1.12) | 12 (2.86) |  |
| Asian or Asian British | 6 (3.37) | 14 (3.33) |  |
| Any other groups | 2 (1.12) | 4 (0.95) |  |
| eqv3 (£) | | | |
| Lowest tertile ($\leq 17,500$) | 53 (29.78) | 94 (22.38) | 0.162 |
| Middle tertile ($> 17,500$ and $\leq 32,216$) | 53 (29.78) | 135 (32.14) |  |
| Highest tertile ($> 32,500$) | 72 (40.45) | 191 (45.48) |  |
| cigsta3 | | | |
| Current cigarette smoker | 19 (10.67) | 66 (15.71) | <0.001 |
| Ex-regular cigarette smoker | 62 (34.83) | 80 (19.05) |  |
| Never regular cigarette smoker | 97 (54.49) | 274 (65.24) |  |
## Table 2 continued

| Variable                                      | General hypertension |
|-----------------------------------------------|----------------------|
|                                              | Yes \((N = 178)\) | No \((N = 420)\) | \(p\) value* |
| **dnift**                                     |                      |                    |              |
| 5–7 days per week                             | 27 (15.17)           | 32 (7.62)          | 0.123        |
| 3–4 days per week                             | 24 (13.48)           | 48 (11.43)         |              |
| 1–2 days per week                             | 44 (24.72)           | 125 (29.76)        |              |
| 1–2 per month                                 | 27 (15.17)           | 71 (16.90)         |              |
| Once every couples of months                  | 14 (7.87)            | 47 (11.19)         |              |
| 1–2 per year                                  | 18 (10.11)           | 45 (10.71)         |              |
| Not at all in the last 12 months/non-drinker  | 24 (13.48)           | 52 (12.38)         |              |
| **bmival (kg/m²)**                            |                      |                    |              |
| Underweight: BMI < 18.5                       | 0 (0.00)             | 14 (3.33)          | < 0.001      |
| Normal (healthy weight): BMI between 18.5 and 25| 37 (20.79)           | 172 (40.95)        |              |
| Overweight: BMI between 25 and 30             | 74 (41.57)           | 153 (36.43)        |              |
| Obese: BMI over 30                            | 67 (37.64)           | 81 (19.29)         |              |
| **whgval**                                    |                      |                    |              |
| For male: less than 0.9, For female: less than 0.80  | 28 (15.73)           | 207 (49.29)        | < 0.001      |
| For male: more than and including 0.90, up to and including 1.00; for female: more than and including 0.80, up to and including 0.85 | 54 (30.34)           | 113 (26.90)        |              |
| For male: more than 1.00; for female: more than 0.85 | 96 (53.93)           | 100 (23.81)        |              |
| **MN**                                        |                      |                    |              |
| Participants with 0–3 nutrients greater than or equal to the mean intake level | 34 (19.10)           | 100 (23.81)        | 0.736        |
| Participants with 4–7 nutrients greater than or equal to the mean intake level | 36 (20.22)           | 81 (19.29)         |              |
| Participants with 8–11 nutrients greater than or equal to the mean intake level | 42 (23.60)           | 101 (24.05)        |              |
| Participants with 12–15 nutrients greater than or equal to the mean intake level | 40 (22.47)           | 84 (19.90)         |              |
| Participants with 16–18 nutrients greater than or equal to the mean intake level | 26 (14.61)           | 54 (12.86)         |              |
| **EnergyDkJ (KJ)**                            |                      |                    |              |
| Q1: 189.46–1294.86                            | 27 (15.17)           | 52 (12.38)         | 0.673        |
| Q2: 1295.07–1627.87                           | 33 (18.54)           | 86 (20.48)         |              |
| Q3: 1628.14–2037.01                           | 52 (29.21)           | 113 (26.90)        |              |
| Q4: 2037.83–4771.28                           | 66 (37.08)           | 169 (40.24)        |              |
| **ProteingD (g)**                             |                      |                    |              |
| Q1: 1.17–11.90                                | 21 (11.80)           | 43 (10.24)         | 0.338        |
| Q2: 11.91–15.42                               | 31 (17.42)           | 91 (21.67)         |              |
| Q3: 15.43–19.31                               | 56 (31.46)           | 107 (25.48)        |              |
| Q4: 19.33–69.00                               | 70 (39.33)           | 179 (42.62)        |              |
| **FatgD (g)**                                 |                      |                    |              |
| Q1: 0.12–10.64                                | 34 (19.10)           | 59 (14.05)         | 0.466        |
| Q2: 10.65–14.21                               | 31 (17.42)           | 83 (19.76)         |              |
| Q3: 14.23–18.71                               | 46 (25.84)           | 110 (26.19)        |              |
| Q4: 18.74–59.89                               | 67 (37.08)           | 168 (40.00)        |              |
| **GlucosegD (g)**                             |                      |                    |              |
| Q1: 0.06–2.19                                 | 41 (23.03)           | 75 (17.86)         | 0.543        |
| Q2: 2.20–3.34                                 | 34 (19.10)           | 88 (20.95)         |              |
| Q3: 3.35–4.88                                 | 45 (25.28)           | 115 (27.38)        |              |
| Q4: 4.89–30.28                                | 58 (32.58)           | 142 (33.81)        |              |
| **SodiummgD (mg)**                            |                      |                    |              |
| Q1: 22.97–327.89                              | 29 (16.29)           | 62 (14.76)         | 0.617        |
| Q2: 327.91–430.23                             | 33 (18.54)           | 86 (20.48)         |              |
| Q3: 430.26–561.96                             | 56 (31.46)           | 114 (27.14)        |              |
| Q4: 562.28–2306.84                            | 60 (33.71)           | 158 (37.62)        |              |
| Variable | General hypertension |
|----------|----------------------|
|          | Yes (N = 178) | No (N = 420) | p value* |
| **FolateugplussuppsD (µg)** | | | |
| Q1: 5.69–35.36 | 20 (11.24) | 54 (12.86) | 0.614 |
| Q2: 36.38–47.85 | 30 (16.85) | 87 (20.71) | |
| Q3: 47.87–65.81 | 52 (29.21) | 109 (25.95) | |
| Q4: 65.86–1426.32 | 76 (42.70) | 170 (40.48) | |
| **qual7** | | | |
| Degree or equivalent | 47 (26.4) | 148 (35.24) | 0.084 |
| Higher education, below degree level; GCE, a level or equivalent | 35 (19.66) | 85 (20.24) | |
| GCSE grades A–G or equivalent/commercial qualifications/apprenticeship | 33 (18.54) | 77 (18.33) | |
| Foreign or other qualifications; no qualifications; still in FT education | 63 (35.39) | 110 (26.19) | |
| **Region** | | | |
| England Central/Midlands | 27 (15.17) | 55 (13.1) | 0.395 |
| England North | 40 (22.47) | 99 (23.57) | |
| England South (including London) | 58 (32.58) | 162 (38.57) | |
| Northern Ireland and Scotland | 12 (6.74) | 32 (7.62) | |
| Wales | 41 (23.03) | 72 (17.14) | |
| **SalHowC** | | | |
| Never | 85 (47.75) | 209 (49.76) | 0.867 |
| Sometimes and usually | 43 (24.16) | 101 (24.05) | |
| Always | 50 (28.09) | 110 (26.19) | |

The results were reported as means (standard deviations (SD)) for continuous variables (E-iAs<sub>ing</sub>,<sub>rice</sub>, E-iAs<sub>ing</sub>,<sub>water</sub> and E-iAs<sub>ing</sub>,<sub>grain</sub>) or as frequencies (percentages (%)) for categorical ones (surveyyr, Quarter, Sex, age, ethgrp5, qual7, cigsta3 and eqv3, dnoft, HessCon, NumChild, Diabetes.combined, WrkStat, MN, EnergyDkJ, ProteingD, FatgD, GlucosegD, SodiummgD, FolateugplussuppsD, bmival, region, SalHowC and whgval).

Differences were computed by hypertension status via χ² tests and Wilcoxon rank-sum tests.

General hypertension: whether participants were diagnosed as general hypertension; E-iAs<sub>ing</sub>,<sub>rice</sub>: daily inorganic arsenic (iAs) intake from rice and rice products; E-iAs<sub>ing</sub>,<sub>water</sub>: daily iAs intake from drinking water; E-iAs<sub>ing</sub>,<sub>grain</sub>: daily iAs intake from grain and grain-based products; surveyyr: NDNS RP 7–8 survey year; Sex: gender; EnergyDkJ: intake of total energy per day (KJ) for diet only; ProteingD: intake of protein per day (g) for diet only; FatgD: intake of fat per day (g) for diet only; GlucosegD: intake of glucose per day (g) for diet only; SodiummgD: intake of sodium per day (mg) for diet only; FolateugplussuppsD: intake of folate (µg) per day for both diets and supplements; MN: daily intake of several micro-nutrients (Potassium (mg) including supplements, calcium (mg) including supplements, magnesium (mg) including supplements, iron (mg) including supplements, copper (mg) including supplements, zinc (mg) including supplements, retinol (mg) including supplements, vitamin A (retinol equivalents) (µg) including supplements, vitamin D (µg) including supplements, vitamin E (µg) including supplements, thiamin (mg) including supplements, riboflavin (mg) including supplements, niacin equivalent (mcg) including supplements, vitamin B6 (mcg) including supplements, vitamin B12 (µg) including supplements, vitamin C (mg) including supplements, iodine (µg) including supplements, selenium (µg) including supplements); region: country people live; NumChild: number of children aged between 0 and 15; age: age of respondent 16 + year old; SalHowC: how often salt added during cooking; Quarter: fieldwork quarter; qual7: qualifications gained; WrkStat: economic status (working condition); ethgrp5: ethnic group; eqv3: equivalized household income; HessCon: whether have any physical/mental health condition/illnesses for 12 months or more; Diabetes.combined: whether respondent is diabetic; cigsta3: cigarette smoking status; dnoft: frequency of alcohol consumption in past 12 months (including non-drinkers); bmival: BMI (kg/m²); whgval: waist-hip ratio groups.

*Indicating whether there is statistically significant relationship between characteristics of population and status of general hypertension.
Table 3 Characteristics of population satisfying inclusion criteria by the distribution of E-iAs_{ing,rice} in the NDNS RP 7–8. Data from NDNS RP 7–8 (MRC Elsie Widdowson Laboratory and NatCen Social Research 2019) with exclusions as detailed in the text (N = 598)

| Characteristic                                      | Quartile of E-iAs_{ing,rice}, μg/person/day | Quartile 1 (0.00–0.00) | Quartile 2 (0.00–0.565) | p value* | Quartile 3 (0.638–3.79) | p value* | Quartile 4 (3.79–41.8) | p value* | p value for trend |
|-----------------------------------------------------|---------------------------------------------|--------------------------|--------------------------|-----------|--------------------------|-----------|--------------------------|-----------|---------------------|
| E-iAs_{ing,grain} (μg/person/day)                   |                                             | 2.98 (1.42)              | 2.90 (1.48)              | 0.966     | 2.69 (1.38)              | 0.304     | 2.77 (1.43)              | 0.572     | 0.235               |
| E-iAs_{ing,water} (μg/person/day)                   |                                             | 0.72 (0.76)              | 0.72 (0.70)              | 0.871     | 1.11 (1.22)              | 0.004     | 1.21 (1.15)              | < 0.001   | < 0.001             |
| Sex                                                 |                                             | Female                   | 86 (57.33)               | 93 (62.42) | 0.436                    | 93 (62.42) | 0.436                    | 75 (50.00) | 0.247               |
|                                                     |                                             | Male                     | 64 (42.67)               | 56 (37.58) | 56 (37.58)               | 75 (50.00) | 0.247               |
| surveyyr                                            |                                             | 2014/15                  | 132 (88.00)              | 10 (6.71)  | < 0.001                  | 75 (50.34) | < 0.001                  | 76 (50.67) | < 0.001             |
|                                                     |                                             | 2015/16                  | 18 (12.00)               | 139 (93.29)| 74 (49.66)               | 74 (49.33) | 0.247               |
| HessCon                                             |                                             | Without any physical/mental health condition/illnesses for 12 months or more | 84 (56.00) | 100 (67.11) | 0.063 | 102 (68.46) | 0.036 | 95 (63.33) | 0.290 | 0.461 |
|                                                     |                                             | With any physical/mental health condition/illnesses for 12 months or more | 66 (44.00) | 49 (32.89) | 47 (31.54) | 55 (36.67) | 0.036 | 95 (63.33) | 0.290 | 0.461 |
| Diabetes combined                                   |                                             | Without diabetes          | 139 (92.67)              | 139 (93.29)| 0.733 | 135 (90.60) | 0.663 | 138 (92.00) | 0.819 | 0.576 |
|                                                     |                                             | Diabetic                  | 11 (7.33)                | 10 (6.71)  | 0.436                    | 94 (9.40) | 12 (8.00) | 0.436 | 75 (50.00) | 0.247 |
| NumChild                                            |                                             | Have no child             | 113 (75.33)              | 100 (67.11)| 0.044 | 97 (65.10) | 0.154 | 101 (67.33) | 0.291 | 0.900 |
|                                                     |                                             | Have 1–2 child            | 31 (20.67)               | 47 (31.54) | 0.354 | 45 (30.20) | 0.032 | 43 (28.67) | 0.003 | 0.005 |
|                                                     |                                             | Have 3–4 child            | 6 (4.00)                 | 2 (1.34)   | 0.354 | 7 (4.70) | 6 (4.00) | 0.032 | 43 (28.67) | 0.003 | 0.005 |
| Age                                                 |                                             | 16–34                     | 32 (21.33)               | 35 (23.49) | 0.543 | 45 (30.20) | 0.032 | 43 (28.67) | 0.003 | 0.005 |
|                                                     |                                             | 35–49                     | 30 (20.00)               | 41 (27.52) | 0.543 | 41 (27.52) | 0.500 | 50 (33.33) | 0.003 | 0.005 |
|                                                     |                                             | 50–64                     | 48 (32.00)               | 39 (26.17) | 0.543 | 39 (26.17) | 0.500 | 36 (24.00) | 0.003 | 0.005 |
|                                                     |                                             | 65+                       | 40 (26.67)               | 34 (22.82) | 0.543 | 24 (16.11) | 0.500 | 21 (14.00) | 0.003 | 0.005 |
| Quarter                                             |                                             | Season 1                  | 30 (20.00)               | 32 (21.48) | 0.695 | 28 (18.79) | 0.543 | 37 (24.67) | 0.788 | 0.992 |
|                                                     |                                             | Season 2                  | 39 (26.00)               | 43 (28.86) | 0.695 | 30 (20.13) | 0.543 | 39 (26.00) | 0.788 | 0.992 |
|                                                     |                                             | Season 3                  | 40 (26.67)               | 36 (24.16) | 0.695 | 41 (27.52) | 0.543 | 36 (24.00) | 0.788 | 0.992 |
|                                                     |                                             | Season 4                  | 41 (27.33)               | 38 (25.50) | 0.695 | 50 (33.56) | 0.543 | 38 (25.33) | 0.788 | 0.992 |
| WkStat                                              |                                             | In full- or part-time employment | 77 (51.33) | 79 (53.02) | 0.860 | 87 (58.39) | 0.267 | 91 (60.67) | 0.131 | 0.053 |
|                                                     |                                             | Full-time student or not working | 73 (48.67) | 70 (46.98) | 0.860 | 62 (41.61) | 0.267 | 59 (39.33) | 0.131 | 0.053 |
| ethngrp5                                            |                                             | Any other group           | 1 (0.67)                 | 2 (1.34)   | 0.548 | 0 (0.00) | 0.232 | 3 (2.00) | < 0.001 | < 0.001 |
|                                                     |                                             | Asian or Asian British    | 3 (2.00)                 | 3 (2.01)   | 0.548 | 0 (0.00) | 0.232 | 3 (2.00) | < 0.001 | < 0.001 |
|                                                     |                                             | Black or Black British    | 1 (0.67)                 | 2 (1.34)   | 0.548 | 1 (0.67) | 0.232 | 10 (6.67) | 0.003 | 0.005 |
|                                                     |                                             | Mixed ethnic group        | 0 (0.00)                 | 3 (2.01)   | 0.548 | 1 (0.67) | 0.232 | 4 (2.67) | 0.003 | 0.005 |
|                                                     |                                             | White                     | 145 (96.67)              | 139 (93.29)| 0.548 | 147 (98.66) | 0.267 | 119 (79.33) | 0.131 | 0.053 |
| eqv3 (£)                                            |                                             | Lowest tertile (≤ 17,500) | 40 (26.67)               | 38 (25.50) | 0.873 | 32 (21.48) | 0.023 | 37 (24.67) | 0.641 | 0.787 |
|                                                     |                                             | Middle tertile (> 17,500 and ≤ 32,216) | 53 (35.33) | 50 (33.56) | 0.873 | 37 (24.83) | 0.023 | 48 (32.00) | 0.641 | 0.787 |
Table 3 continued

| Characteristic                                      | Quartile of E-iAs<sub>ing,rice</sub>, μg/person/day | p value* | Quartile of E-iAs<sub>ing,rice</sub>, μg/person/day | p value* | Quartile of E-iAs<sub>ing,rice</sub>, μg/person/day | p value* | Quartile of E-iAs<sub>ing,rice</sub>, μg/person/day | p value* |
|----------------------------------------------------|-----------------------------------------------------|----------|-----------------------------------------------------|----------|-----------------------------------------------------|----------|-----------------------------------------------------|----------|
|                                                    | Quartile 1 (0.00–0.00) | Quartile 2 (0.00–0.565) | Quartile 3 (0.638–3.79) | Quartile 4 (3.79–41.8) | N = 150 | N = 149 | N = 149 | N = 150 |
| Highest tertile (> 32,500) ciga3                   | 57 (38.00) 61 (40.94) 80 (53.69) 65 (43.33) | 23 (15.33) 20 (13.42) 0.892 23 (15.44) 0.475 19 (12.67) 0.297 0.182 |
| Current cigarette smoker                           | 40 (26.67) 40 (26.85) 31 (20.81) 31 (20.67) |
| Ex-regular cigarette smoker                        | 87 (58.00) 89 (59.73) 95 (63.76) 100 (66.67) |
| Never regular cigarette smoker                     | 24 (16.00) 14 (9.40) 0.211 21 (14.09) 0.599 17 (11.33) 0.225 0.749 |
| Not at all in the last 12 months/ non-drinker      | 19 (12.67) 20 (13.42) 11 (7.38) 13 (8.67) |
| 1–2 per year                                       | 13 (8.67) 21 (14.09) 12 (8.05) 15 (10.00) |
| 1–2 per month                                      | 20 (13.33) 26 (17.45) 27 (18.12) 25 (16.67) |
| Once every couples of months                       | 43 (28.67) 33 (22.15) 42 (28.19) 51 (34.00) |
| 1–2 days per week                                  | 13 (8.67) 20 (13.42) 19 (12.75) 20 (13.33) |
| 3–4 days per week                                  | 18 (12.00) 15 (10.07) 17 (11.41) 9 (6.00) |
| 5–7 days per week                                  | 6 (4.00) 4 (2.68) 0.117 2 (1.34) 0.214 2 (1.33) 0.179 0.872 |
| Normal (healthy weight): 18.5 and below 25         | 42 (28.00) 59 (39.60) 52 (34.90) 56 (37.33) |
| Overweight: 25 and below 30                        | 60 (40.00) 54 (36.24) 63 (42.28) 50 (33.33) |
| Obese: over 30                                     | 42 (28.00) 32 (21.48) 32 (21.48) 42 (28.00) |
| whgval                                             | 50 (33.33) 61 (40.94) 0.354 59 (39.60) 0.123 65 (43.33) 0.204 0.321 |
| For male: less than 0.9; For female: less than 0.80| 42 (28.00) 40 (26.85) 49 (32.89) 36 (24.00) |
| For male: more than and including 0.90, up to and  | 58 (38.67) 48 (32.21) 41 (27.52) 49 (32.67) |
| including 1.00; For female: more than and including 0.80, up to and including 0.85 | 38 (25.33) 34 (22.82) 0.678 36 (24.16) 0.881 26 (17.33) 0.329 0.007 |
| For male: more than 1.00; for female: more than 0.85| 25 (16.67) 32 (21.48) 30 (20.13) 30 (20.00) |
| MN Participants with 0–3 nutrients greater than or equal to the mean intake level | 36 (24.00) 41 (27.52) 33 (22.15) 33 (22.00) |
| Participants with 4–7 nutrient 4 greater than or equal to the mean intake level | 29 (19.33) 23 (15.44) 32 (21.48) 40 (26.67) |
| Participants with 8–11 nutrients greater than or equal to the mean intake level | 22 (14.67) 19 (12.75) 18 (12.08) 21 (14.00) |
| Participants with 12–15 nutrients greater than or equal to the mean intake level | 28 (18.67) 18 (12.08) 0.221 21 (14.09) 0.432 12 (8.00) 0.012 0.013 |
| Participants with 16–18 nutrients greater than or equal to the mean intake level | 33 (22.00) 32 (21.48) 30 (20.13) 24 (16.00) |
| EnergyDkJ (KJ) Q1: 189.46–1294.86 Q2: 1295.07–1627.87 Q3: 1628.14–2037.01 | 33 (22.00) 46 (30.87) 44 (29.53) 42 (28.00) |
### Table 3 continued

| Characteristic | Quartile of E-iAs<sub>ing, rice</sub>, μg/person/day | Quartile 1 (0.00–0.00) | Quartile 2 (0.00–0.565) | Quartile 3 (0.638–3.79) | Quartile 4 (3.79–4.18) | p value* for trend |
|----------------|----------------------------------------------------|-------------------------|------------------------|------------------------|------------------------|--------------------|
| **Q4**: 2037.83–4771.28 | 56 (37.33) | 53 (35.57) | 54 (36.24) | 72 (48.00) | 0.044 | 0.045 |
| **ProteinD (g)** | | | | | | |
| Q1: 1.17–11.90 | 17 (11.33) | 20 (13.42) | 17 (11.41) | 10 (6.67) | 0.045 |
| Q2: 11.91–15.42 | 38 (25.33) | 27 (18.12) | 34 (22.82) | 23 (15.33) | |
| Q3: 15.43–19.31 | 37 (24.67) | 44 (29.53) | 41 (27.52) | 41 (27.33) | |
| Q4: 19.33–69.00 | 58 (38.67) | 58 (38.93) | 57 (38.26) | 76 (50.67) | |
| **FatgD (g)** | | | | | | |
| Q1: 0.12–10.64 | 22 (14.67) | 19 (12.75) | 29 (19.46) | 23 (15.33) | 0.127 | 0.592 |
| Q2: 10.65–14.21 | 36 (24.00) | 21 (14.09) | 36 (24.16) | 21 (14.00) | |
| Q3: 14.23–18.71 | 31 (20.67) | 50 (33.56) | 33 (22.15) | 42 (28.00) | |
| Q4: 18.74–59.89 | 61 (40.67) | 59 (39.60) | 51 (34.23) | 64 (42.67) | |
| **GlucosegD (g)** | | | | | | |
| Q1: 0.06–2.19 | 34 (22.67) | 34 (22.82) | 26 (17.45) | 22 (14.67) | 0.302 | 0.269 |
| Q2: 2.20–3.34 | 29 (19.33) | 29 (19.46) | 31 (20.81) | 33 (22.00) | |
| Q3: 3.35–4.88 | 35 (23.33) | 37 (24.83) | 45 (30.20) | 43 (28.67) | |
| Q4: 4.89–30.28 | 52 (34.67) | 49 (32.89) | 47 (31.54) | 52 (34.67) | |
| **SodiummgD (mg)** | | | | | | |
| Q1: 22.97–327.89 | 24 (16.00) | 22 (14.77) | 23 (15.44) | 22 (14.67) | 0.216 | 0.317 |
| Q2: 327.91–430.23 | 36 (24.00) | 27 (18.12) | 29 (19.46) | 27 (18.00) | |
| Q3: 430.26–561.96 | 44 (29.33) | 44 (29.53) | 44 (29.53) | 38 (25.33) | |
| Q4: 562.28–2306.84 | 46 (30.67) | 56 (37.58) | 53 (35.57) | 63 (42.00) | |
| **FolateugplussuppsD (μg)** | | | | | | |
| Q1: 5.69–35.36 | 17 (11.33) | 20 (13.42) | 22 (14.77) | 15 (10.00) | 0.049 | 0.313 |
| Q2: 36.38–47.85 | 32 (21.33) | 36 (24.16) | 23 (15.44) | 26 (17.33) | |
| Q3: 47.87–65.81 | 33 (22.00) | 34 (22.82) | 39 (26.17) | 55 (36.67) | |
| Q4: 65.86–1426.32 | 68 (45.33) | 59 (39.60) | 65 (43.62) | 54 (36.00) | |
| **Foreign or other qualifications; No qualifications; Still in FT education** | | | | | | |
| | 48 (32.00) | 47 (31.54) | 42 (28.19) | 36 (24.00) | 0.266 | 0.025 |
| | | | | | | |
| GCSE grades A–G or equivalent/commercial qualifications/apprenticeship | 27 (18.00) | 33 (22.15) | 28 (18.79) | 22 (14.67) | |
| Higher education, below degree level; GCE, A level or equivalent | 28 (18.67) | 30 (20.13) | 28 (18.79) | 24 (22.67) | |
| Degree or equivalent | 47 (31.33) | 39 (26.17) | 51 (34.23) | 58 (38.67) | |
| **Region** | | | | | | |
| England Central/Midlands | 25 (16.67) | 21 (14.09) | 16 (10.74) | 20 (13.33) | 0.442 | 0.155 |
| England North | 40 (26.67) | 36 (24.16) | 27 (18.12) | 36 (24.00) | |
| England South (including London) | 46 (30.67) | 56 (37.58) | 59 (39.60) | 59 (39.33) | |
| Northern Ireland and Scotland | 8 (5.33) | 11 (7.38) | 14 (9.40) | 11 (7.33) | |
| Wales | 31 (20.67) | 25 (16.78) | 33 (22.15) | 24 (16.00) | |
| **SalHowC** | | | | | | |
| Never | 76 (50.67) | 68 (45.64) | 86 (57.72) | 64 (42.67) | 0.381 | 0.088 |
| Sometimes and usually | 38 (25.33) | 32 (21.48) | 30 (20.13) | 44 (29.33) | |
though not the most standing out, also significantly contributed to more than 10%. Such phenomenon could be supported by previous researches, which indicated that age and BMI (Biino et al. 2013; Lelong et al. 2019) with about 11–17% of the hypertension risks due to overweight (Geleijnse et al. 2005). However, cigsta3, E-iAs ing,water, HessCon, NumChild were all significantly associated with the hypertension risks, but only explained a small percentage of those risks. In addition, due to its low level, E-iAs ing,rice alone did not play an important role in those blood pressure endpoints, contributing even less than 1%.

Aiming at quantifying 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. Based on the results, there were significantly interactive effects only between SodiummgD and E-iAs ing,rice on the variability of meanPulse (Table 5).

The relationships between E-iAs ing,rice and hypertension risks

After comparing models with and without considering the effects of E-iAs ing,rice (Table 6), we found that adding E-iAs ing,rice did not contribute to significantly better models for all the blood pressure endpoints, indicating that the association between E-iAs ing,rice and hypertension risks is weak.

To further analyse the dose–response associations between E-iAs ing,rice and hypertension risks, univariate and multivariate GLMs were used in the linear regression and logistic regression models. In general, E-iAs ing,rice was negatively but not significantly

### Table 3 continued

| Characteristic          | Quartile of E-iAs ing,rice, μg/person/day | p value* | Quartile of E-iAs ing,rice, μg/person/day | p value* | Quartile of E-iAs ing,rice, μg/person/day | p value* | Quartile of E-iAs ing,rice, μg/person/day | p value* |
|-------------------------|-------------------------------------------|----------|-------------------------------------------|----------|-------------------------------------------|----------|-------------------------------------------|----------|
|                         | Quartile 1 (0.00–0.00)                     |          | Quartile 2 (0.00–0.565)                    | p value  | Quartile 3 (0.638–3.79)                    | p value* | Quartile 4 (3.79–41.8)                    | p value* |
|                         | N = 150                                   |          | N = 149                                   |          | N = 149                                   |          | N = 150                                   |          |
| Always                  | 36 (24.00)                                |          | 49 (32.89)                                |          | 33 (22.15)                                |          | 42 (28.00)                                |          |

The results were reported as means (standard deviations (SD)) for continuous variables (E-iAs ing,water and E-iAs ing,grain) or as frequencies (percentages (%)) for categorical ones (surveyyr, quarter, sex, age, ethgrp5, qual7, cigsta3 and eqv3, dnoft, HessCon, NumChild, Diabetes.combined, WrkStat, MN, EnergyDkJ, ProteingD, FatgD, GlucosegD, SodiummgD, FolateugplussuppsD, bmival, region, SalHowC and whgval)

Differences across quartiles were computed by exposure categories via χ² tests or Wilcoxon rank-sum tests with Tukey post hoc test. p values for trend were obtained from analysis of variance (ANOVA) test with type II error where the characteristic factors were treated as continuous variables, indicating whether or not there is a statistically significant relationship between those characteristics of the population and iAs intake

E-iAs ing,rice: daily inorganic arsenic (iAs) intake from rice and rice products; E-iAs ing,water: daily iAs intake from drinking water; E-iAs ing,grain: daily iAs intake from grain and grain-based products; surveyyr: NDNS RP 7–8 Survey year; Sex: gender; EnergyDkJ: intake of total energy per day (KJ) for diet only; ProteingD: intake of protein per day (g) for diet only; FatgD: intake of fat per day (g) for diet only; GlucosegD: intake of glucose per day (g) for diet only; SodiummgD: intake of sodium per day (mg) for diet only; FolateugplussuppsD: intake of folate (μg) per day for both diets and supplements; MN: daily intake of several micro-nutrients (potassium (mg) including supplements, calcium (mg) including supplements, magnesium (mg) including supplements, iron (mg) including supplements, copper (mg) including supplements, zinc (mg) including supplements, retinol (mg) including supplements, vitamin A (retinol equivalents) (μg) including supplements, vitamin D (μg) including supplements, vitamin E (μg) including supplements, thiamin (mg) including supplements, riboflavin (mg) including supplements, niacin equivalent (mg) including supplements, vitamin B6 (mg) including supplements, vitamin B12 (μg) including supplements, vitamin C (mg) including supplements, iodine (μg) including supplements, selenium (μg) including supplements); region: country people live; NumChild: number of children aged between 0 and 15; age: age of respondent 16 + ; SalHowC: how often salt added during cooking; Quarter: fieldwork quarter; qual7: qualifications gained; WrkStat: Economic status (working condition); ethgrp5: ethnic group; eqv3: equivalized household income; HessCon: whether have any physical/mental health condition/illnesses for 12 months or more; Diabetes.combined: whether respondent is diabetic; cigsta3: cigarette smoking status; dnoft: frequency of alcohol consumption in past 12 months (including non-drinkers); bmival: BMI (kg/m²); whgval: waist-hip ratio groups

*Compared with Quartile 1 (referent group) (0.00–0.00 μg/person/day)
Table 4 Individual contributions of different factors to the variability of hypertension risks. Data from NDNS RP 7–8 (MRC Elsie Widdowson Laboratory and NatCen Social Research 2019) with population satisfying inclusion criteria as detailed in the text ($N = 598$)

| Factor               | DBP add 10 Contribution (%) | $p$ value* | SBP add 10 Contribution (%) | $p$ value* | AP Contribution (%) | $p$ value* | meanPulse Contribution (%) | $p$ value* | General hypertension Contribution (%) | $p$ value* |
|----------------------|-----------------------------|------------|-----------------------------|------------|---------------------|------------|-----------------------------|------------|----------------------------------------|------------|
| E-iASing,rice        | 0.70                        | 0.040      | 0.93                        | 0.018      | 0.92                | 0.019      | 0.03                        | 0.661      | 0.71                                   | 0.023      |
| E-iASing,water       | 0.95                        | 0.017      | 1.63                        | 0.002      | 1.41                | 0.004      | 0.48                        | 0.090      | 1.60                                   | 0.001      |
| E-iASing,grain       | 0.72                        | 0.037      | 0.07                        | 0.514      | 0.41                | 0.118      | 0.93                        | 0.018      | 0.35                                   | 0.110      |
| Sex                  | 0.27                        | 0.201      | 2.11                        | < 0.001    | 0.99                | 0.014      | 2.15                        | 0.003      | 0.13                                   | 0.339      |
| surveyyr             | 0.00                        | 0.970      | 0.32                        | 0.166      | 0.07                | 0.533      | 0.04                        | 0.641      | 0.03                                   | 0.618      |
| HessCon              | 2.58                        | < 0.001    | 4.73                        | < 0.001    | 3.96                | < 0.001    | 0.00                        | 0.995      | 5.19                                   | < 0.001    |
| Diabetes.combined    | 0.34                        | 0.153      | 1.12                        | 0.009      | 0.72                | 0.037      | 0.35                        | 0.150      | 3.08                                   | < 0.001    |
| NumChild             | 1.36                        | 0.017      | 7.83                        | < 0.001    | 4.06                | < 0.001    | 0.00                        | 0.372      | 4.92                                   | < 0.001    |
| Age                  | 13.28                       | < 0.001    | 24.87                       | < 0.001    | 17.66               | < 0.001    | 0.07                        | 0.937      | 20.25                                  | < 0.001    |
| Quarter              | 0.42                        | 0.470      | 1.33                        | 0.046      | 0.64                | 0.283      | 0.48                        | 0.414      | 0.62                                   | 0.213      |
| WrkStat              | 0.44                        | 0.106      | 3.39                        | < 0.001    | 0.21                | 0.262      | 0.44                        | 0.103      | 2.65                                   | < 0.001    |
| ethgrp5              | 0.44                        | 0.620      | 1.00                        | 0.200      | 0.58                | 0.482      | 1.13                        | 0.147      | 0.46                                   | 0.506      |
| eqv3                 | 0.08                        | 0.789      | 0.21                        | 0.528      | 0.01                | 0.972      | 0.42                        | 0.285      | 0.50                                   | 0.162      |
| cigsta3              | 1.88                        | 0.003      | 2.42                        | 0.001      | 2.40                | 0.002      | 1.00                        | 0.050      | 2.33                                   | < 0.001    |
| dnoft                | 2.13                        | 0.045      | 3.37                        | 0.002      | 2.92                | 0.007      | 1.63                        | 0.135      | 1.39                                   | 0.121      |
| bmival               | 10.32                       | < 0.001    | 9.19                        | < 0.001    | 11.32               | < 0.001    | 2.22                        | 0.004      | 5.85                                   | < 0.001    |
| whgval               | 12.02                       | < 0.001    | 12.11                       | < 0.001    | 13.90               | < 0.001    | 2.80                        | < 0.001    | 10.26                                  | < 0.001    |
| MN                   | 1.13                        | 0.147      | 1.98                        | 0.018      | 1.54                | 0.055      | 1.55                        | 0.053      | 0.27                                   | 0.738      |
| EnergyDkJ            | 0.17                        | 0.796      | 0.04                        | 0.974      | 0.08                | 0.927      | 0.61                        | 0.301      | 0.21                                   | 0.679      |
| ProteingD            | 0.29                        | 0.628      | 0.07                        | 0.931      | 0.13                | 0.851      | 1.17                        | 0.072      | 0.46                                   | 0.341      |
| FatgD                | 0.36                        | 0.543      | 0.03                        | 0.979      | 0.20                | 0.754      | 1.45                        | 0.033      | 0.35                                   | 0.471      |
| GlucosegD            | 0.11                        | 0.887      | 0.13                        | 0.861      | 0.09                | 0.910      | 1.74                        | 0.015      | 0.30                                   | 0.542      |
| SodiummgD            | 0.06                        | 0.954      | 0.34                        | 0.565      | 0.15                | 0.822      | 0.36                        | 0.544      | 0.24                                   | 0.623      |
| FolateuglussuppsD    | 0.66                        | 0.266      | 1.42                        | 0.036      | 1.09                | 0.088      | 2.02                        | 0.007      | 0.26                                   | 0.597      |
The individual contributions of E-iAS<sub>rice</sub> and all the potential confounders to the variability of hypertension risks were quantified through a generalized linear model (GLM) (contributions (%) = 100*(null deviance-residual deviance)/null deviance) (Bjorndal et al. 2013)

DBP add 10: Omron valid mean diastolic blood pressure (DBP) incremented by 10 mmHg is added if anti-hypertension medication is taken (mmHg); SBP add 10: Omron valid mean systolic blood pressure (SBP) incremented by 10 mmHg is added if anti-hypertension medication is taken (mmHg); AP: mean arterial pressure (mmHg); meanPulse: mean pulse pressure (mmHg); general hypertension: whether participants were diagnosed as general hypertension; E-iAS<sub>rice</sub>: daily inorganic arsenic (iAs) intake from rice and rice products; E-iAS<sub>grain</sub>: daily iAs intake from grain and grain-based products; E-iAS<sub>water</sub>: daily iAs intake from drinking water; surveyyr: NDNS RP 7–8 Survey year; Sex: gender; EnergyDkJ: intake of total energy per day (KJ) for diet only; ProteingD: intake of protein per day (g) for diet only; FatgD: intake of fat per day (g) for diet only; GlucosegD: intake of glucose per day (g) for diet only; SodiummgD: intake of sodium per day (mg) for diet only; FolateugplussuppsD: intake of folate (µg) per day for both diets and supplements; MN: daily intake of several micro-nutrients (potassium (mg) including supplements, calcium (mg) including supplements, magnesium (mg) including supplements, iron (mg) including supplements, copper (mg) including supplements, zinc (mg) including supplements, vitamin A (retinol equivalents) (µg) including supplements, vitamin D (µg) including supplements, vitamin E (mg) including supplements, thiamin (mg) including supplements, riboflavin (mg) including supplements, niacin (mg) including supplements, vitamin B6 (mg) including supplements, vitamin B12 (µg) including supplements, vitamin C (mg) including supplements, iodine (µg) including supplements, selenium (µg) including supplements); region: country people live; NumChild: number of children aged between 0 and 15; age: age of respondent 16 + ; SalHowC: how often salt added during cooking; Quarter: fieldwork quarter; qual7: qualifications gained; WrkStat: economic status (working condition); ethgrp5: ethnic group; eqv3: equivalized household income; HessCon: whether have any physical/mental health condition/illnesses for 12 months or more; Diabetes.combined: whether respondent is diabetic; cigsta3: cigarette smoking status; dnoft: frequency of alcohol consumption in past 12 months (including non-drinkers); bmival: BMI (kg/m<sup>2</sup>); whgval: waist-hip ratio groups

*The p value for the contribution of each single factor was obtained by analysis of variance (ANOVA) with type II error

|                | DBP add 10 | SBP add 10 | AP          | meanPulse | General hypertension |
|----------------|------------|------------|-------------|-----------|----------------------|
|                | Contribution (%) | p value* | Contribution (%) | p value* | Contribution (%) | p value* | Contribution (%) | p value* |
| qual7          | 0.86       | 0.161      | 0.56        | 0.340     | 0.13                | 0.849   | 0.85            | 0.165     | 0.92            | 0.083   |
| Region         | 1.41       | 0.075      | 1.27        | 0.107     | 1.26                | 0.108   | 1.02            | 0.189     | 0.56            | 0.400   |
| SalHowC        | 0.15       | 0.646      | 0.03        | 0.920     | 0.03                | 0.921   | 0.10            | 0.732     | 0.04            | 0.873   |
Table 5 Importance of the interactive effects between E-iAs_{ing,rice} and all the potential confounders on the variability of hypertension risks. Data from NDNS RP 7–8 (MRC Elsie Widdowson Laboratory and NatCen Social Research 2019) with population satisfying inclusion criteria as detailed in the text \((N = 598)\)

|          | DBP add 10 |          | SBP add 10 |          | AP |          | meanPulse |          | general hypertension |
|----------|------------|----------|------------|----------|-----|----------|------------|----------|----------------------|
|          | RERI\(a\) Contribution (\%) |          | RERI\(a\) Contribution (\%) |          | RERI\(a\) Contribution (\%) |          | RERI\(a\) Contribution (\%) |          |
| E-iAs_{ing,water} | 0.00 | 0.00 | 0.864 | 0.00 | 0.29 | 0.191 | 0.00 | 0.04 | 0.614 | 0.00 | 0.17 | 0.318 | \(-0.05\) | 0.44 | 0.075 |
| E-iAs_{ing,grain} | 0.00 | 0.41 | 0.118 | 0.00 | 0.27 | 0.202 | 0.00 | 0.08 | 0.123 | 0.00 | 0.09 | 0.458 | 0.03 | 0.30 | 0.141 |
| Sex | 0.00 | 0.07 | 0.513 | 0.00 | 3.45 | 0.611 | 0.00 | 0.17 | 0.318 | 0.00 | 0.25 | 0.201 | 0.06 | 0.22 | 0.208 |
| surveyyr | 0.00 | 0.26 | 0.631 | 0.00 | 0.05 | 0.581 | 0.00 | 0.00 | 0.969 | 0.00 | 0.05 | 0.597 | \(-1.20\) | 0.04 | 0.614 |
| HessCon | 0.01 | 0.10 | 0.439 | 0.00 | 0.08 | 0.502 | 0.01 | 0.10 | 0.433 | 0.00 | 0.05 | 0.576 | 0.02 | 0.03 | 0.671 |
| Diabetes.combined | 0.02 | 0.46 | 0.257 | 0.01 | 0.25 | 0.478 | 0.01 | 0.41 | 0.299 | 0.01 | 0.06 | 0.836 | 0.45 | 0.17 | 0.566 |
| NumChild | 0.01 | 0.17 | 0.800 | 0.00 | 0.19 | 0.778 | 0.03 | 0.08 | 0.926 | \(-0.02\) | 0.65 | 0.274 | 1.34 | 0.07 | 0.921 |
| Age | 0.01 | 0.01 | 0.102 | 0.01 | 0.46 | 0.438 | \(-0.04\) | 0.161 | \(-0.01\) | 0.62 | 0.300 | 0.05 | 0.88 | 0.166 |
| Quarter | 0.00 | 0.07 | 0.533 | 0.00 | 0.05 | 0.572 | \(-0.08\) | 0.744 | \(-0.01\) | 0.24 | 0.15 | 0.924 | \(-1.20\) | 1.32 | 0.049 |
| WrkStat | \(-0.08\) | 0.24 | 0.845 | 0.00 | 0.05 | 0.572 | 0.00 | 0.07 | 0.526 | 0.00 | 0.37 | 0.138 | 0.01 | 0.06 | 0.528 |
| ethgrp5 | 0.01 | 0.29 | 0.418 | 0.01 | 0.25 | 0.483 | 0.01 | 0.31 | 0.397 | 0.01 | 0.94 | 0.061 | 0.19 | 0.15 | 0.594 |
| eqv3 | \(-0.05\) | 0.50 | 0.228 | 0.00 | 0.05 | 0.483 | \(-0.08\) | 0.744 | \(-0.01\) | 0.24 | 0.15 | 0.924 | \(-1.20\) | 1.32 | 0.049 |
| cigsta3 | 0.05 | 1.07 | 0.390 | 0.00 | 0.05 | 0.483 | \(-0.06\) | 0.744 | 0.00 | 0.22 | 0.518 | \(-0.07\) | 0.46 | 0.194 |
| dnoft | 0.03 | 0.51 | 0.388 | 0.00 | 0.05 | 0.483 | \(-0.06\) | 0.744 | 0.00 | 0.22 | 0.518 | \(-0.07\) | 0.46 | 0.194 |
| bmival | 0.04 | 0.10 | 0.738 | 0.03 | 0.61 | 0.163 | \(-0.04\) | 0.431 | \(-0.01\) | 0.01 | 0.985 | \(-0.09\) | 0.02 | 0.950 |
| whgval | 0.02 | 0.48 | 0.586 | 0.02 | 0.38 | 0.294 | \(-0.02\) | 0.381 | \(-0.02\) | 1.86 | 0.025 | \(-0.09\) | 1.36 | 0.044 |
| MN | 0.00 | 0.01 | 0.185 | 0.00 | 0.02 | 0.301 | \(-0.01\) | 0.195 | \(-0.01\) | 1.57 | 0.025 | 0.14 | 0.51 | 0.298 |
| EnergyDkJ | 0.00 | 0.75 | 0.218 | 0.00 | 0.35 | 0.557 | 0.01 | 0.33 | 0.581 | 0.01 | 0.35 | 0.557 | 0.37 | 0.44 | 0.370 |
| ProteinD | 0.00 | 0.28 | 0.651 | 0.00 | 0.15 | 0.826 | \(-0.01\) | 0.760 | 0.01 | 1.59 | 0.023 | 0.00 | 0.21 | 0.684 |
| FatgD | 0.00 | 0.20 | 0.758 | 0.01 | 0.35 | 0.561 | 0.01 | 0.27 | 0.659 | 0.02 | 0.26 | 0.667 | 0.12 | 0.10 | 0.873 |
| GlucoseD | 0.00 | 0.25 | 0.682 | 0.00 | 0.15 | 0.826 | \(-0.01\) | 0.760 | 0.01 | 1.59 | 0.023 | 0.00 | 0.21 | 0.684 |
| SodiummgD | 0.00 | 0.05 | 0.958 | 0.00 | 0.20 | 0.826 | \(-0.02\) | 0.760 | 0.01 | 1.59 | 0.023 | 0.00 | 0.21 | 0.684 |
| FolateuqualsupsD | 0.00 | 0.22 | 0.732 | 0.01 | 0.51 | 0.387 | 0.00 | 0.30 | 0.625 | 0.00 | 0.20 | 0.762 | 0.18 | 0.45 | 0.358 |
| qul7 | 0.00 | 0.27 | 0.810 | 0.00 | 0.41 | 0.663 | 0.04 | 0.24 | 0.837 | \(-0.01\) | 6.81 | 0.874 | 0.14 | 0.97 | 0.138 |
The interactive contributions between E-iAs ing,rice and all the potential confounders to the variability of hypertension risks were quantified through a generalized linear model (GLM) (contributions (%) = 100*(null deviance-residual deviance)/null deviance) (Bjorndal et al. 2013).

DBP add 10: Omron valid mean diastolic blood pressure (DBP) incremented by 10 mmHg is added if anti-hypertension medication is taken (mmHg); SBP add 10: Omron valid mean systolic blood pressure (SBP) incremented by 10 mmHg is added if anti-hypertension medication is taken (mmHg); AP: mean arterial pressure (mmHg); meanPulse: mean pulse pressure (mmHg); general hypertension: whether participants were diagnosed as general hypertension; E-iAs ing,rice: daily inorganic arsenic (iAs) intake from rice and rice products; E-iAs ing,water: daily iAs intake from drinking water; E-iAs ing,grain: daily iAs intake from grain and grain-based products; surveyyr: NDNS RP 7–8 Survey year; Sex: gender; EnergyDkJ: intake of total energy per day (KJ) for diet only; ProteingD: intake of protein per day (g) for diet only; FatgD: intake of fat per day (g) for diet only; GlucosegD: intake of glucose per day (g) for diet only; SodiummgD: intake of sodium per day (mg) for diet only; FolateugplussuppsD: intake of folate (l g) per day for both diets and supplements; MN: daily intake of several micro-nutrients (potassium (mg) including supplements, calcium (mg) including supplements, magnesiu (mg) including supplements, iron (mg) including supplements, copper (mg) including supplements, zinc (mg) including supplements, retinol (mg) including supplements, vitamin A (retinol equivalents) (µg) including supplements, vitamin D (µg) including supplements, vitamin E (mg) including supplements, thiamin (mg) including supplements, riboflavin (mg) including supplements, niacin (equivale (mg) including supplements, vitamin B6 (mg) including supplements, vitamin B12 (µg) including supplements, vitamin C (mg) including supplements, iodine (µg) including supplements, selenium (µg) including supplements); region: country people live; NumChild: number of children aged between 0 and 15; age: age of respondent 16 + ; SalHowC: how often salt added during cooking; quarter: fieldwork quarter; qual7: qualifications gained; WrkStat: economic status (working condition); ethgrp5: ethnic group; eqv3: equivalized household income; HessCon: whether have any physical/mental health condition/illnesses for 12 months or more; Diabetes.combined: whether respondent is diabetic; cigsta3: cigarette smoking status; dnoft: frequency of alcohol consumption in past 12 months (including non-drinkers); bmival: BMI (kg/m²); whgval: waist-hip ratio groups

The $p$ values for interaction were obtained by adding a cross-product term between continuous E-iAs ing,rice and different confounders to the linear model via an analysis of variance (ANOVA) with type II error.

The importance of two-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: $\beta_1$ is the continuous coefficient of E-iAs ing,rice; $\beta_2$ is the coefficient of the potential confounder; and $\beta_3$ is the interactive term coefficient, with an estimation over zero indicating the presence of synergetic effects.

| SalHowC | RERI* Contribution (%) | 0.02 | 0.08 | 0.790 | 0.00 | 0.21 | 0.531 | 0.00 | 0.12 | 0.708 | 0.00 | 0.33 | 0.379 | 0.00 | 0.12 | 0.643 |
|---------|------------------------|------|------|-------|------|------|-------|------|------|-------|------|------|-------|------|------|-------|

Table 5 continued
DBP add 10: Omron valid mean diastolic blood pressure (DBP) incremented by 10 mmHg is added if anti-hypertension medication is taken (mmHg); SBP add 10: Omron valid mean systolic blood pressure (SBP) incremented by 10 mmHg is added if anti-hypertension medication is taken (mmHg); AP: mean arterial pressure (mmHg); meanPulse: mean pulse pressure (mmHg); general hypertension: whether participants were diagnosed as general hypertension; E-iAs ing,rice: daily inorganic arsenic (iAs) intake from rice and rice products; E-iAs ing,grain: daily iAs intake from grain and grain-based products; Sex: gender; FatgD: intake of fat per day (g) for diet only; FolateugplussuppsD: intake of folate (μg) per day for both diets and supplements; MN: daily intake of several micro-nutrients (Potassium (mg) including supplements, calcium (mg) including supplements, magnesium (mg) including supplements, iron (mg) including supplements, copper (mg) including supplements, zinc (mg) including supplements, retinol (mg) including supplements, vitamin A (retinol equivalents) (μg) including supplements, vitamin D (μg) including supplements, vitamin E (mg) including supplements, thiamin (mg) including supplements, riboflavin (mg) including supplements, niacin equivalent (mg) including supplements, vitamin B6 (mg) including supplements, vitamin B12 (μg) including supplements, vitamin C (mg) including supplements, iodine (μg) including supplements, selenium (μg) including supplements); region: country people live; NumChild: number of children aged between 0 and 15; age: age of respondent 16 + ; Quarter: fieldwork quarter; qual7: qualifications gained; HessCon: whether have any physical/mental health condition/illnesses for 12 months or more; Diabetes.combined: whether respondent is diabetic; cigsta3: cigarette smoking status; bmival: BMI (kg/m²); whgval: waist-hip ratio groups

For DBP add 10: model with DBP add 10 as dependent variable with E-iAs ing,rice was constructed by ‘stepwise’ function in R language based on AIC values which was adjusted by E-iAs ing,rice, age, bmival, whgval, qual7, E-iAs ing,grain, HessCon and region; Model with DBP add 10 as dependent variable without E-iAs ing,rice was constructed by ‘stepwise’ function in R language based on AIC values which was adjusted by age, bmival, whgval, qual7, E-iAs ing,grain, HessCon and region

For SBP add 10: model with SBP add 10 as dependent variable with E-iAs ing,rice was constructed by ‘stepwise’ function in R language based on AIC values which was adjusted by E-iAs ing,rice, age, bmival, whgval, qual7, E-iAs ing,grain, HessCon and region; Model with SBP add 10 as dependent variable without E-iAs ing,rice was constructed by ‘stepwise’ function in R language based on AIC values which was adjusted by age, bmival, whgval, qual7, E-iAs ing,grain, HessCon and region

For AP: model with AP as dependent variable with E-iAs ing,rice was constructed by ‘stepwise’ function in R language based on AIC values which was adjusted by E-iAs ing,rice, age, bmival, whgval, Sex, HessCon, NumChild, MN, whgval; Model with AP as dependent variable without E-iAs ing,rice was constructed by ‘stepwise’ function in R language based on AIC values which was adjusted by age, bmival, whgval, Sex, HessCon, NumChild, MN, whgval

For meanPulse: model with meanPulse as dependent variable with E-iAs ing,rice was constructed by ‘stepwise’ function in R language based on AIC values which was adjusted by E-iAs ing,rice, whgval, Sex, FolateugplussuppsD, bmival, MN, cigsta3, FatgD; Model with meanPulse as dependent variable without E-iAs ing,rice was constructed by ‘stepwise’ function in R language based on AIC values which was adjusted by whgval, Sex, FolateugplussuppsD, bmival, MN, cigsta3, FatgD

For the odds ratio of general hypertension: model with the odd ratio of general hypertension as dependent variable with E-iAs ing,rice was constructed by ‘stepwise’ function in R language based on AIC values which was adjusted by E-iAs ing,rice, age, bmival, Diabetes.combined, HessCon; Model with the odds ratio of general hypertension as dependent variable without E-iAs ing,rice was constructed by ‘stepwise’ function in R language based on AIC values which was adjusted by age, bmival, Diabetes.combined, HessCon

related to all the blood pressure endpoints (DBP add 10, SBP add 10, AP, meanPulse and general hypertension) and the associations were stronger in the population with the highest intake level (Tables 7, 8, 9, 10, 11). To be specific, for the continuous analysis of the best-fitted linear models using AIC as the primary selection criterion (Model 4 in Tables 7, 8, 9, 10, 11), every increase of 1 μg/person/day E-iAs ing,rice was associated with lower hypertension risks, ranging from a decrease of 0.2% DBP add 10 to 2% odds ratio
Table 7  Modelling analysis of the categorical and continuous association of DBP add 10 with E-iAs$_{\text{ng, rice}}$ (μg/person/day). Data from NDNS RP 7–8 (MRC Elsie Widdowson Laboratory and NatCen Social Research 2019) with population satisfying inclusion criteria as detailed in the text ($N = 598$)

| Model | Quartile of E-iAs$_{\text{ng, rice}}$ (μg/person/day) | p value* | Quartile 3 (0.638–3.79) | p value* | Quartile 4 (3.79–41.8) | p value* | DBP add 10 per 1 μg/person/day increase of E-iAs$_{\text{ng, rice}}$ | p value for trend | AIC Contributions (%) |
|-------|----------------------------------------------------|----------|-------------------------|----------|-------------------------|----------|--------------------------------------------------------------------------------|------------------|----------------------|
| Model 1 | Quartile 1 (0.00–0.00) | 1 (Referent) | 0.97 | 0.053 | 0.96 | 0.032 | 0.95 | 0.012 | 0.997 | 0.041 | 4694.9 | 0.7 |
|         | Quartile 2 (0.00–0.565) | 0.96 | 0.046 | 0.97 | 0.054 | 0.95 | 0.006 | 0.999 | 0.053 | 4620.3 | 29.5 |
| Model 2 | Quartile 3 (0.638–3.79) | 0.98 | 0.038 | 0.97 | 0.010 | 0.97 | 0.035 | 0.999 | 0.132 | 4570.8 | 23.8 |
|         | Quartile 4 (3.79–41.8) | 0.98 | 0.038 | 0.97 | 0.010 | 0.97 | 0.035 | 0.999 | 0.132 | 4570.8 | 23.8 |

Nonlinear model: DBP add10 ~ E-iAs$_{\text{ng, rice}}$ + E-iAs$_{\text{ng, grain}}$ + age + bmival + whgval + qual1 + E-iAs$_{\text{ng, rice}}$ + HessCon + region

The differences of DBP add 10 across four quartiles were obtained from Wald tests for E-iAs$_{\text{ng, rice}}$ coefficients, and the $p$ value for linear and nonlinear trends was obtained from an analysis of variance (ANOVA) analysis with type II error where E-iAs$_{\text{ng, rice}}$ is a continuous measure of intake

DBP add 10: Omron valid mean diastolic blood pressure (DBP) incremented by 10 mmHg is added if anti-hypertension medication is taken (mmHg); E-iAs$_{\text{ng, rice}}$: daily inorganic arsenic (iAs) intake from rice and rice products; E-iAs$_{\text{ng, water}}$: daily iAs intake from drinking water; E-iAs$_{\text{ng, grain}}$: daily iAs intake from grain and grain-based products; survey year: NDNS RP 7–8 Survey year; Sex: gender; EnergyDkJ: intake of total energy per day (KJ) for diet only; ProteinD: intake of protein per day (g) for diet only; FatgD: intake of fat per day (g) for diet only; GlucosegD: intake of glucose per day (g) for diet only; SodiummgD: intake of sodium per day (mg) for diet only; FolateugD: intake of folate (l/g) per day for both diets and supplements; MN: daily intake of several micro-nutrients (potassium (mg) including supplements, calcium (mg) including supplements, magnesium (mg) including supplements, iron (mg) including supplements, copper (mg) including supplements, zinc (mg) including supplements, retinol (mg) including supplements, vitamin A (retinol equivalents) (μg) including supplements, vitamin D (μg) including supplements, vitamin E (mg) including supplements, thiamin (mg) including supplements, riboflavin (mg) including supplements, niacin equivalent (mg) including supplements, vitamin B6 (mg) including supplements, vitamin B12 (μg) including supplements, vitamin C (mg) including supplements, iodine (μg) including supplements, sodium (mg) including supplements, selenium (μg) including supplements); region: country people live; NumChild: number of children aged between 0 and 15; age: age of respondent; SalHowC: how often salt added during cooking; Quarter: fieldwork quarter; qual7: qualifications gained; WrkStat: economic status (working condition); ethgrp5: ethnic group; eqv3: Equivalized household income; HessCon: whether have any physical/mental health condition/illnesses for 12 months or more; Diabetes.combined: whether respondent is diabetic; cigsta3: cigarette smoking status; dnoft: frequency of alcohol consumption in past 12 months (including non-drinkers); bmival: BMI (kg/m²); whgval: waist-hip ratio groups

Model 1: crude with DBP add 10 only (univariate model)

Model 2: full model, adjusted by E-iAs$_{\text{ng, water}}$, E-iAs$_{\text{ng, grain}}$, age, bmival, cigsta3, region, Diabetes.combined, dnoft, eqv3, ethgrp5, SalHowC, HessCon, MN, NumChild, qual7, Quarter, Sex, survey yr, whgval, WrkStat, EnergyDkJ, ProteingD, FatgD, GlucosegD, SodiummgD, FolateugD

Model 3: adjusted by variables with $p$ value lower than 0.2 in the univariate analysis: E-iAs$_{\text{ng, water}}$, E-iAs$_{\text{ng, grain}}$, age, bmival, cigsta3, region, Diabetes.combined, dnoft, HessCon, MN, NumChild, qual7, Sex, whgval, WrkStat

Model 4: constructed by 'stepwise' function in R language based on AIC values which were adjusted by age, bmival, whgval, qual7, E-iAs$_{\text{ng, grain}}$, HessCon and region

*Compared with Quartile 1 (referent group) (0.00–0.00 μg/person/day)
Table 8: Modelling analysis of the categorical and continuous association of SBP add 10 with E-iAs_{ng,rice} (μg/person/day). Data from NDNS RP 7–8 (MRC Elsie Widdowson Laboratory and NatCen Social Research 2019) with population satisfying inclusion criteria as detailed in the text (N = 598)

| Model | Quartile of E-iAs_{ng,rice} (μg/person/day) | SBP add 10 per 1 μg/person/day increase of E-iAs_{ng,rice} | p value for trend | AIC Contributions (%) |
|-------|---------------------------------------------|-----------------------------------------------------------|------------------|-----------------------|
|       | Quartile 1 (0.00–0.00) | Quartile 2 (0.00–0.565) | Quartile 3 (0.638–3.79) | Quartile 4 (3.79–41.8) | p value* |
| Model 1 | 1 | 0.95 | 0.004 | 0.96 | 0.008 | 0.94 | < 0.001 | 0.994 | (0.990, 0.999) | 0.019 | 5209.6 | 0.9 |
| (Referent) | (0.92, 0.98) | (0.93, 1.00) | (0.91, 0.97) | (0.92, 0.98) | (0.93, 0.99) |
| Model 2 | 1 | 0.96 | 0.032 | 0.98 | 0.125 | 0.95 | 0.003 | 0.964 | (0.91, 1.00) | 0.964 | (0.90, 1.00) | 0.095 | 5055.3 | 38.4 |
| (Referent) | (0.93, 1.00) | (0.95, 1.01) | (0.92, 0.98) | (0.94, 1.00) | (0.95, 1.00) |
| Model 3 | 1 | 0.96 | 0.013 | 0.98 | 0.115 | 0.95 | 0.002 | 0.964 | (0.91, 1.00) | 0.964 | (0.90, 1.00) | 0.101 | 5025.3 | 36.8 |
| (Referent) | (0.92, 0.99) | (0.95, 1.01) | (0.92, 0.98) | (0.94, 1.00) | (0.95, 1.00) |
| Model 4 | 1 | 0.97 | 0.029 | 0.98 | 0.171 | 0.96 | 0.006 | 0.964 | (0.91, 1.00) | 0.964 | (0.90, 1.00) | 0.080 | 4999.2 | 34.6 |
| (Referent) | (0.94, 1.00) | (0.95, 1.01) | (0.92, 0.98) | (0.94, 1.00) | (0.95, 1.00) |
| Nonlinear model | SBP add10 ~ E-iAs_{ng,rice} + E-iAs_{ng,rice}^2 + age + bmi val + Sex + Quarter + NumChild + HessCon + MN + whgval | 0.426 | 5000.5 | 34.7 |

The differences of SBP add 10 across four quartiles were obtained from Wald tests for E-iAs_{ng,rice} coefficients, and the p value for linear and nonlinear trends was obtained from an analysis of variance (ANOVA) with type II error where E-iAs_{ng,rice} is a continuous measure of intake.

SBP add 10: Omron valid mean systolic blood pressure (SBP) incremented by 10 mmHg is added if anti-hypertension medication is taken (mmHg); E-iAs_{ng,rice}: daily inorganic arsenic (iAs) intake from rice and rice products; E-iAs_{ng,water}: daily iAs intake from drinking water; E-iAs_{ng,grain}: daily iAs intake from grain and grain-based products; surveyyr: NDNS RP 7–8 Survey year; Sex: gender; EnergyDkJ: intake of total energy per day (KJ) for diet only; ProteingD: intake of protein per day (g) for diet only; FatgD: intake of fat per day (g) for diet only; GlucosegD: intake of glucose per day (g) for diet only; SodiummgD: intake of sodium per day (mg) for diet only; FolateugplussuppD: intake of folate (μg) per day for both diets and supplements; MN: daily intake of several micro-nutrients (Potassium (mg) including supplements, calcium (mg) including supplements, magnesium (mg) including supplements, iron (mg) including supplements, copper (mg) including supplements, zinc (mg) including supplements, retinol (μg) including supplements, vitamin A (retinol equivalents) (μg) including supplements, vitamin D (μg) including supplements, vitamin E (μg) including supplements, thiamin (μg) including supplements, riboflavin (μg) including supplements, niacin equivalent (mg) including supplements, vitamin B6 (mg) including supplements, vitamin B12 (μg) including supplements, vitamin C (mg) including supplements, iodine (μg) including supplements, selenium (μg) including supplements); region: country people live; NumChild: number of children aged between 0 and 15; age: age of respondent 16 to 65; SalHowC: how often salt added during cooking; Quarter: fieldwork quarter; qual7: qualifications gained; WrkStat: economic status (working condition); ethgrp5: ethnic group; eqv3: Equalized household income; HessCon: whether have any physical/mental health condition/illnesses for 12 months or more; Diabetes.combined: whether respondent is diabetic; cigsta3: cigarette smoking status; dnoft: frequency of alcohol consumption in past 12 months (including non-drinkers); bmi val: BMI (kg/m^2); whgval: waist-hip ratio groups

Model 1: crude with SBP add 10 only (univariate model)

Model 2: full model, adjusted by E-iAs_{ng,water}, E-iAs_{ng,grain}, age, bmi val, cigsta3, region, Diabetes.combined, dnoft, eqv3, ethgrp5, SalHowC, HessCon, MN, NumChild, qual7, Quarter, Sex, surveyyr, whgval, WrkStat, EnergyDkJ, ProteinD, FatgD, GlucosegD, SodiummgD, FolateugplussuppD

Model 3: adjusted by variables with p value lower than 0.2 in the univariate analysis: E-iAs_{ng,water}, age, bmi val, cigsta3, region, Diabetes.combined, dnoft, ethgrp5, HessCon, MN, NumChild, Quarter, Sex, surveyyr, whgval, WrkStat, FolateugplussuppD

Model 4: constructed by ‘stepwise’ function in R language based on AIC values which were adjusted by age, bmi val, Sex, Quarter, HessCon, NumChild, MN, whgval

*Compared with Quartile 1 (referent group) (0.00–0.00 μg/person/day)
Table 9  Modelling analysis of the categorical and continuous association of AP with \( E-i\text{As}_{\text{ng,rice}} \) (\( \mu \text{g}/\text{person/day} \)). Data from NDNS RP 7–8 (MRC Elsie Widdowson Laboratory and NatCen Social Research 2019) with population satisfying inclusion criteria as detailed in the text (\( N = 598 \))

| Model   | Quartile of \( E-i\text{As}_{\text{ng,rice}} \) (\( \mu \text{g}/\text{person/day} \)) | AP per 1 \( \mu \text{g}/\text{person/day} \) increase of \( E-i\text{As}_{\text{ng,rice}} \) | \( p \) value for trend | AIC | Contributions (%) |
|---------|-------------------------------------------------|-----------------------------------|------------------|-----|------------------|
|         | Quartile 1 (0.00–0.00)                          | Quartile 2 (0.00–0.565)           | Quartile 3 (0.638–3.79) | Quartile 4 (3.79–41.8) |                                 |
| Model 1 | 0.96                                           | 0.96                              | 0.95             | 0.001 | 0.99,             | 0.019 | 4805.5 | 0.9 |
|         | (Referent) (0.93, 0.99)                        | (Referent) (0.96, 0.99)           | (Referent) (0.92, 0.98) | (Referent) (0.99, 1.00) |                                 |
| Model 2 | 0.96                                           | 0.97                              | 0.95             | 0.003 | 0.99,             | 0.067 | 4704.2 | 32.7 |
|         | (Referent) (0.96, 1.00)                        | (Referent) (0.94, 1.00)           | (Referent) (0.92, 0.98) | (Referent) (0.99, 1.00) |                                 |
| Model 3 | 0.98                                           | 0.98                              | 0.96             | 0.005 | 0.99,             | 0.069 | 4665.0 | 30.8 |
|         | (Referent) (0.95, 1.01)                        | (Referent) (0.95, 0.99)           | (Referent) (0.93, 0.99) | (Referent) (0.99, 1.00) |                                 |
| Model 4 | 0.97                                           | 0.98                              | 0.96             | 0.006 | 0.99,             | 0.060 | 4648.4 | 27.5 |
|         | (Referent) (0.95, 1.00)                        | (Referent) (0.95, 0.99)           | (Referent) (0.93, 0.99) | (Referent) (0.99, 1.00) |                                 |
| Nonlinear model | \( \text{AP} \sim E-i\text{As}_{\text{ng,rice}} + E-i\text{As}_{\text{ng,grain}} + \text{age} + \text{bmival} + \text{whgval} + \text{Sex} + \text{HessCon} + E-i\text{As}_{\text{ng,grain}} + \text{MN} \) | 0.248 | 4649.1 | 27.7 |

The differences of AP across four quartiles were obtained from Wald tests for \( E-i\text{As}_{\text{ng,rice}} \) coefficients, and the \( p \) value for linear and nonlinear trends was obtained from an analysis of variance (ANOVA) with type II error where \( E-i\text{As}_{\text{ng,rice}} \) is a continuous measure of intake.

AP: mean arterial pressure (mmHg); \( E-i\text{As}_{\text{ng,rice}} \): daily inorganic arsenic (iAs) intake from rice and rice products; \( E-i\text{As}_{\text{ng,grain}} \): daily iAs intake from grain and grain-based products; surveyyr: NDNS RP 7–8 Survey year; Sex: gender; EnergyDkJ: intake of total energy per day (KJ) for diet only; ProteinD: intake of protein per day (g) for diet only; FatgD: intake of fat per day (g) for diet only; GlucosegD: intake of glucose per day (g) for diet only; SodiummgD: intake of sodium per day (mg) for diet only; FolateugplussuppsD: intake of folate (µg) per day for both diets and supplements; MN: daily intake of several micro-nutrients (Potassium (mg) including supplements, calcium (mg) including supplements, magnesium (mg) including supplements, iron (mg) including supplements, copper (mg) including supplements, zinc (mg) including supplements, retinol (µg) including supplements, vitamin A (retinol equivalents) (µg) including supplements, vitamin D (µg) including supplements, vitamin E (mg) including supplements, thiamin (mg) including supplements, riboflavin (mg) including supplements, niacin equivalent (mg) including supplements, vitamin B6 (mg) including supplements, vitamin B12 (µg) including supplements, vitamin C (mg) including supplements, selenium (µg) including supplements, vitamin B12 (mg) including supplements, vitamin D (mg) including supplements, iodine (µg) including supplements, vitamin B12 (µg) including supplements, vitamin D (mg) including supplements, iodine (µg) including supplements, selenium (µg) including supplements, vitamin B12 (mg) including supplements, vitamin D (mg) including supplements, iodine (µg) including supplements, selenium (µg) including supplements); region: country people live; NumChild: number of children aged between 0 and 15; age: age of respondent ≥16; SalHowC: how often salt added during cooking; Quarter: fieldwork quarter; qual7: qualifications gained; WrkStat: economic status (working condition); ethgrp5: ethnic group; eqv3: equivalized household income; HessCon: whether have any physical/mental health condition/illnesses for 12 months or more; Diabetes.combined: whether respondent is diabetic; cigsta3: cigarette smoking status; dnoff: frequency of alcohol consumption in past 12 months (including non-drinkers); bmival: BMI (kg/m²); whgval: waist-hip ratio groups.

Model 1: crude with AP only (univariate model)

Model 2: full model, adjusted by \( E-i\text{As}_{\text{ng,water}} \), \( E-i\text{As}_{\text{ng,grain}} \), age, bmival, cigsta3, region, Diabetes.combined, dnoff, eqv3, ethgrp5, SalHowC, HessCon, MN, NumChild, qual7, Quarter, Sex, surveyyr, whgval, WrkStat, EnergyDkJ, ProteinD, FatgD, GlucoseD, SodiumD, FolateD, HessCon, MN, NumChild, qual7, Sex, whgval, FolateD

Model 3: adjusted by variables with \( p \) value lower than 0.2 in the univariate analysis: \( E-i\text{As}_{\text{ng,water}} \), \( E-i\text{As}_{\text{ng,grain}} \), age, bmival, cigsta3, region, Diabetes.combined, dnoff, HessCon, MN, NumChild, qual7, Sex, whgval

Model 4: constructed by ‘stepwise’ function in R language based on AIC values which were adjusted by age, bmival, whgval, Sex, HessCon, \( E-i\text{As}_{\text{ng,grain}} \), MN

*Compared with Quartile 1 (referent group) (0.00-0.00 µg/person/day)
Table 10  Modelling analysis of the categorical and continuous association of meanPulse with E-iAs<sub>ing,rice</sub> (µg/person/day). Data from NDNS RP 7–8 (MRC Elsie Widdowson Laboratory and NatCen Social Research 2019) with population satisfying inclusion criteria as detailed in the text (N = 598)

| Model  | Quartile of E-iAs<sub>ing,rice</sub> (µg/person/day) | meanPulse per 1 µg/person/day increase of E-iAs<sub>ing,rice</sub> | p value for trend | AIC | Contributions (%) |
|-------|---------------------------------|------------------|------------------|-----|------------------|
|       | Quartile 1 (0.00–0.00) | Quartile 2 (0.00–0.565) | Quartile 3 (0.638–3.79) | Quartile 4 (3.79–41.8) |
| Model 1 | 1 | 1.00 | 0.816 | 0.837 | 0.98 | 0.187 | 0.99<sup>b</sup> | 0.661 | 4525.9 | 0.0<sup>a</sup> |
|        | (Referent) | (0.96, 1.03) | (0.96, 1.03) | (0.94, 1.01) | (0.99<sup>b</sup>, 1.00) |
| Model 2 | 1 | 0.98 | 0.382 | 0.98 | 0.401 | 0.97 | 0.128 | 1.00 | 0.970 | 4533.8 | 18.5 |
|        | (Referent) | (0.94, 1.02) | (0.95, 1.02) | (0.93, 1.01) | (0.99<sup>b</sup>, 1.00) |
| Model 3 | 1 | 1.00 | 0.927 | 1.00 | 0.995 | 0.99 | 0.416 | 1.00 | 0.773 | 4517.1 | 15.3 |
|        | (Referent) | (0.97, 1.03) | (0.97, 1.03) | (0.95, 1.02) | (0.99<sup>b</sup>, 1.00) |
| Model 4 | 1 | 0.99 | 0.677 | 1.00 | 0.764 | 0.98 | 0.174 | 1.00 | 0.913 | 4493.6 | 10.8 |
|        | (Referent) | (0.96, 1.03) | (0.96, 1.03) | (0.94, 1.01) | (0.99<sup>b</sup>, 1.00) |
| Nonlinear model | meanPulse ~ E-iAs<sub>ing,rice</sub> + E-iAs<sub>ing,rice</sub><sup>2</sup> + whgval + Sex + FolateugplussuppsD + bmiwal + MN + cigsta3 + FatgD | 0.207 | 4494.0 | 11.1 |

The differences of meanPulse across four quartiles were obtained from Wald tests for E-iAs<sub>ing,rice</sub> coefficients, and the p value for linear and nonlinear trends was obtained from an analysis of variance (ANOVA) with type II error where E-iAs<sub>ing,rice</sub> is a continuous measure of intake.

meanPulse: mean pulse pressure (mmHg); E-iAs<sub>ing,rice</sub>: daily inorganic arsenic (iAs) intake from rice and rice products; E-iAs<sub>ing,water</sub>: daily iAs intake from drinking water; E-iAs<sub>ing,grain</sub>: daily iAs intake from grain and grain-based products; surveyyr: NDNS RP 7–8 Survey year; Sex: gender; EnergyDkJ: intake of total energy per day (KJ) for diet only; ProteingD: intake of protein per day (g) for diet only; FatgD: intake of fat per day (g) for diet only; GlucosegD: intake of glucose per day (g) for diet only; SodiummgD: intake of sodium per day (mg) for diet only; FolateugplussuppsD: intake of folate (µg) per day for both diets and supplements; MN: daily intake of several micro-nutrients (Potassium (mg) including supplements, calcium (mg) including supplements, magnesium (mg) including supplements, iron (mg) including supplements, copper (mg) including supplements, zinc (mg) including supplements, retinol (µg) including supplements, vitamin A (retinol equivalents) (µg) including supplements, vitamin D (µg) including supplements, vitamin E (µg) including supplements, thiamin (mg) including supplements, riboflavin (mg) including supplements, niacin equivalent (mg) including supplements, vitamin B6 (mg) including supplements, vitamin B12 (µg) including supplements, vitamin C (mg) including supplements, iodine (µg) including supplements, selenium (µg) including supplements); region: country people live; NumChild: number of children aged between 0 and 15; age: age of respondent 16 + ; SalHowC: how often salt added during cooking; Quarter: fieldwork quarter; qual7: qualifications gained: WrkStat: economic status (working condition); ethgrp5: ethnic group; eqv3: equivalized household income; HessCon: whether have any physical/mental health condition/illnesses for 12 months or more; Diabetes.combined: whether respondent is diabetic; cigsta3: cigarette Smoking Status; dnoft: frequency of alcohol consumption in past 12 months (including non-drinkers); bmiwal: BMI (kg/m²); whgval: waist-hip ratio groups

Model 1: crude with meanPulse only (univariate model)

Model 2: full model, adjusted by E-iAs<sub>ing,water</sub>, E-iAs<sub>ing,grain</sub>, age, bmiwal, cigsta3, region, Diabetes.combined, dnoft, eqv3, ethgrp5, SalHowC, HessCon, MN, NumChild, qual7, Quarter, Sex, surveyyr, whgval, WrkStat, EnergyDkJ, ProteingD, FatgD, GlucosegD, SodiummgD, FolateugplussuppsD

Model 3: adjusted by variables with p value lower than 0.2 in the univariate analysis E-iAs<sub>ing,water</sub>, E-iAs<sub>ing,grain</sub>, bmiwal, cigsta3, region, Diabetes.combined, dnoft, ethgrp5, MN, qual7, Sex, whgval, WrkStat, ProteingD, FatgD, GlucosegD, SodiummgD, FolateugplussuppsD

Model 4: constructed by ‘stepwise’ function in R language based on AIC values which were adjusted by whgval, Sex, FolateugplussuppsD, bmiwal, MN, cigsta3, FatgD

*Compared with Quartile 1 (referent group) (0.00–0.00 µg/person/day)
Table 11 Modelling analysis of the categorical and continuous association of the odds ratio of general hypertension with E-iAs in rice (μg/person/day). Data from NDNS RP 7–8 (MRC Elsie Widdowson Laboratory and NatCen Social Research 2019) with exclusion as detailed in the text (N = 598)

| Model | Quartile of E-iAs in rice (μg/person/day) | Odds ratio of general hypertension per 1 μg/person/day increase of E-iAs in rice | p value for trend | AIC Contributions (%) |
|-------|------------------------------------------|--------------------------------------------------------------------------------|-------------------|-----------------------|
|       | Quartile 1 (0.00–0.00) | Quartile 2 (0.00–0.565) | Quartile 3 (0.638–3.79) | Quartile 4 (3.79–41.8) |                      |
| Model 1 | 1 | 0.61 | 0.043 | 0.57 | 0.023 | 0.44 | 0.001 | 0.95 | 0.023 | 727.0 | 0.7 |
|        | (Referent) | (0.37, 0.98) | (0.35, 0.92) | (0.26, 0.72) | (0.91, 0.99) |
| Model 2 | 1 | 0.50 | 0.088 | 0.55 | 0.090 | 0.30 | 0.002 | 0.94 | 0.047 | 631.8 | 31.6 |
|        | (Referent) | (0.22, 1.11) | (0.27, 1.09) | (0.14, 0.62) | (0.87, 1.00) |
| Model 3 | 1 | 0.69 | 0.220 | 0.69 | 0.227 | 0.50 | 0.030 | 0.97 | 0.364 | 586.7 | 27.7 |
|        | (Referent) | (0.38, 1.26) | (0.38, 1.26) | (0.27, 0.93) | (0.92, 1.03) |
| Model 4 | 1 | 0.76 | 0.270 | 0.75 | 0.330 | 0.54 | 0.043 | 0.98 | 0.413 | 565.5 | 25.1 |
| Nonlinear model | | | | | | | | | | | |

The differences of odds ratio of general hypertension across four quartiles were obtained from Wald tests for E-iAs in rice coefficients, and the p value for linear and nonlinear trends was obtained from an analysis of variance (ANOVA) with Type II error where E-iAs in rice is a continuous measure of intake.

general hypertension: whether participants were diagnosed as general hypertension; E-iAs in rice: daily inorganic arsenic (iAs) intake from rice and rice products; E-iAs in water: daily iAs intake from drinking water; E-iAs in grain: daily iAs intake from grain and grain-based products; surveyyr: NDNS RP 7–8 Survey year; Sex: gender; EnergyDkJ: intake of total energy per day (KJ) for diet only; ProteinD: intake of protein per day (g) for diet only; FatD: intake of fat per day (g) for diet only; GlucoseD: intake of glucose per day (g) for diet only; SodiumD: intake of sodium per day (mg) for diet only; FolateD: intake of folate (μg) per day for both diets and supplements; MN: daily intake of several micro-nutrients (Potassium (mg) including supplements, calcium (mg) including supplements, magnesium (mg) including supplements, iron (mg) including supplements, copper (mg) including supplements, zinc (mg) including supplements, retinol (μg) including supplements, vitamin A (retinol equivalents) (μg) including supplements, vitamin D (μg) including supplements, vitamin E (μg) including supplements, thiamin (mg) including supplements, riboflavin (mg) including supplements, niacin equivalent (mg) including supplements, vitamin B6 (mg) including supplements, vitamin B12 (μg) including supplements, vitamin C (mg) including supplements, iodine (μg) including supplements, selenium (μg) including supplements); region: country people live; NumChild: number of children aged between 0 and 15; age: age of respondent 16 + ; SalHowC: how often salt added during cooking; Quarter: fieldwork quarter; qual7: qualifications gained; WrkStat: economic status (working condition); ethgrp5: ethnic group; eqv3: equivalized household income; HessCon: whether have any physical/mental health condition/illnesses for 12 months or more; Diabetes.combined: whether respondent is diabetic; cigsta3: cigarette smoking status; dnoft: frequency of alcohol consumption in past 12 months (including non-drinkers); bmival: BMI (kg/m²); whgval: waist-hip ratio groups.

Model 1: crude with the odds ratio of general hypertension only (univariate model)

Model 2: full model, adjusted by E-iAs in water, E-iAs in grain, age, bmival, cigsta3, region, Diabetes.combined, dnoft, eqv3, ethgrp5, SalHowC, HessCon, MN, NumChild, qual7, Quarter, Sex, surveyyr, whgval, WrkStat, EnergyDkJ, ProteinD, FatD, GlucoseD, SodiumD, FolateD, SuppleD

Model 3: adjusted by variables with p value lower than 0.2 in the univariate analysis E-iAs in water, E-iAs in grain, age, bmival, cigsta3, Diabetes.combined, dnoft, eqv3, HessCon, NumChild, qual7, whgval, WrkStat

Model 4: constructed by 'stepwise' function in R language based on AIC values which were adjusted by age, bmival, Diabetes.combined, HessCon

*Compared with Quartile 1 (referent group) (0.00–0.00 μg/person/day)
of general hypertension. For the categorical results of the best-fitted linear model, the higher three quartiles of iAs intake were associated with decreased odds ratios of general hypertension [1.00 (referent), 0.76 (95% CI 0.41, 1.28), 0.75 (95% CI 0.42, 1.34), and 0.54 (95% CI 0.30, 0.98)] in the overall population with similar pattern being found for other blood pressure endpoints as well (Model 4 in Tables 7, 8, 9, 10, 11). Moreover, taking anti-hypertension medications which likely induce artificially lower blood pressure cannot confound our results as excluding participants with such medications yielded results similar to those described above (Table S3). In addition, we examined the assumption of the nonlinear relationships by including higher order polynomial terms of iAs intake variable in the models, but found no significant departure from linearity based on the significance for the higher order terms (nonlinear models in Tables 7, 8, 9, 10, 11).

When E-iAs rgb,rice have been divided into 15 groups, more complex dose–response relationships between E-iAs rgb,rice and hypertension risks became evident (Table S4). Though not significant, higher hypertension risks could be found for some subgroups which could be supported by the role of As in inducing oxidative stress and altering the release of vasoactive mediators in blood vessel (Cifuentes et al. 2009). However, as no consistent dose–response patterns presented (Table S4), such higher risks may be due, at least in part, to just randomness or small sample sizes, indicating that the overall associations between E-iAs rgb,rice and hypertension were not strong at all.

Modification effects of several well-established risk factors for the relationships between E-iAs rgb,rice and hypertension risks.

The associations between E-iAs rgb,rice and hypertension risks estimated in the subgroup analysis were somewhat consistent across most of the subgroups by participants characteristics. However, higher DBP add 10 could be observed among participants with alcohol consumption once or twice a week. Similarly, there was higher risk among mixed ethnic group on the changes of SBP add 10 (Fig. S1–S4). In dose–response analysis, the adverse associations of iAs on the odds ratios of general hypertension were more apparent among participants who are male, aged between 35 and 49, overweight, or alcohol consumer when compared with their accordingly counterparts. To be noted, Asian or Asian British, Black or Black British and mixed ethnic group were found to be more vulnerable to the effects of iAs on the risks of general hypertension when compared with their White counterparts (Fig. S5).

Discussion

This cross-sectional study conducted across four countries of the UK indicated negative but not significant associations between E-iAs rgb,rice and hypertension risks (DBP add 10, SBP add 10, AP, meanPulse and general hypertension), with relatively higher risks being found among subgroups who are male, aged between 35 and 49, overweight, alcohol consumers or belonging to Asian or Asian British, Black or Black British and mixed ethnic group when compared with their counterparts (Table 6, 7, 8, 9, 10, 11 and Table S4 and Fig. S1–S5). Though exploratory, our study was the first bridging the gap, at least partly, between individual level iAs intake from rice and rice products and hypertension risks, being important especially in areas where there is little exposure from drinking water but an increasing rice intake. Given the model uncertainties, including the fact that iAs in water or foods were not measured directly, low sample size in some stratified groups, the intrinsic shortages of cross-sectional studies and those limiting extrapolation to other potential confounders, the present study was still inconclusive and further model exploration as well as larger scale cohort studies are required (cf. Moon et al. 2013).

Combining the contributions of different factors to the variability of blood pressure endpoints estimated in the present study (Table 4) with the fact that a number of factors are widely known to be important indicators of hypertension risks, such as age, obesity, gender, smoking status, alcohol consumption and sodium intake (Biino et al. 2013; He et al. 2018; NHLBI Obesity Education Initiative Expert Panel on the Identification Evaluation and Treatment of Obesity in Adults (US) 1998), it should be acknowledged that E-iAs rgb,rice is likely to be of much lesser importance than other factors. Therefore, this study, not surprisingly, found only weak and not significant associations between E-iAs rgb,rice and hypertension risks (DBP add 10, SBP add 10, AP, meanPulse and general hypertension) (Table 6, 7, 8, 9, 10, 11 and Table S4).
The present study is somewhat consistent with previous research on the association of low-level As exposure from drinking water on hypertension risks which are largely inconclusive (Navas-Acien et al. 2006, 2019; Tsuji et al. 2014). For example, a cross-sectional study from Bangladesh, though revealing an adverse effect of low to moderate level As exposure (< 8 to 864 μg/L) on pulse pressure, only showed weak or no apparent associations for general, systolic or diastolic hypertension (Chen et al. 2007). Similarly, although it has been indicated that respondents exposed to well-water As concentrations greater than 10 μg/L have higher blood pressure when compared with those exposed to well-water As concentrations less than 2 μg/L (Zierold et al. 2004), that analysis was based on self-reported outcome assessment which makes such a conclusion less robust. In addition, at the low to moderate As drinking water levels typical of much of the US population in the National Health and Nutrition Examination Survey, total As, total As minus arsenobetaine in urine were not found to be associated with the prevalence of hypertension, SBP or DBP levels (Jones et al. 2011). Moreover, in an experiment in cells in vitro, a low dose of As was even reported to have a protective effect against CVD related to oxidative stress (Snow et al. 2005). Therefore, given the fact that the exact mechanisms by which As affect hypertension risks are still not clear (Chen et al. 2007), the negative and insignificant associations estimated in our study might be a real one especially for such low doses. Nevertheless, a weak or even significant adverse effects of As that is impossible to detect with the method used on this secondary dataset still cannot be ruled out, suggesting larger scale cohort studies are needed to investigate the effect of low-level iAs intake from rice and rice products on the hypertension risks.

There are already several well-established risk factors for hypertension, ranging from smoking (Chen et al. 2004; Kim and Lee 2019), gender (Watanabe et al. 2001), age (Camici et al. 2009) to diabetes (Epstein 1997), obesity (Derosa and Chiarolanza 2005; Re 2009) and genetic factors (Klatsky 2008; Tada et al. 2011) and genetic factors (Miller et al. 2004; Tanus-Santos et al. 2001), all of which may be indistinguishable in their impacts from those of either iAs.

There are further limitations to this study including uncertainties in the estimation of iAs intake and blood pressure measurements: these errors may have weakened or even masked a possible underlying dose–response association. These errors include: (1) iAs concentration of different foodstuffs were not evaluated directly in the NDNS RP 7–8. In this study, instead, the European Food Safety Authority (2014) report was used to estimate mean iAs concentration in each foodstuff, leading to potential inaccuracies in our estimation of iAs intake, and thus in the modelled associations. (2) Dietary intakes were quantified by a food diary (MRC Elsie Widdowson Laboratory and
measurements error are expected as the days selected for the dietary record might not represent their long-term dietary pattern and the weight of different foodstuffs estimated by participants themselves might not be precise; (3) Casual blood pressure readings cannot wholly represent the entire 24-h pattern, although there is no evidence of any systematic measurement errors in blood pressure measurements and the consistency between consecutive measurements was good (MRC Elsie Widdowson Laboratory and NatCen Social Research 2019). Also, the observed relationship between blood pressure and widely accepted major risk factors were in agreement with those of previously reported (Epstein 1997; Klatsky 2003; Mohtasham-Amiri et al. 2018; Neaton and Wentworth 1992; Owolabi et al. 2016), further suggesting the validity of the blood pressure measurements in this study.

Limitations could also exist in terms of the residual confounding issues. Some variables, ranging from age (Biino et al. 2013), diabetes (Epstein 1997), smoking (Chen et al. 2004; Kim and Lee 2019), obesity (Derosa and Chiarolanza 2005; Re 2009), household income (Mohtasham-Amiri et al. 2018; Owolabi et al. 2016) to education level (Cirera et al. 1998), glucose concentration (Banda et al. 2010), salt consumption (Lelong et al. 2019) and some nutrients intake (Betts and Foote 1985; Chen et al. 2007; Jarrah et al. 2018) are well recognized as important predictors of either hypertension risks or As intake, most of which have already been accounted for. However, factors such as individual level genetic information (Gong and O’Bryant 2012; Hsieh et al. 2017), metabolic syndrome (Zamora-Kapoor et al. 2018), history of pre-eclampsia (Zamora-Kapoor et al. 2018) or hypercholesterolemia (Cappuccio et al. 2003), physical activity (Banda et al. 2010) and some dietary-related information, including fatty acid intake (Zhao et al. 2011) which might be protective against hypertension risks perhaps ideally should have been taken into consideration in the present study as well. For French adults, more than 1% of new cases of hypertension were attributable to low physical activity (Lelong et al. 2019). Also, it has been reported that 5–13% population attributable risks of hypertension were due to physical inactivity with 3–16% due to a low intake of fatty acid in Finland, Italy, the Netherlands, UK and USA (Geleijnse et al. 2005). Similarly, some genetic factors, such as Angiotensinogen M235T genotype (Sethi et al. 2003) and CYP2J2*7 genotype (King et al. 2005), have been regarded to be partially responsible for hypertension risks. Unfortunately, due to lack of data sources or too many missing data, these variables were not considered in the present modelling analysis, meaning that the lower hypertension risks observed in the present study might not be mainly due to higher E-iAs_{ing,rice} but rather due to one or more of those unadjusted protective confounders, whether behavioural, dietary or genetic. Thus, Japanese population who have higher consumption level of rice and rice products than most of the UK population but also have adequate marine-derived n-3 fatty acids in their diets generally have lower hypertension risks (Sekikawa et al. 2008; Tada et al. 2011). Similarly, ethnic minorities in the UK with higher rice consumption level but found to be less prevalent in hypercholesterolemia (Cappuccio et al. 2003) may also suffer lower hypertension risks.

In addition, there may be dietary iAs intake from other sources. According to some surveys conducted in European countries and a probabilistic exposure modelling analysis in the USA, vegetables, fruit, and some dairy products may also be important contributors to dietary iAs exposure, with vegetables even accounting for more than 20% of iAs exposure for the general US population (European Food Safety Authority 2014; Henderson et al. 2003; Xue et al. 2010). However, NDNS RP 7–8 indicated that those sources might not contribute too much to the dietary iAs intake in the UK (MRC Elsie Widdowson Laboratory and NatCen Social Research 2019) and thus might not confound our estimated associations substantially. Similarly, as seafood usually contains organoarsenic compounds such as arsenobetaine and arsenosugars, which can be transformed to toxic arsenic metabolites after storage and cooking, As intake from seafood should also be considered (Taylor et al. 2017). However, there is no strong evidence of human toxicity reported currently from such sources (Chen et al. 2010; Ferrante et al. 2019).

Moreover, due to the intrinsic characteristics of a cross-sectional design, the possibility of recall bias when collecting information such as the frequency of smoking and alcohol consumption during the previous one year cannot be excluded. In addition, whilst there have been biologically plausible mechanistic processes previously proposed to support a causal link between iAs exposure and hypertension risks (Lee...
et al. 2005), cross-sectional studies themselves do merely indicate an association rather than causality.

Unlike many studies using ecologic measures of iAs intake (Bulka et al. 2016; Han et al. 2009; Mahram et al. 2013), this study assessed food consumption levels and thus iAs intake individually, with blood pressure measured via a standardized protocol (MRC Elsie Widdowson Laboratory and NatCen Social Research 2019). Also, as it is population-based, this study considered participants selection of whom depended neither on iAs exposure nor blood pressure status. Given the high-quality data collection methods and rigorous laboratory methods of NDNS RP 7–8 (MRC Elsie Widdowson Laboratory and NatCen Social Research 2019), the quality of the data obtained from NDNS RP 7–8 is considered to be good.

Taken together, this was the first study quantifying the individual-level dose–response associations between iAs intake from rice and rice products and CVD health, being of importance especially in a country such as the UK where there is little exposure from drinking water. This exploratory study suggests a negative but not significant association between exposure to iAs through eating rice or rice products and hypertension risks. However, due to the above-mentioned limitations in the present study, the possibility of any small positive or even significantly positive associations that are impossible to detect within the current study design and dataset still cannot be eliminated. This study does, however, highlight the need for further research in the area of the association between iAs exposure from rice and rice products and CVD health outcomes. In particular, larger scale cohort studies involving with more statistical power are indicated for better assessing such effects.

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Author contributions The study was jointly conceived by LX and DP and executed by LX under the supervision of DP. Both authors contributed to the writing and revision of the manuscript.

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