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Influence of dietary patterns on urinary excretion of cadmium in an Italian population: A cross-sectional study

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ABSTRACT

Introduction: Cadmium is a toxic heavy metal with detrimental effects on human health. Apart from smoking and occupational factors, diet is the main source of cadmium. However, the relation between adherence to so-called "healthy" dietary patterns and cadmium exposure has not been investigated in detail. In this study, we aimed at assessing such association in a Northern Italian population.

Methods: Using a cross-sectional study design, we investigated a population of non-smokers aged 30–60 years in the period 2017–2019. Each subject completed a validated food frequency questionnaire (FFQ) in order to estimate adherence to four dietary patterns, namely the Dietary Approach to Stopping Hypertension-DASH diet, Greek Mediterranean Index-GMI, the Italian Mediterranean Index-IMI, and the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet. We collected a fasting morning urinary sample to measure urinary levels of cadmium and cotinine. The association between increasing adherence to dietary patterns and cadmium exposure was evaluated using a cubic spline regression non-linear model and adjusting for relevant confounders (age, sex, body mass index, urinary cotinine levels, intake of fiber, and alcohol).

Results: We recruited 137 participants (males/females: 62/75) with median (interquartile range-IQR) age of 47 (IQR: 43–53) years. Median scores for the investigated dietary patterns were 24 (IQR: 21–28), 4 (IQR: 3–6), 4 (IQR: 3–5), and 7.5 (IQR: 6.5–8.5) for DASH, GMI, IMI and MIND diets, respectively. The median urinary cadmium level was 0.21 μg/L (IQR: 0.11–0.34 μg/L). Spline regression analysis showed an inverse linear association between increasing adherence to the DASH and MIND diets and urinary cadmium levels, reaching a plateau at high adherence scores, approximately > 25 and > 9 for DASH and MIND diets, respectively. An increase of cadmium exposure with increasing MIND score also emerged. Conversely, the association was almost null for IMI, and slightly positive for GMI.

Conclusions: The present findings suggest that increasing adherence to the DASH and MIND diets are associated with decreased cadmium levels only at moderate level. Overall, these results indicate that public health strategies, including the decrease of cadmium contamination in healthy foods should be implemented.

1. Introduction

The last decades showed an increased worldwide prevalence of obesity and its consequences related to general inflammation, such as diabetes, non-alcoholic fatty liver disease, cardiovascular diseases (CVDs) and dementias; and they are thought to be on the rise [1–4].

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Indeed the prevalence of obesity nearly tripled between 1975 and 2016 all over the world [5]. Nowadays, low- and middle-income countries are the most affected, with a major concern among children and adolescents [6]. These trends could be caused by a transition to a Western-style dietary pattern and an increase in sedentary behavior [7].

Dietary patterns have been shown to play a crucial role in human health, in particular through modulation of immune system, inhibition of oxidative stress and inflammation [8–10]. Three well-known dietary patterns that have been extensively investigated are the DASH (Dietary Approaches to Stop Hypertension) diet, Mediterranean diet indexes, and the MIND (Mediterranean-DASH Intervention for Neurodegenerative Delay) diet.

The DASH diet emphasizes consuming fruits, vegetables, whole grains, low-fat dairy, fish, beans, nuts, vegetable oils, and white meat while limiting fatty meats, saturated and trans fats, salt, and sugar. It is usually associated with other lifestyle changes, such as sodium restriction [11]. The DASH diet was initially developed to help individuals with hypertension reduce their blood pressure, but further research has shown that it can also reduce mortality from heart disease, stroke, and cancer [12].

The Mediterranean diet is a plant-based eating plan that contains a larger daily intake of whole grains, olive oil, fruits, vegetables, legumes, nuts, herbs, and spices. Foods like animal proteins are eaten in smaller quantities, with the preferred animal protein being fish and seafood [13]. The Mediterranean diet has been associated with numerous health benefits, including reduced risk of overall mortality, cardiovascular diseases, coronary heart disease, myocardial infarction, overall cancer incidence, neurodegenerative diseases, and type 2 diabetes [14].

In recent years several studies have shown that the MIND diet can reduce the risk of developing cognitive impairment and Alzheimer's disease [15]. The MIND diet is a dietary pattern that combines aspects of the DASH and Mediterranean diets, with a specific focus on promoting brain health; it contains foods rich in certain vitamins, carotenoids, and flavonoids that are believed to protect the brain by reducing oxidative stress and inflammation [16]. The MIND diet recommends to include specific "brain healthy" foods emphasizing the consumption of foods such as leafy greens, berries, nuts, whole grains, fish, and poultry while limiting the intake of red meat, butter and margarine, cheese, sweets, fried or fast food [17].

Cadmium (Cd) is a toxic heavy metal, associated with an increased risk of atherosclerosis [18], hypertension [19], type 2 diabetes [20,21], and some types of cancer [22–24]. The main sources of exposure are through smoking, air pollution, occupational activities, and diet [25–28]. Indeed, in the non-smoking general population, diet accounts for approximately 90 % of the total exposure. It is well recognized that the main food sources that contribute to cadmium exposure are cereals and vegetables [26]. Nonetheless, little is known about the overall contribution of dietary patterns to cadmium exposure, including the previous mentioned healthy patterns.

In this study, we aimed at assessing the association between adherence to dietary patterns and cadmium exposure, as assessed through urinary cadmium concentrations, in a Northern Italian population.

2. Methods

2.1. Study participants

As previously described [29] the population enrolled for this study has been recruited from the Transfusion Medicine Center "Casa del Dono" of AUSL-IRCCS of Reggio Emilia from April 2017 to April 2019. We recruited healthy blood donors, non-smokers, without a history of chronic disease or cancer, 148 agreed to participate the study; four participants withdrew before the conclusion of the study and seven were excluded because of elevated cotinine levels (> 30 μg/L) that we felt they were inconsistent with the self-declared non-smoker status [30]. We eventually included 137 subjects, for whom we obtained written informed consent as required by the Ethics Committee of the province of Reggio Emilia (approval of protocol no. 2016/0022799). Each participant completed a questionnaire regarding sociodemographic information, medical and residential history as well as lifestyle habits [31]. We also collected a fasting morning urinary sample to measure urinary levels of cadmium and cotinine (being the latter a biomarker of smoking exposure).

2.2. Analytical determinations

Cadmium in urine was analyzed by inductively coupled plasma mass spectrometry (X Series II, Thermo Scientific, Rodano, Italy) as described before [32]. The limit of quantification (LOQ) was 0.01 μg/L. The internal quality assurance was performed using quality controls (QCs) for metals in urine Lyphochek Urine Metals Control (Bio-Rad Laboratories, Anaheim, CA, USA), and Seronorm® (Sero AS, Billingstad, Norway). QC accuracy was between 98 % and 103 % and precision, evaluated as coefficient of variation, ranged between 9 % and 3 %.

Cotinine in urine was analyzed by liquid chromatography coupled with triple quadrupole mass spectrometry (TSQ Quantum Access, Thermo Scientific, Rodano, Italy) with a heated electrospray ionization source operating in positive ion mode, as previously described [33]. The LOD was 0.1 μg/L. Accuracy ranged between 93 % and 109 % and precision, as coefficient of variation, was < 10 %.

2.3. Dietary pattern adherence

Using a validated semi-quantitative food frequency questionnaire (FFQ) developed within the European Prospective Investigation into Cancer and nutrition (EPIC) project we estimated adherence to four a priori defined dietary patterns as previously reported in detail [34–36].

The DASH diet was calculated through scores given to 8 components: a higher intake of fruits, vegetables, nuts and legumes, low-fat dairy products, and whole grains gave higher DASH scores, while a higher intake of sodium, sweetened beverages, and red and processed meats yielded lower scores. After the classification of participants into quintiles according to the intake of each component, the component scores were summed to obtain the DASH score adherence (range 8–40). The GMI was based on the Mediterranean diet scale previously constructed [37]. The GMI score was based on the consumption of 9 foodstuffs: vegetables, legumes, fruit and nuts, dairy products, cereals, meat and meat products, fish, and alcohol. Classification of participants was made according to the intake above or below the median value of the overall population. The IMI was developed by adapting the GMI to Italian eating behavior [38] and it was based on the intake of 11 items: 6 foods or food groups belonging to a typical Mediterranean diet (pasta, typical Mediterranean vegetables, such as raw tomatoes, leafy vegetables, onion and garlic, salad, and fruiting vegetables, fruit, legumes, olive oil, and fish) and 4 non-Mediterranean foods (butter, potatoes, red meat, and soft drinks). Alcohol consumption was also taken into account. Participants were then classified according to tertiles of intake of each component. 1 point was given for the consumption of each typical Mediterranean food in the upper tertile and for the consumption of each non-Mediterranean food in the lowest tertile. For alcohol consumption, participants received 1 point for intake up to 12 g/day; abstainers and persons who consumed > 12 g/day received 0 points. GMI and IMI ranged from 0 to 9 and 0–11, respectively. Finally, the MIND diet score was calculated according to the intake of 10 food components associated with a healthy brain (green leafy vegetables, other vegetables, berries, nuts, whole grains, fish not fried, beans, poultry not fried, wine, and olive oil) and consumption of 5 foods considered detrimental for neurocognitive function (red meat and relative products, butter and margarine, cheese, fast fried food, and pastries and sweets) with overall range 0–15 [17]. For all dietary patterns, higher score indicates higher adherence.

2.4. Statistical analysis

We evaluated the association between increasing adherence to dietary patterns and cadmium exposure using a cubic spline regression model with three knots at fixed percentiles (10, 50, and 90) and adjusting for relevant confounders including age, sex, body mass index (BMI), urinary cotinine levels, intake of fiber and alcohol [39,40]. Stratified analyses according to sex, age (< 50 and ≥ 50 years) and BMI (< 25 – non-overweight, and ≥ 25 – overweight) were also conducted. The influence of iron intake was also taken into consideration.

3. Results

Table 1 summarizes the characteristics of the 137 participants composing the study population. The median age was 48.2 years, higher in females than in males, while the median BMI was 24.6, higher in males compared to females. Cotinine levels were higher in females (median 0.32 μg/L) compared to males (0.20 μg/L). Males exhibited higher median consumption of alcohol compared to females, while it was the opposite for fiber intake. Median urinary cadmium levels were very similar in males (0.21 μg/L) and females (0.22 μg/L). For what concerns adherence to dietary patterns, females were more adherent to the DASH diet compared to males (median score 27 vs. 22), while median adherence to Mediterranean diet-based indexes and the MIND diet was similar in both sexes.

Results of the spline regression analyses in the overall population are shown in Fig. 1. The DASH diet was inversely related to urinary cadmium levels until 25-score while above this point it slightly increased. The Mediterranean pattern GMI showed a null relation approximately till the median value (i.e., 4-score), while at higher levels it showed a positive association with urinary cadmium. Conversely, a substantial null relation can be noted between IMI and cadmium levels. Interestingly, the relation with the MIND diet was U-shaped, with a negative association below the median level of adherence (7.5-score) and a positive one for higher scores.

In sex-stratified analyses (Fig. 2), the DASH diet appeared to be inversely and non-linearly associated with urinary cadmium in males, while in females a trend resembling what observed in the overall population seemed depicted. The GMI was positively correlated with urinary cadmium levels in females, but almost unrelated in males. For what concerns the IMI, in males a negative association was observed until the score of 4, with the curve flattened above that value, while in females the association was null. In males, the MIND diet appeared almost null associated with urinary cadmium until slightly above the median value (i.e., 8-score), while at higher levels a negative association was observed. On the contrary, the association between the MIND diet and urinary cadmium levels in females resembled the overall population, being U-shaped with median value of adherence (i.e., 7.5) as turning point.

Analysis stratified by age group are reported in Supplementary Fig. S1. The DASH diet showed an inverse association in both younger (< 50 years) and older (≥ 50 subjects) as in the overall population, although the association was almost linear in those aged ≥ 50 years. The GMI showed a positive association until the score of 4 with urinary cadmium in younger subjects, while the association was linear in older ones. For IMI, a stronger inverse association emerged for older subjects compared to the overall population, while a U-shaped association emerged in younger individuals with turning point at the score of 4. The MIND diet showed a similar U-shaped association with urinary cadmium comparable to the overall population, stronger in younger than older subjects.

Analysis stratified by non-overweight and overweight subjects is reported in Supplementary Fig. S2. The DASH diet showed a U-shaped association in subjects with BMI < 25 (turning point 25), while it was inverse and linear in those with BMI ≥ 25. The GMI diet showed a positive association in both groups, almost linear in non-overweight subjects, while the curve flattened above the score of 4 in overweight individuals. The association between IMI and urinary cadmium (null in the overall population), showed an opposite trend with a positive association in non-overweight subjects above the score of 5, but inverse linear association in overweight ones. For the MIND diet a U-shaped association emerged with urinary cadmium in both subgroups, similarly to the overall population, although less evident in those with BMI ≥ 25.

4. Discussion

Along with the already known carcinogenic effects [22], cadmium exposure is also associated with cardiovascular disease risk, with established pro-atherosclerotic effects independent of smoking [41]. Furthermore, cadmium is deemed as possible etiological factor of cognitive disorders in humans [42,43]. For these reasons, it is particularly relevant from a public health perspective to assess both cadmium contamination in the food chain and levels in both general and vulnerable populations. Cadmium levels demonstrated great variations across the world. In the European population, median urinary cadmium levels were found to be higher among Polish individuals (0.43 μg/L), while the lowest were observed among Portuguese subjects (0.12 μg/L) [44]. In our study, median concentrations of urinary cadmium were 0.21 μg/L, thus being in line with median levels of the overall European population [45]. From a toxicological point of view, cadmium is characterized by negative effects on mitochondria. It has the potential to modify the activity of numerous mitochondrial proteins causing the disruption of mitochondrial membrane potential, mitochondrial swelling, and suppression of respiratory function. In addition, it exerts adverse effects on cell proliferation and differentiation, thus contributing to their apoptosis and necrosis [46,47]. Although cadmium is an established carcinogen

Table 1
Median (50th) and interquartile range (IQR) of main characteristics, urinary cadmium distribution, and adherence to dietary patterns in the overall study population (n = 137) and divided by sex (n males/females = 62/75).

	All subjects		Males		Females	
	50th	IQR	50th	IQR	50th	IQR
Age (years)	48.2	(42.7–53.0)	47.7	(41.3–52.6)	49.1	(43.6–53.6)
Body mass index	24.6	(22.4–26.9)	24.8	(23.3–26.6)	24.5	(22.0–27.0)
Cotinine (μg/L)	0.27	(0.05–0.86)	0.20	(0.05–0.77)	0.32	(0.05–0.94)
Alcohol intake (μg/day)	7.3	(1.6–15.1)	11.9	(3.7–26.0)	4.1	(0.7–13.2)
Fiber intake (μg/day)	17.5	(13.9–24.9)	16.2	(13.1–24.4)	17.9	(14.1–25.9)
Urinary Cd concentration (μg/L)	0.21	(0.11–0.34)	0.21	(0.11–0.35)	0.22	(0.11–0.34)
DASH diet	24	(21–28)	22	(19–25)	27	(22–29)
GMI	4	(3–6)	4	(3–5)	4	(3–6)
IMI	4	(3–5)	4	(3–5)	4	(3–6)
MIND diet	7.5	(6.5–8.5)	7.5	(6.5–8.0)	8.0	(7.0–9.0)

Abbreviations: DASH: Dietary Approaches to Stop Hypertension; GMI: Greek Mediterranean Index; IMI: Italian Mediterranean Index; IQR: interquartile range; MIND: Mediterranean-DASH Intervention for Neurodegenerative Delay.

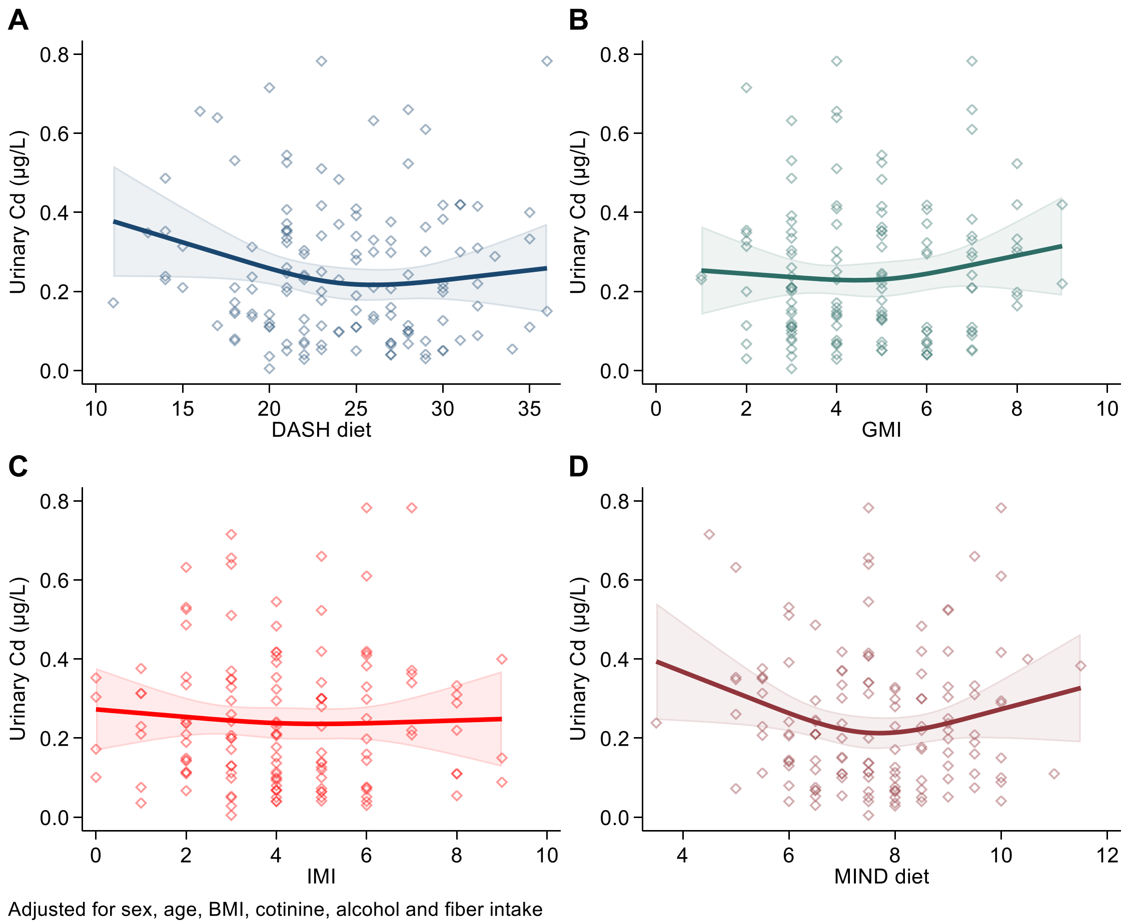

Fig. 1. Spline regression analysis of the association between dietary patterns [A-DASH (Dietary Approaches to Stop Hypertension) diet; B-Greek Mediterranean Index; C-Italian Mediterranean Index; D-MIND (Mediterranean-DASH Intervention for Neurodegenerative Delay) diet] and urinary cadmium (Cd) levels. Adjusted for age, sex, body mass index, cotinine, alcohol, and fiber intake.

exerting toxic effects on kidneys, skeletal and respiratory systems [48], it is still contained in several agricultural fertilizers [49]. This issue along with the release of atmospheric cadmium from industrial processes, contributes to soil contamination with consequent uptake in crops, bred animals and aquatic organisms thus accumulating in the food chain [50–55]. The main sources of cadmium are generally plant-based foods, primarily cereals/grains, followed by vegetables, with also significant contribution of meat products and fish/seafood [56–58]. For these reasons, remediation strategies from cadmium in soil and water are recently proposed to decrease food contamination [59, 60].

In this cross-sectional study composed of healthy subjects, we found that a high degree of adherence to healthy dietary patterns, particularly the MIND diet, the GMI and partially also the DASH diet, was associated with higher excretion of urinary cadmium. In a population of non-smokers and non-occupationally exposed individuals, as that in our study, the primary source of cadmium is from diet, i.e. from foods and beverages [61]. All the dietary patterns we investigated emphasize consumption of fruit and vegetables [62], the food components characterized by the highest contribution to cadmium intake along with cereals [63,64] as seen in our study population along with vegetables [65]. This may explain the positive association with high adherence to healthy dietary patterns. However, the different pattern of association of the IMI compared to other dietary patterns may be explained by differences in specific food components (e.g., alcohol, fish and seafood), as well as in quantities/servings recommended.

There are a limited number of studies examining the associations between adherence to healthy dietary patterns and urinary excretion of this heavy metal. A recent study found positive associations between urinary cadmium and the Western and Prudent dietary patterns [66]. Previous studies already showed a positive association between cadmium levels and Mediterranean-type diet [67]. In our study, for the Mediterranean-type specific patterns, only the GMI was non-linearly associated with urinary cadmium levels, while almost a null association was observed for the IMI. In a recent study, an inverse association between the DASH diet and whole blood concentrations of cadmium emerged in a population of Japanese pregnant women [68], similarly to what we observed in our study. However, in our population, at higher levels of adherence, only a slight further increase of cadmium exposure can be noted. Those differences may be explained by the different status of subjects (pregnancy condition of women vs. healthy blood donor subjects) or by the different exposure assessment methods (whole blood vs. urine).

In our study, the association between dietary patterns and cadmium was particularly strong in females, while in males flattened and null associations emerged and a reduction in urinary cadmium excretion was observed especially for higher adherence to the MIND diet. This may be explained by sex differences in the intake of single components composing the healthy dietary patterns. As previously discussed, in our study males had higher mean levels of consumption of cereals, meat, fish, and wine compared to females. Conversely, females exhibited a higher mean dietary intake of vegetables, dairy products, fruits, and olive oil [69]. Thus, males and females with comparable high scores of adherence to the MIND diet may actually reflect consumption of different foods, having different cadmium content. Alternatively, differences in cadmium absorption, metabolism and excretion may exist

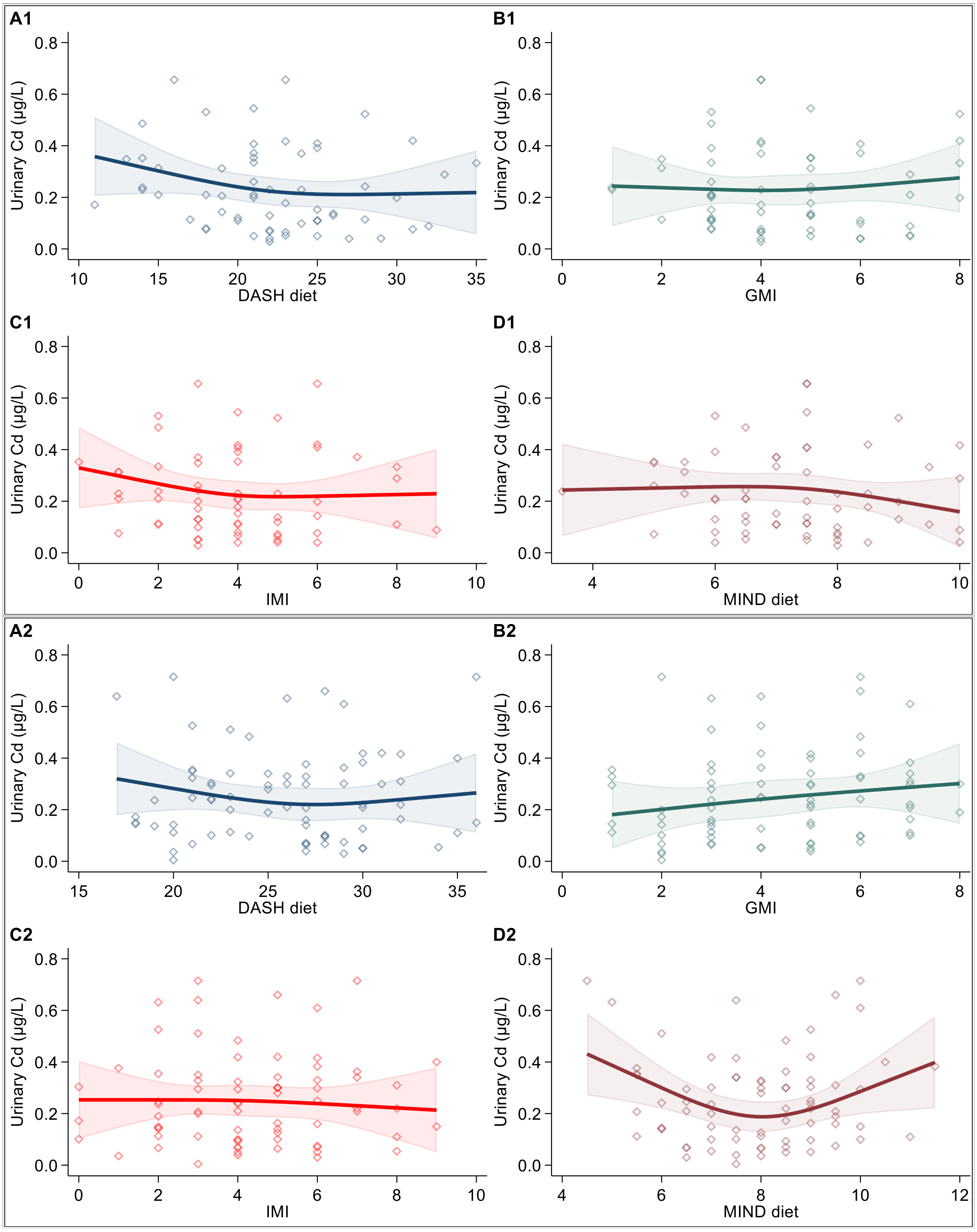

Fig. 2. Spline regression analysis of the association between dietary patterns and urinary cadmium (Cd) levels stratified by sex (A1–D1 males; A2–D2 females). Adjusted for age, body mass index, cotinine, alcohol, and fiber intake.

between females and males [70,71]. For instance, cadmium uptake may use the same transporters for divalent metals [72], especially iron characterized by higher absorption in females [39,40,73]. Also age and BMI affected the relation between the investigated dietary patterns and urinary cadmium. Such associations were stronger and enhanced in younger and non-overweight subjects compared to the overall population. Possible explanations may related to the higher cadmium levels generally found in older subjects [25,32,73] with accumulation in the kidney and slow release in the long-term [74]. In addition, overweight subjects generally showing lower cadmium levels compared to non-overweight individuals [32,73] are probably characterized by dietary habits with lower intake of those foods with higher contribution to cadmium intake, particularly vegetables [26].

Our study has some limitations, such as its cross-sectional design that hampered the assessment of the effects of long-term dietary pattern adherence on cadmium levels. In addition, the limited sample size of our population has affected the statistical precision of our estimates. Finally, we could not rule out some exposure misclassification, resulting from additional dietary and non-dietary sources of cadmium intake.

Among the strengths of our study there is the healthy status of the study subjects, thus limiting the possibility of reverse causation related to change in diet due to chronic disease, the use of statistical tools to assess non-linear associations between the variables, the use of four different dietary patterns, and the consideration of several confounders such as alcohol and fiber intake, and cotinine levels. Smoking habits and passive smoking history were also accounted for. Finally, we used urinary level as a biomarker of cadmium exposure, which is considered to adequately reflect long-term exposure to this heavy metal [74].

5. Conclusions

In this study, assessing for the first time the relation between adherence to four different dietary patterns and cadmium exposure as evaluated through urinary levels, higher adherence to healthy dietary patterns was unfortunately associated to a higher cadmium exposure. Public health measures are warranted in order to decrease exposure to cadmium in healthy foods considered to be beneficial for human health.

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CRediT authorship contribution statement

TF and MV conceived the study. SF, EP and SSu performed analytical measurement. MM collected data on dietary habits with further analysis of CA and SSi. NN and CM contributed to recruitment. TU, PV and TF extracted and analyzed data. All authors interpreted the data. TU, PV and TF prepared the first draft of the manuscript with contribution of SF and MV. All authors read and approved the final 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.jtemb.2023.127298.

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