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Exploring the relationship between blood toxic metal(oid)s and serum insulin levels through benchmark modelling of human data: Possible role of arsenic as a metabolic disruptor

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ABSTRACT

The major goal of this study was to estimate the correlations and dose-response pattern between the measured blood toxic metals (cadmium (Cd), mercury (Hg), chromium (Cr), nickel (Ni))/metalloid (arsenic (As)) and serum insulin level by conducting Benchmark dose (BMD) analysis of human data. The study involved 435 non-occupationally exposed individuals (217 men and 218 women). The samples were collected at health care institutions in Belgrade, Serbia, from January 2019 to May 2021. Blood sample preparation was conducted by microwave digestion. Cd was measured by graphite furnace atomic absorption spectrophotometry (GF-AAS), while inductively coupled plasma-mass spectrometry (ICP-MS) was used to measure Hg, Ni, Cr and As. BMD analysis of insulin levels represented as quantal data was done using the PROAST software version 70.1 (model averaging methodology, BMD response: 10%). In the male population, there was no correlation between toxic metal/metalloid concentrations and insulin level. However, in the female population/whole population, a high positive correlation for As and Hg, and a strong negative correlation for Ni and measured serum insulin level was established. BMD modelling revealed quantitative associations between blood toxic metal/metalloid concentrations and serum insulin levels. All the estimated BMD intervals were wide except the one for As, reflecting a high degree of confidence in the estimations and possible role of As as a metabolic disruptor. These results indicate that, in the case of As blood concentrations, even values higher than BMD (BMDL): 3.27 (1.26) (male population), 2.79 (0.771) (female population), or 1.18 (2.96) μg/L (whole population) might contribute to a 10% higher risk of insulin level alterations, meaning 10% higher risk of blood insulin increasing from within reference range to above reference range. The obtained results contribute to the current body of knowledge on the use of BMD modelling for analysing human data.

1. Introduction

Metals and metalloids are broadly dispersed in nature, and their compositions fluctuate by location, resulting in variations in surrounding concentrations (Jaishankar et al., 2014; Wang et al., 2020). They are known to be widespread in lentic compartments (water, sediment, fishes, plants) as a consequence of both natural and manmade processes, causing dangerously high quantities of these substances in natural ecosystems (Meena et al., 2018; Rahman and Singh, 2019; Vareda et al., 2019). Metal (oid)s may be detected in a wide variety of items and consumer goods, including food, water, air, cigarette smoke, and alcoholic drinks (Pizent et al., 2012; Turner, 2019). Food is considered the

Abbreviations: cadmium (Cd), mercury (Hg); chromium (Cr), nickel (Ni); arsenic (As), Benchmark dose (BMD); inductively coupled plasma-mass spectrometry (ICP-MS), graphite furnace atomic absorption spectrophotometry (GF-AAS); lower confidence limit for the computed Benchmark dose (BMDL), upper confidence limit for the computed Benchmark dose (BMDU); Benchmark dose interval (BMDI), U.S. Environmental Protection Agency (US EPA); European Food Safety Authority (EFSA), World Health Organization (WHO); Dutch National Institute for Public Health and the Environment (RIVM), International Agency for Research on Cancer (IARC).

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principal route of intake for the majority of non-occupationally exposed people, but metal (oid)s can reach the human body by inhalation as well (Ejaz et al., 2007; Martí-Cid et al., 2008; Satarug et al., 2019). For example, smoking causes the inhalation of hazardous metals and metalloids, especially cadmium (Cd) and mercury (Hg), that preferentially partition into the smoke phase after burning (Afridi et al., 2008). It is crucial to note that both non-essential and essential metal (oid)s can be harmful to living organisms in specific levels (Vareda et al., 2019). Hence, the relationship between environmental exposure to arsenic (As), Cd, Hg, and lead (Pb), as well as nickel (Ni), chromium (Cr), cobalt, and antimony, and numerous human diseases has been extensively researched (Buha et al., 2018; Djordjevic et al., 2019; Wallace et al., 2020; Wallace and Buha et al., 2020; Živančević et al., 2021). Moreover, metal (oid)s pose a serious threat to human health, particularly considering that people are exposed to mixtures of numerous chemicals in their daily lives via different intake routes (Tsatsakis et al., 2016). Four of these metal (oid)s (As, Cd, Cr, and Ni) have even been identified as category 1 carcinogens by the International Agency for Research on Cancer (IARC), suggesting that they are detrimental to people (IARC, 2018a, 2018b, 2012).

Some of these toxic metal (oid)s have also been labelled as endocrine disrupting chemicals (EDCs), substances that, once present in the human body, interfere with the endocrine system's function, impersonating hormones and/or inhibiting their receptors (Kasonga et al., 2021; Nascimento et al., 2018). Several issues in this area of research are now being handled, such as developing methods for determining EDCs, limiting their low-dose consequences, the non-monotonic dose-response phenomenon (NMDR), as well as the applicability of the threshold paradigm (Goumenou et al., 2021; Roig et al., 2013). EDCs affect the entire body, having a deleterious influence on metabolism and altering cellular functions, further contributing to the development of thyroid diseases, infertility, diabetes, obesity, and various homeostatic disturbances, including insulin impairment (Baralić et al., 2022; Buha Djordjevic et al., 2021; Ghosh et al., 2022; Kasonga et al., 2021; Nascimento et al., 2018). Insulin-mediated glucose elimination varies greatly between populations, while insulin resistance can or cannot be reversed based on the scope of compensatory hyperinsulinemia (Yeni-Komshian et al., 2000). This lack of sensitivity can lead to glucose intolerance, high plasma triglyceride levels, low HDL concentrations, and hypertension, which, if not resolved, may ultimately lead to the development of type 2 diabetes mellitus (Reaven, 2004). The World Health Organization (WHO) predicted in 2016 that the worldwide incidence of diabetes mellitus will rise from 422 million cases in 2014 to 592 million cases by 2035 (Li et al., 2019; Stojanoska et al., 2017; WHO, 2016). In addition to genetic and lifestyle variables, the influence of environmental factors on type 2 diabetes mellitus development has recently been acknowledged (Ding et al., 2021; Zhou et al., 2021), while, throughout the last two decades, EDCs have gained increasing relevance in the progression of this disease (Sargis and Simmons, 2019; Stojanoska et al., 2017; Zhang et al., 2013). EDCs linked with insulin resistance/DM development include both natural and manmade inorganic and organic compounds, such as polychlorinated biphenyls, organochlorine insecticides, phthalates, bisphenol A, as well as toxic metals (Buha et al., 2020; Sargis and Simmons, 2019). These substances have been proposed to affect whole-body glucose homeostasis and/or modify insulin secretion or action (Weiss et al., 2022). It is theorised that the build-up of toxic metal (oid)s in human body causes decreased functioning and apoptosis of β-cells, as well as interferences with insulin intracellular signalling pathways in adipocytes and muscle cells, causing the disruption of the glucose uptake (Wang et al., 2020). However, gender differences related to the exposure to hazardous metal (oid)s have also been investigated and verified in various animal/human studies, confirming different mechanism of toxicity depending on the studied sex (Jacquet et al., 2018; Maull et al., 2012; Farkhondeh et al., 2019; Sobocanec et al., 2003; Behl and Lezoualc'h 1998; Jacquet et al., 2018) as well as differences in measured metal concentrations (Yamauchi et al., 1992; Noor et al., 2019).

In recent years, regulatory recognised technique for dose-response analysis, the benchmark dose (BMD) approach, has been utilised to produce health-based guidelines for chemicals in human health risk assessment. It has been recommended as a substitute for the no observed adverse effect level (NOAEL). The BMD approach uses chemical dose-response modelling to predict the extent of a potential harmful effect in the researched population given a certain exposure level (Hardy et al., 2017). Whereas the NOAEL method yields the maximum tested dosage with no adverse effects in a particular experiment, BMD is a quantitatively computed level that indicates variability in the pace of reaction to an unfavourable impact (Pink et al., 2020). Although it might be used in animal studies, scientists are highly urged to utilise it in the analysis of epidemiological data sets (Hardy et al., 2017), which has been recommended by both the U.S. Environmental Protection Agency (US EPA) and European Food Safety Authority (EFSA) (Haber et al., 2018). Using this method, in a prior study, we sought to assess the dose-response association between Cd concentrations in breast tissue and blood estradiol levels in 96 women (Buha Djordjevic et al., 2021). Additionally, we performed a dose–response modelling between blood Cd, As, Hg, Ni, and Cr and serum reproductive hormones in men, obtaining the dose-response relationships for all the investigated hormone-metal (oid)s pairs (Baralić et al., 2022). Finally, we demonstrated that measured metal (oid)s increased the risk of testosterone level changes in women compared to median values seen in the general population (Marić et al., 2022). Given the limited number of studies evaluating human data using the BMD approach, these findings may be useful for future dose-response analyses of data obtained from such research.

Having in mind our hypothesis that the link between toxic metals (Cd, Hg, Ni, Cr)/metalloid (As) and insulin impairment might exist and that the connected changes might be gender-specific, in the current study, by applying correlation analysis and BMD methodology, we aimed to investigate gender-related differences and the dose-response relationship between these substances and serum insulin level in samples collected from a cross-sectional study in population from Belgrade, Serbia.

2. Material and methods

2.1. Study population

This cross-sectional study was conducted from January 2019 to May 2021 and samples were collected at health care institutions in Belgrade, Serbia. Participants (n = 435; age ≥18) comprised of 217 men and 218 women from five different groups:

- healthy volunteers (136)
- prostate/testicular cancer patients (104),
- breast cancer and benign breast dysplasia patients (96),
- pancreatic cancer patients (22)
- thyroid and metabolic disorders patients (77)

All groups were taken into consideration together and later referred to as "general population" throughout all the stages of our investigation considering our aim to evaluate the potential correlations and dose-response relationships between toxic metal (oid)s levels in blood and serum insulin in the entire investigated population. The individuals were not occupationally exposed to the examined toxic metal (oid)s and had a median age of 46 (min - 18; max - 94). Blood sampling in all oncology patients was performed prior surgery and prior starting therapy to avoid the influence of any kind of treatment on insulin level. Blood was sampled in the morning after 8–12 h fasting period. Samples for insulin level measurement and metal analysis were collected at the same time, in additive-free vacutainers for serum separation and K2-EDTA vacutainers, respectively. After the venepuncture, every sample was marked with an identification code, the participant's name and

surname, and the date and time of the blood collection. Everyone who took part in the investigation completed a written consent form. The research was planned and carried out in accordance with the Declaration of Helsinki's Ethical Guidelines and appropriate approvals were obtained:

- Scientific and Ethical Committee of the University Hospital Medical Center Bežanijska kosa (licence number 9740/3)
- Ethical Committee of the Clinical Center of Serbia (licence numbers 526/9, 31/8, and 579/19)
- School of Medicine University of Belgrade (licence number 1322/XII-5)
- Ethics Committee for Biomedical Research, University of Belgrade – Faculty of Pharmacy (license number 650/2 and 288/2)

2.2. Sample preparation and metal (oid)/insulin analysis

Toxic metal/metalloid assessment was performed using an aliquot of blood in metal-free Vacutainer tubes with K_2EDTA (BD Vacutainer® system). The samples were mineralised for toxic metal (oid)s determination in the microwave oven (Milestone START D, SK-10 T, Milestone Srl, Sorisole, Italy) with 7 ml % HNO_3 and 1 ml % H_2O_2, while the following program was applied:

1. Heating to 180 °C (15 min)
2. Keeping the temperature at 180 °C (15 min)
3. Ventilation (15 min)

After chilling, samples were filled into a final volume of 10 ml. Together with the samples, a blank comprising of 7 ml of 65% HNO_3 and 1 ml of H_2O_2 was tested. Cd analysis was performed using graphite furnace atomic absorption spectrophotometry (AAS GTA 120 graphite tube atomizer, 200 series AA, Agilent technologies, Santa Clara, CA, USA). The ICP-MS technique (ICP-MS 7700, Agilent technologies, Santa Clara, CA, USA) was used to determine As, Hg, Cr, and Ni. Both AAS and ICP-MS accuracy were confirmed using standard reference material (SRM) whole blood Level 2 (Seronorm TM, Sero, Billingstad, Norway). SRM preparation and analysis followed the same technique as EDTA-blood samples. The trueness varied from 89.5 to 103.2% for Cd, 97.3–114.7% for As, 96.5–107.2% for Hg, 91.6–112.7% for Cr, and 91.9–106.2% for Ni. The limit of detection (LoD) was 0.013, 0.0045, 0.0055, 0.0035 and 0.0255 μg/L for Cd, As, Ni, Cr, Hg.

For insulin determination, blood was collected in additive-free vacutainers. Following blood coagulation (20 min; room temperature), serum was separated by centrifugation (3000 g for 30 min). Insulin was determined in serum samples was outsourced and performed in accredited laboratory by standard tests and procedures by electrochemiluminescence immunoassay "ECLIA" and commercial reagents on a Cobas e411 analyser (Roche Ltd, Switzerland). IRP WHO Reference Standard 66/304 was used to standardise this method (NIBSC). Precision was assessed using Elecsys reagents and pooled human sera in a CLSI (Clinical and Laboratory Standards Institute) modified procedure (EP5A): 6 times daily for 10 days (n = 60); repeatability on MODULAR ANALYTICS E170 analyser, n = 21.

2.3. Benchmark dose-response modelling

BMD modelling was performed using the PROASTweb 70.1 application (https://proastweb.rivm.nl/; Dutch National Institute for Public Health and the Environment, RIVM) in line with the software requirements and EFSA guidelines (Hardy et al., 2017). Dose-response analysis was conducted between the metal/metalloid concentrations (Cd, As, Hg, Ni, Cr) and insulin level. BMD specifies the dosage interval equivalent to a predetermined BMR (often 5% or 10%), whereas BMDL represents the lower confidence limit for the computed BMD (Hardy et al., 2017). To obtain a level of toxic substance that is unlikely to cause harmful effects on human health, a BMDL value is necessary as a reference point. A BMDU (upper limit of BMD reliability) is also required to establish a BMDU/BMDL link and present BMD interval as the final result of the BMD analysis, which is highly recommended (Edler et al., 2014).

Settings applied for the software analysis were:

- Data type: quantal (0 – within the reference range, 1 – outside the reference range)
- Insulin reference range: 2.6–24.9 μU/ml
- Models used in the averaging approach:
  two stage
  log-logistic
  Weibulllog-probabilistic
  gamma exponential
  Hill
- Number of bootstrap runs: 200
- Benchmark response (BMR): 10%

In the instance of quantal response, BMR is stated as extra risk - an absolute change in frequency of response (additional risk in percentage, in this case – 10%) divided by the non-affected proportion in the control group (100 minus the background response in percent) (Hardy et al., 2017). Model averaging (i.e. fitting all available models) is used by the programme to provide the BMD interval (BMDI) as the final results (Hardy et al., 2017) and is recommended by the EFSA scientific committee instead of single model investigations because it adjusts for model and data errors (EFSA, 2017; Hardy et al., 2017). By EFSA and RIVM consideration, after 200 bootstrap iterations the uncertainty in the confidence interval is around 10%, which is adequate for risk assessment (Slob, 2018).

2.4. Statistical analyses

All data were analysed with Graph Pad Prism 6 software (GraphPad Software Inc, San Diego, USA). After testing the normality of the distribution, homogeneity, and variance, Spearman correlation analysis was performed to investigate the association between toxic metal (oid)s (Cd, As, Hg, Cr, Ni) concentrations measured in blood samples of the population from Serbia and serum insulin level.

3. Results

Age (median with range and geometric mean value) is shown in the Supplementary Table 1 for each group of participants of the study, presented for both genders, and individually, for male and female

Table 1
Descriptive data for toxic metal (oid)s (Cd, As, Hg, Cr, Ni) measured in blood samples of male, female and whole investigated population from Belgrade, Serbia.

Number of participants	Male population	Female population	Whole population
Metal/metalloid	***N* = 217**	***N* = 218**	***N* = 435**
Cd (μg/L)	1.476 (0.032–4.280)	1.962 (0.030–6.448)	1.800 (0.030–5.801)
As (μg/L)	0.971 (0.004–17.491)	10.443 (0.023–29.526)	2.170 (0.004–25.670)
Hg (μg/L)	5.219 (0.022–48.892)	3.444 (0.022–30.764)	3.986 (0.022–39.220)
Cr (μg/L)	1.324 (0.004–11.522)	1.060 (0.004–44.904)	1.210 (0.004–18.855)
Ni (μg/L)	7.609 (0.005–48.035)	8.278 (0.005–87.202)	8.054 (0.005–62.807)
Insulin (μU/ml)	15.38 (9.988–19.88)	12.30 (7.380–35.13)	14.06 (7.980–24.62)

The results are shown as the median and range (5–95 percentile).

individuals.

In Table 1, parameters of descriptive statistics (median and range (5–95 percentile)) are presented for each of the 5 measured metal (oid)s (Cd, As, Hg, Cr, Ni) for male, female, as well as the whole investigated population. As seen in the table, when all participants were considered, regardless the gender, the highest median was obtained for Ni. This was also the case for the male population, where median for Ni was the highest. On the other hand, the highest median value in female population was calculated for As. Higher insulin median values were determined for male population when compared to the population as a whole and female population.

After Spearman's correlation analysis (serum insulin level vs. blood toxic metal (oid)s concentrations), no correlation was observed for toxic metal/metalloid concentrations and insulin level in male population. On the contrary, in female population, strong positive correlation was observed for As and Hg, while strong negative correlation was observed for Ni. The same observations were made when the whole population was regarded (Table 2).

By applying BMD-modelling, the quantal dose-response connection between the levels of five chosen metal (oid)s (Cd, As, Hg, Cr, Ni) in blood and serum insulin levels was investigated. The dose-response connection was verified for all the examined metal/metalloid-insulin pairings. Model averaging was done in 200 iterations using the bootstrap method, and models were weighted using the Akaike information criteria (AIC) (Jensen et al., 2019). The findings of different models are merged and appraised according to model fit in this technique, so that models that are more closely connected to the data contribute more to the evaluation. Table 3 shows the model weights for all the analysed variables, which influence the strength of fit of multiple models to a dose–response data.

The BMR is defined for quantal data as a rise in the prevalence over background, and the confidence interval for the estimated background shows how well it could be established considering the data presented (EFSA, 2014). The model averaging results were denoted by BMDL and BMDU, which represent the lower and upper boundaries of the 95 percent confidence interval, respectively. The collected results are shown in Table 4. As seen in the table, all of the intervals were wide apart from As, which was less than a factor 10 wide, indicating a high level of conviction in the estimations (Vieira Silva et al., 2021). The obtained wide BMDI ranges might be attributable to model statistical uncertainties and/or inadequate data. (Hardy et al., 2017).

By using the PROAST software, the creation of the plot with bootstrap curves for male, female, as well as the whole investigated population was conducted, while the final results of the model averaging are presented in Fig. 1, Fig. 2 and Fig. 3, respectively.

4. Discussion

Even very low doses of EDCs were found to affect endocrine function, and these compounds can occasionally express NMDR, meaning that maximum responses may occur at incredibly low and exceptionally high doses, as well as in the middle of the dosage range (Lagarde et al., 2015; Renieri et al., 2017; Vandenberg, 2014). This illustrates that high-dose animal studies cannot always be used to predict what kind of biological reaction low-dose investigations would elicit. Furthermore, animal toxicological studies commonly test a single chemical via only one route of administration in limited dosing regimen, sometimes with only a single dosage, and over a brief span of time (Goumenou et al., 2021; Hernandez et al., 2019).

Thus, having in mind that epidemiologic research can study realistic exposure routes and durations and offers important information on the link between environmental exposures and human health outcomes, the present study was conducted to elucidate the relationship between toxic metal (oid)s (Cd, As, Hg, Cr, Ni) concentrations and serum insulin levels in samples collected from a study in the population living in Serbia, but also explore gender-specific differences. No correlation was observed between toxic metal (oid)s concentrations and insulin level in male population, while, in female population (which also influenced the outcomes in the whole population), strong positive correlation was observed for As and Hg, and strong negative correlation for Ni. Gender specific differences were explored and confirmed in several animal/human studies. For example, Jacquet et al. (2018) investigated gender-specific differences in rats after chronic and low Cd exposure and found that female animals exhibited a significant increase of both fasting and glucose-stimulated plasma insulin. These authors suggested that gender differences could be attributed to the difference in the antioxidant response or to the scavenging effect of oestrogens (Sobocanec et al., 2003; Behl and Lezoualc'h 1998; Jacquet et al., 2018). This could also be the case for As, for which production of oxidative stress, inflammation, apoptosis are considered the main mechanisms behind its connection with insulin resistance and diabetes mellitus, which could further be linked with interferences of glucose uptake and transport, gluconeogenesis, adipocyte differentiation, and Ca^{2+} signalling (Maull et al., 2012; Farkhondeh et al., 2019; Tseng, 2004). Population-based studies have demonstrated sex-dependent differences regarding As-associated diabetes mellitus, while women were found to have higher standardized mortality ratios and hazard ratios for diabetes mellitus-related death and disease development in association with As (D'Ippoliti et al., 2015; Lewis et al., 1999; Chiu et al., 2006; Martin et al., 2017). These findings have been substantiated by *in vivo* animal studies where female rodents were more susceptible than male to As diabetogenic effects (Palacios et al., 2012; Shukla et al., 2021). For example, after mice

Table 3
The models used in model averaging and model weights for all the investigated insulin-metal pairs.

	Model	Cd	As	Hg	Cr	Ni
Insulin	two.stage	0.1502	0	2.00E-04	0.1506	0.1501
	log.logist	0.1502	0	0.1655	0.1506	0.1501
	Weibull	0.1502	0	0.0994	0.1476	0.1279
	log.prob	0.1502	1e-04	0.1497	0.1506	0.1501
	gamma	0.1676	0	0.046	0.1491	0.1345
	EXP	0.1579	0.7807	0.4922	0.1258	0.1372
	HILL	0.0738	0.2192	0.0469	0.1258	0.1501

Table 2
Results of Spearman's correlation analysis between toxic metal/metalloid (Cd, As, Hg, Cr, Ni) measured in blood samples of male, female, as well as the whole investigated population from Belgrade, Serbia and serum insulin level.

	Parameter	Insulin vs. Cd	Insulin vs. As	Insulin vs. Hg	Insulin vs. Cr	Insulin vs. Ni
Male population	r	−0.1329	−0.08933	−0.1354	−0.1699	−0.121
	95% confidence interval	−0.2999 to 0.04196	−0.2611 to 0.08792	−0.3086 to 0.04646	−0.3395 to 0.01041	−0.2907 to 0.05604
	P value	0.1244	0.3084	0.1322	0.0571	0.1669
Female population	r	0.07571	0.3197	0.3908	0.0826	−0.3288
	95% confidence interval	−0.06749 to 0.2158	0.1786 to 0.4480	0.2381 to 0.5247	−0.1042 to 0.2638	−0.4592 to −0.1845
	P value	0.2854	<0.0001	<0.0001	0.3718	<0.0001
Whole population	r	−0.05021	0.2699	0.213	0.006782	−0.2525
	95% confidence interval	−0.1515 to 0.05217	0.1699 to 0.3644	0.1032 to 0.3176	−0.1107 to 0.1241	−0.3503 to −0.1492
	P value	0.3221	<0.0001	0.0001	0.9075	<0.0001

Table 4
Benchmark dose (BMD) confidence intervals (BMDL - BMDU) and insulin concentration determined in blood samples from male, female, as well as the whole investigated population of Belgrade, Serbia: PROAST web 70.1 software, https://proastweb.rivm.nl; model averaging approach based on quantal BMR of 10%.

	Male population			Female population			Whole population		
Metal	BMDL	BMD	BMDU	BMDL	BMD	BMDU	BMDL	BMD	BMDU
Cd (μg/L)	0.134	161000.07	322,000	0.00717	17,600	35,200	0.00139	11,100	22,200
As (μg/L)	1.26	3.27	5.27	0.771	2.79	4.81	1.18	2.96	4.74
Hg (μg/L)	0.322	140.66	281	0.0113	2.29	4.57	0.000416	17.95	35.9
Cr (μg/L)	0.0619	457500.03	915,000	0.000386	246,500	493,000	8.62e-06	19,000	38,000
Ni (μg/L)	0.147	1005000.07	2,010,000	0.119	1310000.06	2,620,000	0.00119	620,000	1,240,000

BMDL: lower 95% confidence limit of the Benchmark dose; BMD: Benchmark dose; BMDU: upper 95% confidence limit of the Benchmark dose.

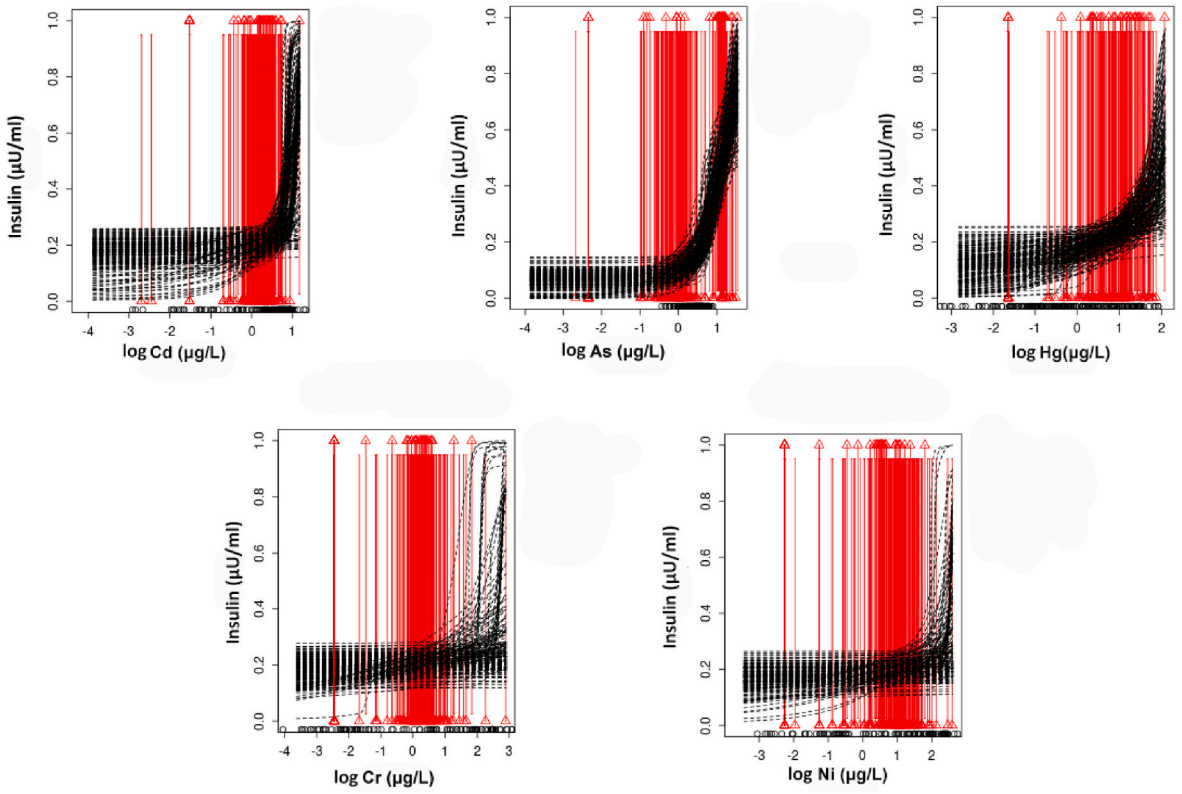

Fig. 1. Bootstrap curves based on the model averaging technique (number of runs: 200). The insulin serum level (U/ml) dependence on the concentrations of Cd, As, Hg, Cr and Ni determined in blood samples from the male population of Belgrade, Serbia: PROASTweb 70.1 software, https://proastweb.rivm.nl; quantal BMR of 10%.

exposure to environmental As dosages (0, 0.04, and 0.4 mg/kg) from 15 days before conception to delivery significant increase in weight gain and relative adiposity occurred only in female offspring due to fat deposition in the inguinal fat depot, as well as a significant impairment in insulin sensitivity and glucose tolerance (Shukla et al., 2021). The influence of oestrogens on sex variations in As methylation ability has been hypothesised as a potential explanation of sex differences in arsenic poisoning outcomes. In human body, inorganic As is metabolised to monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA). Intermediate reduced forms of the methylated metabolites MMA (III) and DMA (III) are extremely hazardous and may contribute to As intoxication (Ferrario et al., 2016). Furthermore, Chung et al. (2015) hypothesised that blood Hg concentration was independently related with an increased risk of metabolic syndrome in men after investigating sex differences in the association between blood Hg content and the higher likelihood of metabolic syndrome in Korean men and women (Chung et al., 2015).

Epidemiological data had been used in various studies to suggest a relationship between toxic metals and insulin resistance/metabolic syndrome/diabetes mellitus. In a study including 313 men aged 50–75 years, Rotter et al. (2015) sought to find correlations between the level of toxic metal/bioelement concentrations and metabolic syndrome. All of the mean metal (oid) concentrations measured in their study (5.60 μg/L Cd, 16.7 μg/L Hg, 15.3 μg/L As and 4.76 μg/L Cr) were slightly higher in comparison with our findings. Furthermore, contrary to our results, these authors found negative correlation between measured insulin and Cd (Rotter et al., 2015). Another research including 39,156 individuals was conducted using the data from the US National Health and Nutrition Examination Survey (NHANES) 2011–2018. In this study, Cd and Hg mean concentrations were slightly lower than in our study (Cd (0.38 μg/L), and Hg (1.023 μg/L)), while these metals were associated with reduced chances of metabolic syndrome. (J. J. Zhou et al., 2022). On the contrary, in a study comprising of 1262 women, aged 45–56, relationship between 15 metals (including Cd, As, Hg and Ni) and increased risk of diabetes mellitus was suggested (Wang et al., 2020). Furthermore, results of a study including 68 healthy and 76 diabetic type 2 pregnant women (age range 30–40 years) and their infants, demonstrated elevated As and Cd, and Pb levels in all biological samples of diabetic women and their babies, suggesting that increased levels of these metal (oid)s may play a role in diabetes mellitus

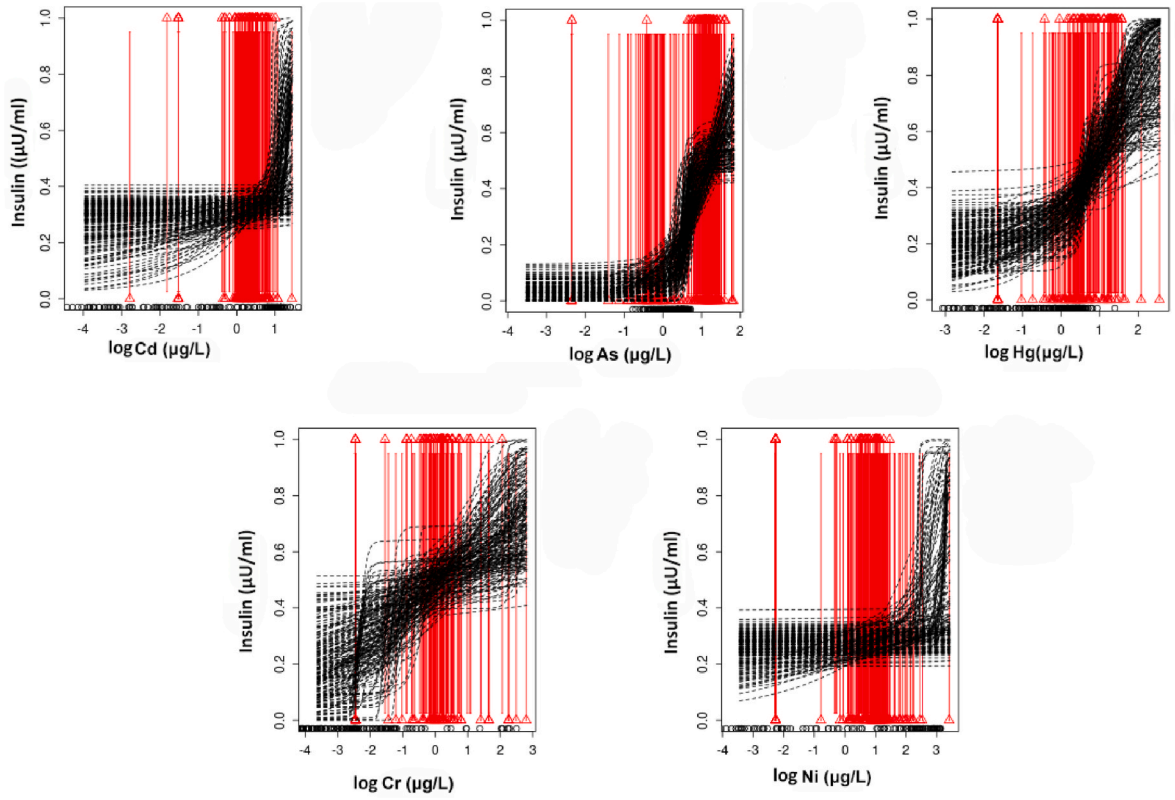

Fig. 2. Bootstrap curves based on the model averaging technique (number of runs: 200). The insulin serum level (U/ml) dependence on the concentrations of Cd, As, Hg, Cr and Ni determined in blood samples from the female population of Belgrade, Serbia: PROASTweb 70.1 software, https://proastweb.rivm.nl; quantal BMR of 10%.

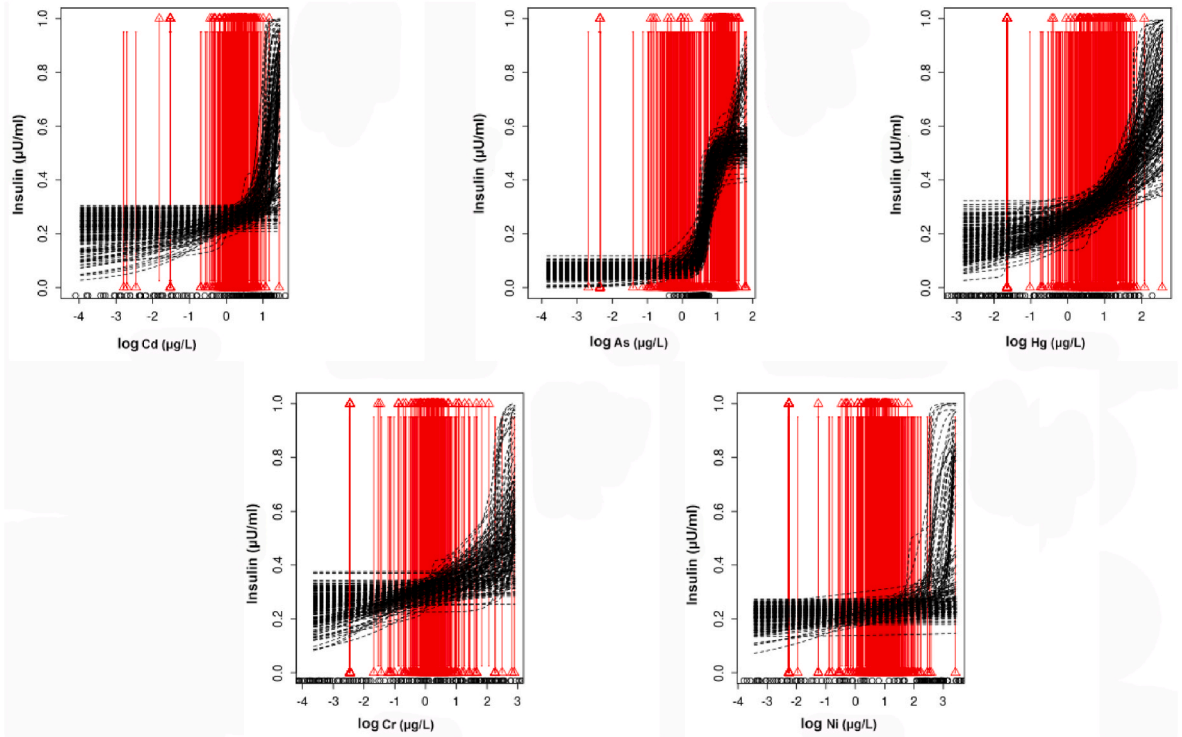

Fig. 3. Bootstrap curves based on the model averaging technique (number of runs: 200). The insulin serum level (U/ml) dependence on the concentrations of Cd, As, Hg, Cr and Ni determined in blood samples from the whole investigated population of Belgrade, Serbia: PROASTweb 70.1 software, https://proastweb.rivm.nl; quantal BMR of 10%.

aetiology. Measured As and Cd blood concentrations in mothers were comparable (in the case of Cd), or lower (in the case of As) compared to those measured in women population in our study (Kolachi et al., 2011). A link between urine total arsenic and insulin resistance was also confirmed in a study including 815 people aged 20–79 years who took part in the 2015–2016 NHANES, (M. M. Zhou et al., 2022).

Another intriguing finding obtained in the current study was the difference between measured As concentration in female in comparison with male participants. Namely, mean As concentration was notably higher in female (10.443 μg/L) in comparison with the male population (0.971 μg/L). Conflicting results were obtained in various studies around the world regarding this issue, in which As concentrations in men was either higher, comparable, or lower than the one measured in women. For example, Yamauchi et al. (1992) measured 0.8 μg/L in men and 0.6 μg/L in women in a group of 35 healthy volunteers. In a cross-sectional study including 63 volunteers, Noor et al. (2019), on the other hand, found slightly higher As concentrations (0.081 μg/L) in women when compared to men (0.069 μg/L), although much lower than those measured in the current investigation. High As values measured in our study might be connected to higher exposure, which could occur via drinking water and food, in particular vegetables and rice, whereas gender-related arsenic exposure might occur mostly in particular industries (e.g. mining and smelting), wood preservation (primarily men), and technological industries that use gallium and indium arsenide (often women) (Vahter et al., 2007). Exposure through drinking water is of particular importance for Serbian population having in mind that As concentrations were found to surpass Serbian and European drinking water As regulations in various regions, particularly Vojvodina, while As levels also varied greatly amongst the supply systems (Jovanovic et al., 2011).

In most of the studies exploring the connections between toxic metal (oid)s and insulin level/diabetes mellitus multivariable linear regression and correlation analysis was most usually employed to examine the link amongst hazardous metals and various endpoints, which differs from the additional BMD analysis method utilised in the current study. PROAST software may be used to analyse the data from the epidemiological research to generate findings based on the link between the toxic agent's internal dose and measurable effects. However, BMD approach studies on human data are still rather scarce. One of the studies that employed the BMD concept in the context of human toxic metal exposure focused on renal failure and attempted to discover the relationship associated to Cd exposure by calculating BMDL values of Cd in urine for the selected renal disfunction biomarkers (Jin et al., 2004). Similarly, Lin et al. (2008) sought to find the connection between Pb concentration and biomarkers of renal damage in individuals occupationally exposed to Pb (Lin et al., 2008). Shi et al. (2021) established a positive correlation for urinary Cd and type 2 diabetes mellitus in a research focusing on NHANES data from 1999 to 2006 (Shi et al., 2021).

In the present study, we indicated that moderate internal doses of toxic metal (oid)s are associated with a greater risk of modified insulin levels, which was obtained using BMD analysis of human data. Quantitative associations between blood metal/metalloid concentrations and serum insulin levels were present for all the measured toxic metal (oid)s and insulin level in the samples from the population. However, all the estimated BMD intervals were wide with BMDU/BMDL ratio higher than 10, except for the one for As, which was less than a factor 10 wide, indicating a high level of certainty in this estimation. These results indicate that, in the case of As blood concentrations, even values higher than BMD (BMDL): 3.27 (1.26) (male population), 2.79 (0.771) (female population), or 1.18 (2.96) μg/L (whole population) might contribute to a 10% higher risk of insulin level alterations, meaning 10% higher risk of blood insulin increasing from within reference range to above reference range. Furthermore, apart from the male population, the obtained BMDL values were lower than the calculated medians for As, which were 0.971, 10.443 and 2.170 μg/L for male, female and whole population, respectively. These values were also comparable or even lower than the mean As values measured in other aforementioned studies (Rotter et al., 2015; Kolachi et al., 2011).

Wang et al. (2015) proposed metabolic disturbance as a key mechanism driving the toxicity of prolonged As exposure, suggesting that aberrant glucocorticoid/glucocorticoid receptor signalling might be connected to substantial metabolic dysfunction, such as obesity, insulin resistance, and type 2 diabetes (Wang et al., 2015). Furthermore, by analysing transcriptome datasets obtained after exposing different human cells to various heavy metal (oid)s (As, Cd, Cr, Hg, Ni, iron, and vanadium), Fatema et al. (2021) found that As had the most profound impact on genes involved in the cellular metabolic pathways. Additionally, they proposed that PPAR downregulation in hepatic tissues might be responsible for As diabetogenic effects (Fatema et al., 2021). Together with our results, all of these data point to this metalloid as a possible endocrine or, to be more precise, metabolic disruptor.

However, in our study, it is questionable if the 10% risk increase for changes in hormone levels, which may be regarded non-disease-specific indicator, is physiologically meaningful, particularly as their serum levels are impacted by a range of factors, such as other environmental influences, hereditary factors, smoking habits, alcohol intake, etc. (Kempenaers et al., 2008). Hence, our upcoming animal experimentation will be designed to determine whether low metal (oid)s doses (extrapolated from acquired human data) may cause negative effects under controlled conditions by exploring various potential mechanisms of toxicity. Another limitation of the current study includes not taking into account mixture effects in the BMD analysis and considering only binary pairs at a time (single metal (oid)-insulin). PROAST was the main tool applied in our study for BMD analysis. The most recent version of PROAST software has the ability to examine the dose-response relationship of mixtures. To do this, doses associated to chemical agents in a mixture experiment, as well as the doses of the individual compounds, are entered into the programme. The model is applied to all chemicals in one fit by including mixture components as covariates in the dose-response analysis (Van Der Ven et al., 2022). However, this form of analysis is presently only applicable for controlled toxicity testing and not in epidemiological studies. Furthermore, having in mind that this study is a cross sectional design, the temporal relationship between the result and the exposure cannot be established considering that they are examined at the same time. Another limitation that should be considered is that factors other than the insulin level which should be considered as a measure of insulin resistance (e.g. blood glucose level, serum cholesterol, HDL, LDL, etc.) (Borai et al., 2007) were not measured, as well as that information about the participants other than age and gender was not considered in the current study, whilelack of consideration of covariates/confounders may, in a certain sense, bias the results.

5. Conclusion

In the current study, four metals (Cd, Hg, Cr, Ni) and metalloid As, were found associated to a greater risk of significant changes in insulin level in samples from the investigated population from Serbia. After the BMD analysis, the existence of a dose-response association between all the measured metal (oid)s and insulin (most notably As) was verified, shedding the light on the possible role of As as a metabolic disruptor. Indeed, the BMDU/BMDL ratio was lowest for As-insulin pair, suggesting a high degree of confidence in the calculations. The results indicated that levels of As lower than those measured in the population from Serbia might contribute to a 10% higher risk of insulin level alterations, namely increasing from within reference range to above reference range. These findings are intriguing enough to merit additional research into As possible role as a metabolic disruptor, as well as the possibility of employing the recommended BMD approach to analyse human data in the future.

Declarations

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Authors' contributions

Danijela Đukić-Ćosić: Conceptualization, Visualization, Formal analysis, Investigation, Writing - Original Draft; **Katarina Baralić**: Formal analysis, Investigation, Data Curation, Writing - Original Draft; **Dragana Javorac**: Investigation, Formal analysis, Data Curation; **Zorica Bulat**: Supervision, Writing - Review & Editing; **Marijana Ćurčić**: Writing - Review & Editing, Data Curation; **Biljana Antonijević**: Methodology, Writing - Review & Editing; **Vladimir Đorđević**: Investigation, Data Curation; **Aleksandra Repić**: Investigation, Formal Analysis; **Aleksandra Buha Djordjevic**: Conceptualization, Visualization, Data Curation, Writing - Review & Editing, Supervision, Funding acquisition, Project administration.

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.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2022.114283.

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