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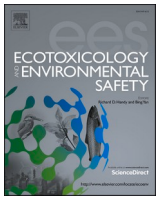

Assessment of hypertension association with arsenic exposure from food and drinking water in Bihar, India

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ABSTRACT

Epidemiological studies have associated chronic exposure to arsenic (As) from drinking water with increased risk of hypertension. However, evidence of an association between As exposure from food and hypertension risks is sparse. To quantify the association between daily As intake from both food (rice, wheat and potatoes) and drinking water (As_{water}) along with total exposure (As_{total}) and hypertension risks in a study population in Bihar, India, we conducted an individual level cross-sectional analysis between 2017 and 2019 involving 150 participants. Arsenic intake variables and three indicators of hypertension risks (general hypertension, low-density lipoprotein (LDL) and high-density lipoprotein (HDL)) were derived, and any relationship was quantified using a series of crude and multivariable log-linear or logistic regression models. The prevalence of general hypertension was 40% for the studied population. The median level of HDL was 45 mg/dL while median value of LDL was 114 mg/dL. Apart from a marginally significant positive relationship between As intake from rice and the changes of LDL (p-value = 0.032), no significant positive association between As intake and hypertension risks could be ascertained. In fact, As_{total} was found to be associated with lower risks of general hypertension and higher levels of HDL (p-value = 0.020 and 0.010 respectively) whilst general hypertension was marginally associated with lower As_{water} (p-value = 0.043). Due to limitations regarding study design and residual confounding, all observed marginal associations should be treated with caution.

1. Introduction

Hypertension, a common form of cardiovascular disease (CVD), is a leading risk factor in global disease burden, hence, an important public health problem in the world (Lim et al., 2012). It has been reported that while the prevalence of hypertension is decreasing in high-income countries, it is still increasing in low and middle-income countries (Zhou et al., 2017). In India, hypertension prevalence has increased over the last three decades (India State-Level Disease Burden Initiative CVD Collaborators, 2018), emerging as the most important risk factor for deaths and disability-adjusted life years (Gupta and Xavier, 2018). Epidemiological studies have shown that chronic exposure to arsenic (As) from drinking water is related to increased risk of CVD in As-contaminated areas of India (Rahman et al., 2009). The severity of the As problem in India is substantial with about 18–30 million people estimated to be exposed from drinking water only (Podgorski et al., 2020). Guha Mazumder et al. (2012) found increased risk of hypertension (odds ratio: 2.87 (95% confidence interval = 1.26–4.83)) in As exposed (mean As concentration in drinking water = 49.7 μg/L, n = 208) over non-exposed populations (mean As concentration in drinking

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water ≤ 3 μg/L, n = 100) of West Bengal, India, in a case-control study and also reported a dose-response relationship for hypertension with increasing cumulative As exposure from drinking water. In another case-control study conducted in West Bengal, the serum levels of inflammatory cytokines, IL6, IL8 and MCP-1, associated with CVD risks, were higher in a population with chronic As exposure (mean As concentration in drinking water = 203 ± 188 μg/L) compared to a control population (As concentration in drinking water ranged between 3 and 10 μg/L) (Das et al., 2012). The underlying possible mechanisms of As exposure caused hypertension risks are complex, including but not limited to oxidative stress, modified vascular response to neurotransmitters, impaired nitric oxide signaling, and renal damage (Martins et al., 2018). While As exposure from different foodstuffs, especially rice and wheat, the two most important food-grains of India and the most consumed cereals especially in rural India (where As exposure is high), have already been considered as an important pathway for As exposure (Mondal et al., 2021), and an extensive body of literature links As exposure from food composites to As in biomarkers (Cascio et al., 2011; deCastro et al., 2014); to date, epidemiological evidence indicating the potential role of As intake from food and adverse health effects including CVD risks in As contaminated areas is sparse. On the contrary, in regions where As exposure through drinking water is minimal, rice and other foods rich in As can contribute significantly to As intake (Cascio et al., 2011) and health risks. For example, Xu et al. (2020) using an ecological study in England and Wales, found As exposure from rice to be associated with age-standardized mortality rates of CVD after adjusting for behavioral and socio-economic confounding factors.

To better understand the complexity associated with the determination of potential associations between As exposure from food and CVD risks in an area where As exposure from drinking water is prevalent, we considered As intake not only from drinking water but also from rice along with two other most consumed food items (wheat and potato) and determined any relationship with CVD markers in an As exposed population of Bihar, India. The reasons for conducting this study in an area of Bihar with previously known As contamination were two-fold. Firstly, we found food which are mostly grown locally (Kumar et al., 2016) to contribute broadly equally to drinking water towards total As exposure in this study population (Mondal et al., 2021). Secondly, to the best of our knowledge, to date, there are no population based studies determining As exposure and CVD risks in Bihar where millions of people are facing health risks due to As exposure (Chakraborti et al., 2017).

The objective of this study was to model the relationships between daily As intake from both food (As_{food}) and drinking water (As_{water}) along with total intake (As_{total}) and hypertension risks in an As exposed study population of Bihar, India using individual level cross sectional analysis. We have also explored the relationship for individual food intakes.

2. Methods

2.1. Study design and population recruitment

In this study, a total of 182 participants from 91 households, one adult male and female from each household across 19 villages from eight known groundwater As affected districts (Begusarai, Bhagalpur, Bhojpur, Buxar, Chapara, Patna, Samastipur, Vaishali) in Bihar took part in the survey between 2017 and 2019 as a part of a project titled, "Nature and nurture in arsenic exposed population of Bihar, India". Details of sampling have been described elsewhere (Mondal et al., 2021). Briefly, the eight As affected districts out of 13 stretching from Buxar to Bhagalpur were selected based on data of the Government of Bihar (Public Health Engineering Department, 2020) and after considering logistical issues, including local field support and distance from the laboratory. In each village, around three to six households were selected to cover different socio-economic strata. Drinking water (N = 90), cooked rice (N = 70), wheat flour (N = 72), and potato (N = 82) samples were collected from each household. If the household was using tube well for drinking water, then the well was sampled but if they were using treated/filtered water for drinking (37%) then that stored water in the house was sampled.

The study was conducted in accordance with national and international guidelines for the protection of human subjects and was approved by both the University of Salford Ethics Committee (STR1718-10) and Mahavir Cancer Sansthan Institutional Ethics Committee.

We excluded (i) women who were pregnant and breastfeeding (N = 10), since the dietary pattern, some socio-demographic characteristics and blood pressure status of pregnant women may change and may be different from the general population (Yoder et al., 2009). We further excluded (ii) participants with missing data on General Hypertension_measured (N = 2), General Hypertension_reported (N = 1), low-density lipoprotein (LDL) (N = 7), high-density lipoprotein (HDL) (N = 7), Age (N = 2), Marital Status (N = 2), Household Income (N = 1), Active Tobacco Use (N = 1), Passive Smoking (N = 1), Activity Level (N = 1), Heart Disease (N = 1), Diabetes (N = 1), body mass index (BMI) (N = 2), Blood Sugar (N = 9), Thyroid Disorder (N = 1), Albumin (N = 8), Cholesterol (N = 7), Wheat flour IR (daily consumption of wheat flour) (N = 18), Rice IR (daily consumption of rice) (N = 18), Potato IR (daily consumption of potato) (N = 18). After such exclusions, the final population size in this study was 150 (A detailed description of this dataset is summarized and provided in Table A.1).

2.2. Daily As intake from food and drinking water

Total daily As intake from both food and drinking water (As_{total}) (μg/day) was calculated as Eq. (1):

$$As_{total} = As_{rice} + As_{wheat\ flour} + As_{potato} + As_{water} \quad (1)$$

Arsenic intake from each component were calculated by the following Eq. (2):

$$As_x = (IR_x \div 1000) \times T\text{-}Asx \quad (2)$$

Where.

IR_x: Drinking water IR, Rice IR, Wheat flour IR or Potato IR: daily intake rate of drinking water, cooked rice, wheat flour and potato (g/day)

T-As_x: total As concentration in drinking water (μg/L) (T-$As_{drinking\ water}$), cooked rice (T-$As_{cooked\ rice}$), wheat flour (T-$As_{wheat\ flour}$) and potato (T-As_{potato}) respectively (μg/kg)

In addition, we also separately calculated daily As intake from food (excluding drinking water) (As_{food}) by using Eq. (3):

$$As_{food} = As_{rice} + As_{wheat\ flour} + As_{potato} \quad (3)$$

The daily consumption level of cooked rice, wheat flour and potato were estimated using the 24-hour recall data which was collected by a trained nutritionist (Mondal et al., 2021). In the absence of detailed data for daily consumption of drinking water for this study population, this was estimated as 3.5 L/day (Kumar et al., 2016). To determine total As concentrations, drinking water samples were collected and then analysed for total As following the protocol as detailed in Richards et al. (2020), and the total As concentration in the food samples were estimated by inductively coupled plasma mass spectrometry (Agilent 7900) based on an established protocol detailed elsewhere (Mondal et al., 2021).

2.3. Hypertension risks

Two important CVD markers - LDL and HDL were measured as indicators of hypertension risks (Mendez et al., 2016) along with measured general hypertension based on systolic and diastolic blood

pressures.

General Hypertension_measured was defined as systolic blood pressure $\geq$ 140 mmHg, or diastolic blood pressure $\geq$ 90 mmHg (World Health Organization, 2019). The blood pressure was measured two times within an interval of 30 min and the lowest systolic and diastolic blood pressure was used to ensure accurate measurement using BP Care Plus (SD Biosensor, Republic of Korea).

For General Hypertension_reported, participants were asked about their general health and anyone reporting any clinically diagnosed hypertension and/or being under regular treatment with anti-hypertension medications was considered as a positive case.

Blood samples (3–5 ml) were collected for the estimation of LDL and HDL. To be specific, LDL was estimated using direct enzymatic methods (Okada et al., 1998) and HDL was measured using PEG/CHOD – PAP method (Grillo et al., 1981) using UV–VIS spectrophotometer (Thermo Scientific).

2.4. Confounding variables

Several variables have been included as confounders in the present study. Certain factors, such as active tobacco use, age, districts, diabetes, gender, heart disease, marital status, passive smoking, and thyroid disorder were determined by interviewing the participants. The activity level was determined based on reported profession and the household income was assessed using information on total number of family members at work and their profession and assets. The albumin and cholesterol were determined by analysing samples in laboratory. The blood sugar was estimated during the survey using digital glucometer "SD Codefree" (SD Biosensor, Republic of Korea) and BMI was calculated using height and weight of participants. Alcohol consumption was not considered as it is prohibited in the state of Bihar.

2.5. Statistics analysis

We quantified the relationship between As_{total} and hypertension risks (General Hypertension_measured, LDL and HDL), utilizing a series of linear and non-linear models. As_{total} was either categorized into tertiles based on its distributions in the study population or was used as a continuous variable.

The missing values of As concentration in cooked rice (N = 42), drinking water (N = 2), wheat flour (N = 38) and potato (N = 10) were imputed using the method of chained equations (White et al., 2011) with a predictive mean matching (Osorio-Yáñez et al., 2020) by the MICE package in R (Buuren and Groothuis-Oudshoorn, 2010). Also, quickpred function was used to reduce the number of predictors and 10 imputed datasets were created for each analysis. After imputation, diagnostic analysis was conducted by comparing the imputed and collected (non-missing) data with Student's T test analysis.

Descriptive analysis was conducted to assess the differences in participants' socio-demographic and lifestyle characteristics and some established or suspected risk factors of hypertension by tertiles of As_{total} (Tertile 1: 6.95–23.04 μg/day; Tertile 2: 24.12–65.45 μg/day; Tertiel 3: 65.46–2733.38 μg/day). The results were reported as median (interquartile range Q1 and Q3) for continuous variables (As_{rice}, As_{water}, $As_{wheat\ flour}$, As_{potato}, As_{food}, As_{total}, LDL and HDL) or as frequencies (percentages) for categorical ones (Active Tobacco Use, Activity Level, Age, Albumin, BMI, Cholesterol, Diabetes, District, Gender, Heart Disease, Household Income, General Hypertension_reported, General Hypertension_measured, Marital Status, Passive Smoking, Blood Sugar and Thyroid Disorder). The p-value for trend for categorical variables was obtained from Pearson's Chi-squared test and p-value for trend for continuous ones was obtained from linear models with As tertile entered as a continuous variable.

Considering the widely known importance of certain factors, such as age, obesity, gender and BMI on the risk of hypertension (Kelishadi et al., 2006), we, then, quantified the individual and interactive contributions of As_{total} and all the potential confounders to the variability of hypertension risks (General Hypertension_measured, LDL and HDL respectively) through generalized linear model (GLM) (contributions (%) = 100 × (null deviance–residual deviance)/null deviance) (Bjorndal et al., 2013). To be specific, the individual contribution of a factor quantified the extent to which the variability of hypertension risks could be explained by this factor. The interactive contributions were calculated by adding a cross-product term between continuous As intake and different confounders to the main model, indicating how much the variability of hypertension risks could be explained by the interactive term. The resultant p-values were computed using analysis of variance (Anova) test with type II error for interaction terms, representing whether there was a significant association between the interactive term and hypertension risks. Relative excess risk for interaction (RERI) was used to assess the additive interactions (Eq. (4)), with RERI > 0 indicating positive interaction, while RERI < 0 the negative (Rothman et al., 2012):

$$RERI = e^{(\beta 1+\beta 2+\beta 3)} - e^{\beta 1} - e^{\beta 2} + 1 \quad (4)$$

where.

β1: the continuous coefficient of As_{total}
β2: the coefficient of each potential confounder
β3: the interactive term coefficient

Because As_{total} was calculated as the sum of As_{rice} and $As_{wheat\ flour}$, As_{water} and As_{potato}, the interactive associations between As_{total} and As_{rice}, $As_{wheat\ flour}$, As_{water} and As_{potato} were not considered.

We finally quantified the association between As_{total} and hypertension risks (General Hypertension_measured, LDL and HDL) with both categorical and continuous intake variables being used in a series of crude and multivariate models. In the categorical analysis, the odds ratios for General Hypertension_measured (binary variable) and their corresponding 95% CIs for higher As_{total} tertiles were calculated by logistic regression using the lowest tertile as the referent. In terms of the continuous analysis, As_{total} was used as a continuous measure to evaluate the changes of hypertension risks (odds ratios for General Hypertension_measured, log-transformed LDL and log-transformed HDL) (As_{total} was log-transformed for the analysis of LDL and HDL). To determine any non-linear relationship, we included higher order polynomial and interactive terms for As_{total} based on the best-fitted linear models. The differences of the hypertension risks across three tertiles of As_{total} were obtained from Wald tests for As_{total} coefficients, and the p values for linear and nonlinear trends were computed with As_{total} as a continuous measure in the model via Anova test in type II error. The contribution of each model indicated the extent to which the variability of hypertension risks could be explained by the model.

To improve the modeled relationship between As_{total} and hypertension risks, the effects of a group of potential confounders were considered. In terms of the selection of those potential confounders, we checked the existence of multi-collinearity problems and conducted stepwise regression using a forward addition technique to select the final model with Akaike information criterion (AIC) as the model selection criteria.

The association between As_{rice}, As_{water}, $As_{wheat\ flour}$, As_{potato}, As_{food} and hypertension risks was also quantified by using similar modeling methods to that of As_{total}. As intake levels in different tertiles were as followed: For As_{potato}, Tertile 1: 0.00–2.11 μg/day; Tertile 2: 2.40–6.77 μg/day; Tertiel 3: 6.57–101.34 μg/day; For As_{rice}, Tertile 1: 0.00–3.48 μg/day; Tertile 2: 3.50–12.60 μg/day; Tertiel 3: 12.90–105.00 μg/day; For As_{water}, Tertile 1: 0.00–4.59 μg/day; Tertile 2: 4.94–19.18 μg/day; Tertiel 3: 19.22–2560.39 μg/day; For $As_{wheat\ flour}$, Tertile 1: 0.00–3.28 μg/day; Tertile 2: 3.30–9.35 μg/day; Tertiel 3: 9.36–103.64; For As_{food}, Tertile 1: 1.95–15.31 μg/day; Tertile 2: 15.32–32.10 μg/day; Tertile 3: 32.38–175.78 μg/day.

Table 1
Socio-demographic characteristic of the study population and hypertension risk factors by As exposure.

Characteristic		Overall	Tertile of As_{total} (μg/day)			p-value
			Tertile 1 (6.9, 23.0)	Tertile 2 (24.1, 65.4)	Tertile 3 (65.5, 2733.4)	
As_{total}, μg/day (median (interquartile range Q1 and Q3))		35.6 (18.7, 79.3)	15.5 (11.8, 18.2)	35.6 (29.3, 45.9)	118.2 (79.9, 322.2)	/
As_{potato}, μg/day (median (interquartile range Q1 and Q3))		4.0 (1.7, 8.3)	3.3 (1.2, 5.7)	3.4 (1.3, 8.1)	6.5 (3.1, 13.4)	< 0.001
As_{water}, μg/day (median (interquartile range Q1 and Q3))		12.6 (2.8, 39.6)	2.4 (0.5, 4.4)	12.8 (6.4, 15.8)	63.6 (23.3, 285.8)	< 0.001
$As_{wheat\ flour}$, μg/day (median (interquartile range Q1 and Q3))		5.2 (2.6, 11.5)	3.3 (2.0, 5.0)	6.7 (2.8, 10.5)	10.9 (3.3, 29.1)	< 0.001
As_{rice}, μg/day (median (interquartile range Q1 and Q3))		7.7 (0.0, 15.7)	3.5 (0.0, 7.1)	10.5 (7.3, 17.1)	15.1 (1.4, 35.7)	< 0.001
As_{food}, μg/day (median (interquartile range Q1 and Q3))		21.3 (13.4, 36.1)	11.7 (7.8, 15.3)	22.4 (16.5, 29.7)	44.8 (33.7, 68.8)	< 0.001
LDL, mg/dL (median (interquartile range Q1 and Q3))		113.6 (96.9, 134.2)	125.6 (110.6, 155.1)	110.9- (97.3, 129.0)	102.9 (93.0, 121.0)	0.003
HDL, mg/dL (median (interquartile range Q1 and Q3))		45.0 (37.7, 55.2)	45.8 (38.2, 51.9)	45.1 (39.6, 58.0)	41.4 (32.9, 58.6)	0.369
Active Tobacco Use (frequencies (percentages (%))	no	92 (61.3)	34 (22.7)	28 (18.7)	30 (20.0)	0.455
	yes	58 (38.7)	16 (10.7)	22 (14.7)	20 (13.3)	
Activity Level (frequencies (percentages (%))	sedentary	92 (61.3)	36 (24.0)	30 (20.0)	26 (17.3)	0.118
	moderate & heavy	58 (38.7)	14 (9.3)	20 (13.3)	24 (16.0)	
Age (frequencies (percentages (%))	19–30	17 (11.3)	1 (0.7)	5 (3.3)	11 (7.3)	0.158
	31–40	25 (16.7)	10 (6.7)	7 (4.7)	8 (5.3)	
	41–50	37 (24.7)	13 (8.7)	11 (7.3)	13 (8.7)	
	51–60	38 (25.3)	14 (9.3)	14 (9.3)	10 (6.7)	
	> 60	33 (22.0)	12 (8.0)	13 (8.7)	8 (5.3)	
Albumin (frequencies (percentages (%))	abnormal	58 (38.7)	13 (8.7)	22 (14.7)	23 (15.3)	0.077
	normal	92 (61.3)	37 (24.7)	28 (18.7)	27 (18.0)	
BMI (frequencies (percentages (%))	underweight	22 (14.7)	6 (4.0)	5 (3.3)	11 (7.3)	< 0.001
	normal	84 (56.0)	19 (12.7)	34 (22.7)	31 (20.7)	
	overweight & obese	44 (29.3)	25 (16.7)	11 (7.3)	8 (5.3)	
Cholesterol (frequencies (percentages (%))	abnormal	16 (10.7)	6 (4.0)	8 (5.3)	2 (1.3)	0.141
	normal	134 (89.3)	44 (29.3)	42 (28.0)	48 (32.0)	
Diabetes (frequencies (percentages (%))	no	138 (92.0)	44 (29.3)	46 (30.7)	48 (32.0)	0.337
	yes	12 (8.0)	6 (4.0)	4 (2.7)	2 (1.3)	
District (frequencies (percentages (%))	Begusarai	8 (5.3)	0 (0.0)	0 (0.0)	8 (5.3)	< 0.001
	Bhagalpur	50 (33.3)	19 (12.7)	24 (16.0)	7 (4.7)	
	Bhojpur	12 (8.0)	3 (2.0)	6 (4.0)	3 (2.0)	
	Buxar	4 (2.7)	0 (0.0)	0 (0.0)	4 (2.7)	
	Chapara	22 (14.7)	5 (3.3)	8 (5.3)	9 (6.0)	
	Patna	27 (18.0)	7 (4.7)	4 (2.7)	16 (10.7)	
	Samastipur	10 (6.7)	3 (2.0)	4 (2.7)	3 (2.0)	
	Vaishali	17 (11.3)	13 (8.7)	4 (2.7)	0 (0.0)	
Gender (frequencies (percentages (%))	female	65 (43.3)	26 (17.3)	18 (12.0)	21 (14.0)	0.264
	male	85 (56.7)	24 (16.0)	32 (21.3)	29 (19.3)	
Heart Disease (frequencies (percentages (%))	no	146 (97.3)	49 (32.7)	47 (31.3)	50 (33.3)	0.165
	yes	4 (2.7)	1 (0.7)	3 (2.0)	0 (0.0)	
Household Income (frequencies (percentages (%))	< 50,000	40 (26.6)	5 (3.3)	9 (6.0)	26 (17.3)	< 0.001
	50,000–100,000	49 (32.7)	20 (13.3)	18 (12.0)	11 (7.3)	
	100,000–200,000	27 (18.0)	10 (6.7)	7 (4.7)	10 (6.7)	
	> 200,000	34 (22.7)	15 (10.0)	16 (10.7)	3 (2.0)	
General Hypertension_measured (frequencies (percentages (%))	no	89 (59.3)	24 (16.0)	28 (18.7)	37 (24.7)	0.025
	yes	61 (40.7)	26 (17.3)	22 (14.7)	13 (8.7)	
General Hypertension_reported (frequencies (percentages (%))	no	127 (84.7)	40 (26.7)	43 (28.7)	44 (29.3)	0.512
	yes	23 (15.3)	10 (6.7)	7 (4.7)	6 (4.0)	
Marital Status (frequencies (percentages (%))	married	141 (94.0)	49 (32.7)	47 (31.3)	45 (30.0)	0.242
	unmarried & widow	9 (6.0)	1 (0.7)	3 (2.0)	5 (3.3)	
Passive Smoking (frequencies (percentages (%))	no	136 (90.7)	44 (29.3)	47 (31.3)	45 (30.0)	0.576
	yes	14 (9.3)	6 (4.0)	6 (5.0)	6 (6.0)	
Blood Sugar (frequencies (percentages (%))	high	37 (24.7)	11 (7.3)	31 (20.7)	43 (28.7)	0.017
	normal	113 (75.3)	39 (26.0)	31 (20.7)	43 (28.7)	
Thyroid Disorder (frequencies (percentages (%))	no	146 (97.3)	48 (32.0)	50 (33.3)	48 (32.0)	0.357
	yes	4 (2.7)	2 (1.3)	0 (0.0)	2 (1.3)	

HDL: Serum high-density lipoprotein level; LDL: Serum low-density lipoprotein level; Asrice, Aswater, Aswheat flour, Aspotato, Asfood and Astotal: daily As intake from rice, drinking water, wheat flour, potato, food (excluding drinking water) and both food and drinking water.
*p-value for trend was obtained from Pearson's Chi-squared test for categorical variables and for the continuous ones it was obtained from linear models with As intake entered as a continuous variable.

Statistical analysis was conducted using R statistical software version 3.4.3 (R Foundation for Statistical Computing).

3. Results

3.1. Characteristics of study participants and relationship among variables

In this study, the median As_{total} was 35.6 μg/day. Median As intake from food (As_{food}) was 21.3 μg/day with As_{water}, $As_{wheat\ flour}$, As_{rice} and As_{potato} being 12.6, 5.2, 7.7 and 4.0 μg/day respectively (Table 1). A significant trend could be found between As_{total} and individual exposure pathways. There were significant associations (p-value for trend lower than 0.05) between As_{total} and a) BMI, with higher proportion of underweight participants having higher exposure and overweight and obese participants having lower exposure; b) study areas (District), with higher proportion of people in Chapara districts exposed with higher level of As_{total}, while higher proportion of people in Vaishali with lower level of As_{total}; c) household income, with participants having lowest household income tending to have higher As_{total}; and d) blood sugar, with participants with high blood sugar tending to have higher As_{total} (Table 1). Based on our measurements we found 40% of surveyed participants had general hypertension as measured in our study while only 15% reported having it. There was a significant relationship between General Hypertension_measured and General Hypertension_reported (p-value for chi-square test < 0.05). Proportion of participants with General Hypertension_measured were found to be higher in the lowest tertile of As_{total}. The median level of HDL for the studied population was 45.0 mg/dL, which is regarded as exerting no effects on developing heart disease (Department of Health and Human Services et al., 2010). Variations in HDL were associated with cholesterol, study area (District) and household income. The median value of LDL (113.6 mg/dL) was higher than 100 mg/dL but still near optimal (100–129 mg/dL) (Lichtenstein, 2003) and participants with higher levels of LDL were found to be in the lowest tertile of As_{total} (Table 1).

The individual and interactive contributions of different factors on hypertension risks in this study are shown in Table 2. Age, BMI, household income, As_{total} and As_{water} were the most five important contributors to the variability of General Hypertension_measured (significantly each accounting for more than 5% variability). In addition, diabetes, blood sugar, activity level, passive smoking, As_{food} and $As_{wheat\ flour}$ were also found to contribute to the risk of General Hypertension_measured. Activity level, study area (District), and heart disease had a significant interactive effect with As_{total} on the risks of general hypertension (p-value for interactive terms lower than 0.05). For the changes of LDL, we found that study area, household income, BMI, cholesterol and heart disease had a significant contribution, among which study area contributed to more than 15% of the variability of LDL. For the changes of HDL, we found that study area, cholesterol and household income made significant contributions, with study area accounting for nearly 40% of the variability. Cholesterol, study area, household income, and blood sugar were found to have interactive effects with As_{total} on the changes of HDL (Table 2).

3.2. Relationship between As exposure and hypertension risks

No significant positive association between total As exposure and hypertension risks could be ascertained in this studied population (Tables 3 and 4). The only observed significant but marginal association was for As exposure from rice intake and increase in LDL (p-value for linear trend $= 0.032$), and with every 10% increase in As_{rice}, 0.05% (95% CI: 0.00%, 0.08%) increase in the LDL was noted (Table 4). Indeed, risks of general hypertension (General Hypertension_measured) were found to be lowered with As_{total} (p-value for trend $= 0.020$) and As_{water} (p-value for trend $= 0.043$, Table 3), although again the significance was marginal. Similar to the protective effect observed for General Hypertension_measured, we found that the HDL increased significantly by 0.20% (95% CI: 0.05%, 0.42%) for an increase of 10% As_{total} (p-value for trend $= 0.010$, Table 4). To test the possibility of non-linear relations between the hypertension risks and As_{total}, higher order polynomial and interactive terms have been added based on the best-fitted linear model. However, no significant non-linear trend could be observed (results not shown). Considering the study design was clustered and from only 91 households, effect size was calculated from post-hoc power analyses and the Cohen's effect size for LDL was 0.27 (power=1-β = 0.84) indicating moderate effect. For HDL Cohen's effect size was 0.08 (1-β = 0.13) indicating trivial effect.

4. Discussion

The prevalence of General Hypertension_measured in this study was 40%, which is somewhat higher than those reported previously from Bihar, likely related to the characteristics of the study population and the small sample size of our study. For example, in the adult (age >20 years) rural population of Katihar, Bihar, while the prevalence of hypertension was around 11% (n = 997), the prevalence was higher (over 25%) in those aged over 50 years (Ghosh et al., 2013), and almost half of the participants in this study were over 50 years. In another study from rural areas of Patna district of Bihar, the overall prevalence of hypertension was 24% (n = 1083), but mean age of hypertensive participants was found to be 50 years (Singh et al., 2013). Hence, given previous studies which confirm the association between age and hypertension risks in Bihar (Kumar et al., 2017), high prevalence in this study could be because of higher participation from elderly participants.

The observed distribution of As concentrations in water samples was similar to that reported in a recent study (Richards et al., 2020); but we found higher concentration of total As in cooked rice (median= 97 and range= 16–1128 μg/kg) than in the previous study (median= 77 and range= 10–728 μg/kg) from Bihar (Kumar et al., 2016) while As concentration in potato was much lower than concentrations reported in vegetables, but not potato (Kumar et al., 2016). Arsenic concentration in wheat flour was limited in previous publications from Bihar.

In this study, apart from the association between LDL and As_{rice}, not only was no clear positive association between As exposure and CVD risks found but also (i) As_{total} was found to be associated with lower risks of general hypertension, and higher level of HDL after adjustment for health and sociodemographic factors and (ii) general hypertension was found to be lowered with As_{water}. In fact, such inconclusive results were also observed in previous studies elsewhere looking at the association of either As exposure with CVD markers or low-level As exposure with hypertension risks. For example, in a cross-sectional study on associations between As exposure from water and multiple markers of cardiometabolic risk in adults (n = 1160 from Chihuahua, Mexico), while increased exposure was associated with several markers of increased cardiometabolic risk, it was also associated with higher rather than lower HDL (Mendez et al., 2016). Previously, Chen et al. (2007) found no apparent association between time-weighted well water As concentration and general or diastolic hypertension and weak association for systolic hypertension using baseline data of HEALS study (n = 10,910) in Bangladesh and suggested that the effect of low-level As exposure may be only pronounced in persons with lower intake of nutrients related to As metabolism and cardiovascular health. However, the observed marginally significant associations in this study should be treated with caution, not least of all because of the many individual exposure groups that have been considered, therefore further studies with increased statistical power and improved methods may be required to robustly detect relatively small effects.

Besides the intrinsic disadvantages of a cross-sectional design and small sample size, this study was limited by some other factors. These include: (i) assessment of daily intake of different foodstuffs, such as cooked rice, wheat flour and potato just based on a 24-h food record. Though 24-h food record is precise in quantifying food consumption

Table 2
Individual and interactive contributions of different factors to the variability of hypertension risks.

Factors	General Hypertension_measured					LDL					HDL				
	Contribution (%)	p-value	Interactive effects			Contribution (%)	p-value	Interactive effects			Contribution (%)	p-value	Interactive effects		
As_{total}	6.19	< 0.001	RERI	Contribution (%)	p-value	0.96	0.229	RERI	Contribution (%)	p-value	1.01	0.218	RERI	Contribution (%)	p-value
Active Tobacco Use	0.01	0.841	+	3.75	0.007	0.55	0.365	–	0.21	0.572	0.07	0.742	+	1.10	0.201
Activity Level	2.54	0.023	+	1.41	0.105	0.17	0.607	–	0.00	0.951	0.01	0.902	+	0.35	0.473
Age	8.06	0.002	–	0.94	0.796	1.98	0.567	–	3.17	0.332	3.90	0.207	–	0.87	0.871
Albumin	0.01	0.841	–	0.00	0.935	1.57	0.124	–	0.48	0.399	0.25	0.534	–	1.01	0.222
BMI	7.83	< 0.001	–	0.35	0.727	5.18	0.017	–	0.15	0.894	2.06	0.212	+	2.18	0.200
Cholesterol	0.31	0.424	–	0.91	0.187	3.30	0.024	+	0.40	0.438	7.49	< 0.001	–	6.04	0.002
Diabetes	3.13	0.011	–	0.00	0.946	0.33	0.478	–	0.02	0.852	0.12	0.667	+	0.01	0.895
Districts	2.16	0.735	–	20.09	< 0.001	15.23	< 0.001	+	1.91	0.918	38.00	< 0.001	+	23.29	< 0.001
Gender	0.11	0.630	+	0.36	0.405	1.29	0.163	+	0.01	0.869	2.23	0.065	+	0.04	0.795
Heart Disease	0.07	0.702	–	2.77	0.021	3.17	0.027	–	1.87	0.094	0.26	0.532	+	1.75	0.106
Household Income	7.27	0.002	+	2.45	0.225	7.90	0.005	+	1.54	0.527	5.40	0.039	–	11.69	< 0.001
Marital Status	0.71	0.228	–	0.67	0.259	0.65	0.321	–	0.28	0.515	0.01	0.918	–	1.20	0.181
Passive Smoking	2.49	0.024	+	0.45	0.356	0.03	0.826	–	0.15	0.637	0.34	0.473	+	0.20	0.580
Blood Sugar	2.56	0.022	+	0.01	0.851	1.98	0.083	+	0.00	0.992	0.49	0.390	–	3.87	0.015
Thyroid Disorder	0.07	0.702	–	0.05	0.755	2.17	0.069	–	0.44	0.418	0.44	0.415	–	0.09	0.716
As_{rice}	0.13	0.636	/	/	/	0.11	0.680	/	/	/	0.06	0.767	/	/	/
As_{potato}	0.66	0.244	/	/	/	0.20	0.584	/	/	/	2.20	0.067	/	/	/
As_{water}	5.32	0.001	/	/	/	0.78	0.280	/	/	/	0.90	0.245	/	/	/
$As_{wheat\ flour}$	2.09	0.039	/	/	/	0.42	0.427	/	/	/	1.97	0.085	/	/	/
As_{food}	2.66	0.020	/	/	/	0.64	0.327	/	/	/	2.41	0.055	/	/	/

HDL: Serum high-density lipoprotein level; LDL: Serum low-density lipoprotein level; Asrice, Aswater, Aswheat flour, Aspotato, Asfood and Astotal: daily As intake from rice, drinking water, wheat flour, potato, food (excluding drinking water) and both food and drinking water.

Table 3
Modeling analysis of the categorical and continuous relations between As intake (μg/day) and the odds ratio of General Hypertension_measured.

Exposure pathway	Tertile of As intake (μg/day)			Coefficient of As intake (95% Confidence Intervals)	Contributions (%)
	Tertile 1	Tertile 2 (95% Confidence Intervals)	Tertile 3 (95% Confidence Intervals)		
As_{total}	1 (Referent)	0.58 (0.25, 1.30)	0.86 (0.43, 1.74)	-0.004 (−0.011, −0.001)	27.0
As_{rice}	1 (Referent)	1.13 (0.47, 1.48)	1.08 (0.51, 2.30)	-0.007 (−0.040, 0.020)	25.8
As_{water}	1 (Referent)	0.49 (0.23, 1.03)	1.36 (0.66, 2.87)	-0.004 (−0.012, 0.000)	25.2
$As_{wheat\ flour}$	1 (Referent)	0.68 (0.30, 1.49)	0.90 (0.43, 1.87)	-0.015 (−0.064, 0.026)	26.8
As_{potato}	1 (Referent)	1.88 (0.87, 4.20)	1.09 (0.53, 2.22)	0.001 (−0.037, 0.035)	26.1
As_{food}	1 (Referent)	0.69 (0.32, 1.45)	1.29 (0.64, 2.63)	-0.014 (−0.035, 0.003)	25.0

Asrice, Aswater, Aswheat flour, Aspotato, Asfood and Astotal: daily As intake from rice, drinking water, wheat flour, potato, food (excluding drinking water) and both food and drinking water; AIC: Akaike information criterion.
Models adjusted by the specific variables are summarized in supplemental materials Table A.2.

Table 4
Modeling analysis of the relations between As intake and the changes of cardiovascular indicators (HDL and LDL).

Target variable	Exposure pathway	Coefficient of log-transformed As intake (95% Confidence Intervals)	Contributions (%)
log-transformed HDL	As_{total}	0.058 (0.014, 0.101)	50.0
	As_{rice}	-0.002 (−0.011, 0.006)	46.3
	As_{water}	0.015 (−0.008, 0.039)	48.1
	$As_{wheat\ flour}$	0.008 (−0.031, 0.055)	46.2
	As_{potato}	0.006 (−0.004, 0.018)	46.7
	As_{food}	0.035 (−0.029, 0.101)	46.5
log-transformed LDL	As_{total}	-0.020 (−0.069, 0.027)	26.7
	As_{rice}	0.011 (0.000, 0.020)	30.7
	As_{water}	-0.021 (−0.043, 0.001)	28.2
	$As_{wheat\ flour}$	-0.003 (−0.041, 0.041)	27.3
	As_{potato}	0.011 (0.000, 0.024)	28.4
	As_{food}	0.037 (−0.034, 0.111)	27.4

HDL: Serum high-density lipoprotein level; LDL: Serum low-density lipoprotein level; Asrice, Aswater, Aswheat flour, Aspotato, Asfood and Astotal: daily As intake from rice, drinking water, wheat flour, potato, food (excluding drinking water) and both food and drinking water; AIC: Akaike information criterion.
Models adjusted by specific variables are summarized in supplemental materials Table A.2.

level for the previous day, unfortunately, this method could not capture the long-term dietary pattern of different foods. However, we assumed that such bias could be ruled out as the diet in rural Bihar does not vary that much (Mondal et al., 2021). Moreover, a subgroup (n = 55) of this studied population was surveyed after a few months and the 24-h recall was repeated. Though the individual food intake rates varied between the two surveys, the observed average wheat, rice and potato intakes in the first (wheat: 250 ± 118; rice: 65 ± 64; potato: 166 ± 132 g/day, respectively) and second (wheat: 261 ± 99; rice: 77 ± 76; potato: 143 ± 105 g/day, respectively) surveys were not significantly different; (ii) consumption of drinking water estimated as 3.5 L/day for all the participants (Kumar et al., 2016). Due to this limitation the calculated As intake from water might not be representative of the exact exposure from water; (iii) other sources of As exposure not being considered, including but not limited to vegetables such as radishes and pulses (Samal et al., 2011), fish and shrimp (Giri and Singh, 2014) as well as indirect water consumption (Hossain et al., 2013). That said, the cereals, mainly wheat and rice, were the major food items consumed by the respondents providing an average 60% of the total calorie's intake. Therefore, biomarker measurements which could better reflect total As exposure should be considered in the future; (iv) blood pressure values being measured just two times with an interval of 30 min, which cannot wholly represent the entire 24-h pattern. However, the blood pressure value was measured with standard protocol and the observed relationship between hypertension indicators and some widely-accepted risk factors were in agreement with those of reported before (Owolabi et al., 2016), confirming the validity of the blood pressure measurements in this study; (v) a certain percentage of As concentrations in cooked rice, as well as wheat flour, drinking water and potato samples being imputed over actual analysis. Though the complete data with imputed concentrations was not significantly different from the original data and we assume that the imputation methods used in this study might not impact the As concentration levels in drinking water and different foodstuffs but using the original data, the sample size decreased to N = 80 and there was no significant association except for lowering of LDL with As_{water} (data not showed); (vi) unable to assess lifetime average As dose rate which may limit its ability to describe the long-term As exposure pattern. Consequently, future studies regarding time-weighted average As and thus lifetime As exposure should be considered.

Limitations regarding residual confounding issues should not be neglected as well. Though this study has already accounted for the effects of some well recognized predictors of either hypertension risks or As intake as potential confounders, the possibility of the confounding effects of some other important factors, especially some diet-related variables such as salt (Lelong et al., 2019) and fatty acid intake (Zhao et al., 2011), environmental exposure to lead and cadmium (Burroughs Peña and Rollins, 2017) genetic information (Hsieh et al., 2017), as well as metabolic differences that might influence As methylating capacity (Hernández et al., 2008) cannot be excluded. Finally, despite sampling being across and being representative of As exposed areas the generalizability is limited and should be dealt with caution given that the target population only included As exposed and didn't cover non-exposed areas or the whole state of Bihar.

Despite of these above-mentioned limitations, the advantages in this study should be highlighted. On one hand, this study quantified food consumption level and As concentration in different foodstuffs individually and directly, on the other, this study considered both the risk of general hypertension and the changes of LDL and HDL as indicators for hypertension risks, providing a more comprehensive view on the association between overall As exposure from drinking water and different food items, unveiling the importance of As intake from different exposure pathways on CVD risks. One thing that is worth noting is the significant positive association between LDL and As_{rice}, while such association was only weak for As_{food}. In the present study, participants with higher As_{food} were often found to have lower LDL (Fig. 1). This could be due to two reasons: (i) As exposure from food was mainly contributed by $As_{wheat\ flour}$; and (ii) we found a slight decrease in LDL levels with intake of wheat flour (Fig. 2, slope=−0.042). This could be

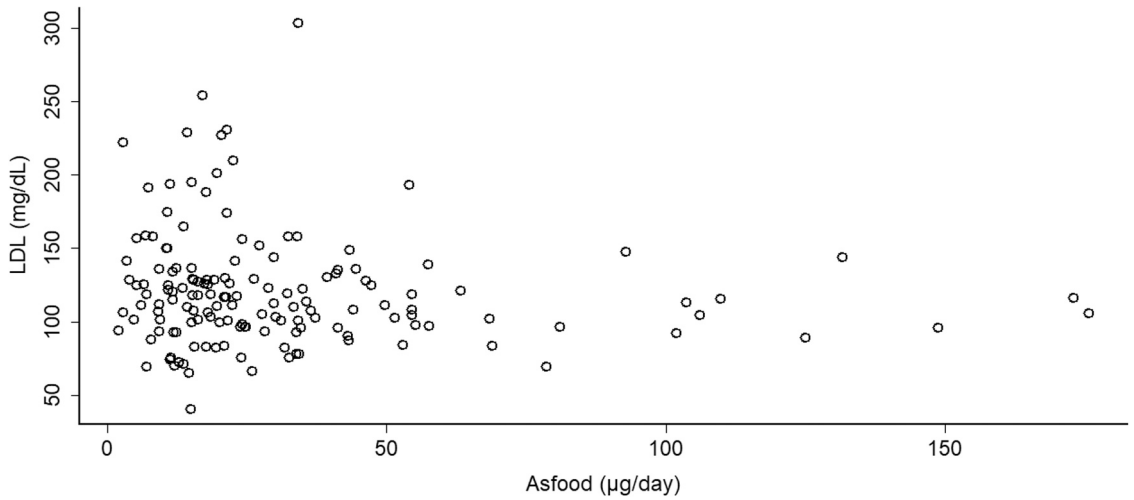

Fig. 1. Scatter plot of the association between As_{food} and LDL (As_{food}: daily arsenic intake from food (excluding drinking water) (μg/day); LDL: low-density lipoprotein (mg/dL)).

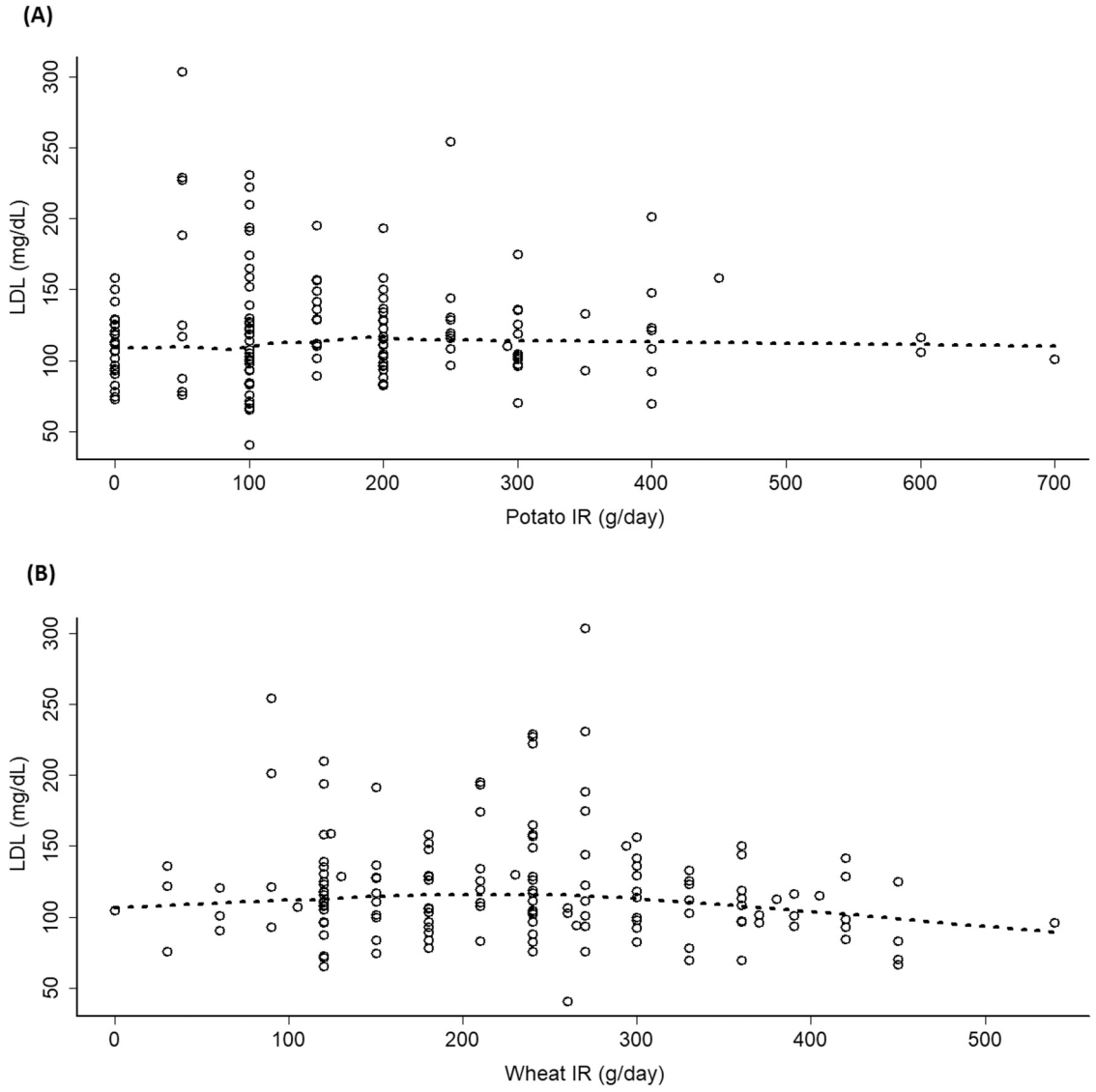

Fig. 2. Scatter plot of the association between (A) Potato IR, (B) Wheat flour IR and LDL (Potato IR: daily consumption level of potato (g/day); Wheat flour IR: daily consumption level of wheat flour (g/day); LDL: low-density lipoprotein (mg/dL); Smooth line was added with span for smooth = 0.5).

attributed to increased intake of fiber, vitamins and some trace minerals such as iron, magnesium, and zinc obtained from wheat flour. In fact, it has already been reported that regular consumption of whole grain foods was associated with a reduction in the incidence of CVD (Lang and Jebb, 2003) and whole grains high in viscous fiber could decrease LDL and blood pressure (Harris and Kris-Etherton, 2010).

Overall, this study quantified the individual level relations between As intake, not only from drinking water but also from few most consumed foods, and hypertension risks in As exposed areas of Bihar, India. Apart from a significantly positive relationship between As_{rice} and the changes of LDL, predisposing to increased CVD risks, this study did not find any significant positive correlation between hypertension risk and As exposure, in fact As_{total} was found to be associated with lower risks of general hypertension and higher levels of HDL and general hypertension was found to be marginally associated with lower As_{water}. Given the limitations mentioned above, especially the limited study design and confounding residual issues, better-designed larger scale prospective and case-control studies along with precise quantification of drinking water intakes, determination of As exposure using biomarkers, As speciation measurements, lifetime As exposure and more statistical power are required for better assessing such effects.

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CRediT authorship contribution statement

Lingqian Xu: Conceptualization, Methodology, Software, Writing – original draft, Writing – review & editing, Data Analysis, **Sidharth Suman**: Writing – review & editing, Data provision, **Pushpa Sharma:** Writing – review & editing, Data provision, **Ranjit Kumar:** Writing – review & editing, Data provision, **Shatrunjay Kumar Singh**: Writing – review & editing, Data provision, **Nupur Bose:** Writing – review & editing, Data provision, **Ashok Ghosh:** Writing – review & editing, Data provision, **Mohammad Mahmudur Rahman:** Supervision, Writing – review & editing, **David A. Polya:** Supervision, Writing – review & editing, **Debapriya Mondal:** Conceptualization, Methodology, Software, Supervision, Writing – review & editing, Data Analysis. All authors: Approval of the manuscript.

Declaration of Competing Interest

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

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ecoenv.2021.112572.

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