stresses

MDPI

Article

Environmental Cadmium Exposure Induces an Increase in Systolic Blood Pressure by Its Effect on GFR

Soisungwan Satarug [1,*], David A. Vesey [1,2], Supabhorn Yimthiang [3], Tanaporn Khamphaya [3], Phisit Pouyfung [4] and Aleksandra Buha Đorđević [5]

[1] Centre for Kidney Disease Research, Translational Research Institute, Woolloongabba, Brisbane, QLD 4102, Australia; david.vesey@health.qld.gov.au
[2] Department of Kidney and Transplant Services, Princess Alexandra Hospital, Brisbane, QLD 4102, Australia
[3] Occupational Health and Safety, School of Public Health, Walailak University, Nakhon Si Thammarat 80160, Thailand; ksupapor@mail.wu.ac.th (S.Y.); tanaporn.kh@mail.wu.ac.th (T.K.)
[4] Department of Community Health, Faculty of Public Health, Mahidol University, Bangkok 20100, Thailand; phisit.pou@mahidol.edu
[5] Department of Toxicology "Akademik Danilo Soldatović", University of Belgrade-Faculty of Pharmacy, 11000 Belgrade, Serbia; aleksandra.buha@pharmacy.bg.ac.rs
* Correspondence: sj.satarug@yahoo.com.au

Abstract: Chronic exposure to the nephrotoxic metal pollutant, cadmium (Cd), has been associated with hypertension, but the mechanism by which it raises blood pressure is not understood. We hypothesize that exposure to Cd reduces the glomerular filtration rate (GFR), which in turn causes a rise in blood pressure. Data were collected from 447 Thai subjects with a mean age of 51.1 years, of which 48.8% had hypertension, 15.4% had diabetes, and 6.9% had an estimated GFR (eGFR) below 60 mL/min/1.73 m^2 (low eGFR). More than half (58.8%) and 23.9% had moderate and severe tubular proteinuria, respectively. The mean blood and urinary Cd concentrations were 2.75 and 4.23 μg/L, respectively. Doubling of body burden of Cd increased the prevalence odds ratios (POR) for low eGFR and severe tubular proteinuria 41% and 48%, respectively. The POR for hypertension rose twofold in those with blood Cd levels of 0.61–1.69 μg/L or urinary Cd excretion levels ≥ 0.98 μg/g creatinine. In the hypertensive group, the eGFR was inversely associated with age (β = −0.517), the Cd excretion rate (β = −0.177), and diabetes (β = −0.175). By mediation analysis, an increase in SBP was attributable totally to the effect of Cd on GFR. Thus, blood pressure appeared to rise as GFR fell. This finding is consistent with the well-known role of the kidney in long-term blood pressure regulation, and explains a universally high prevalence of hypertension among patients with low eGFR.

Keywords: blood pressure; cadmium; glomerular filtration rate; hypertension; kidneys; mediation analysis; tubular proteinuria

check for updates

Citation: Satarug, S.; Vesey, D.A.; Yimthiang, S.; Khamphaya, T.; Pouyfung, P.; Đorđević, A.B. Environmental Cadmium Exposure Induces an Increase in Systolic Blood Pressure by Its Effect on GFR. *Stresses* **2024**, *4*, 436–451. https://doi.org/10.3390/stresses4030029

Academic Editor: Andrea Bolognesi

Received: 11 May 2024
Revised: 2 July 2024
Accepted: 11 July 2024
Published: 15 July 2024

Copyright: © 2024 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

1. Introduction

Hypertension, indicated by systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg, is a common risk factor for cardiovascular disease (CVD) and can be both a cause and a consequence of chronic kidney disease (CKD) [1–3]. Concerningly, mortality from CKD rose from the 13th leading cause of death in 2000 to the 7th in 2021, and it is projected to be the 5th leading cause of years of life lost by 2040 [4,5].

Because of its ubiquitous environmental presence, exposure to the nephrotoxic metal pollutant cadmium (Cd) is also a significant risk factor for CVD [6] and CKD [7]. A 75% increase in deaths from any cause among those with CKD was associated with Cd exposure even at low levels, reflected by urinary Cd levels ≥ 0.60 μg/g creatinine [8]. The risk of having CVD rose 2.58-fold and 2.79-fold at blood Cd level of 1 μg/L and urinary Cd

excretion rate of 0.5 μg/g creatinine, respectively [6]. Notably, environmental Cd exposure appeared to adversely affect females and males differently [9–12].

In the U.S. general population, an overall mean urinary Cd excretion was 0.5 μg/g creatinine, and 2.5%, 7.1%, and 16% of non-smoking women (aged ≥ 20 years) had urinary Cd levels > 1, >0.7, and >0.5 μg/g creatinine, respectively [13]. In comparison, a study from Thailand reported a 22.5% prevalence of Cd excretion ≥ 1 μg/g creatinine in non-smoking women who had low body iron stores [14]. Thus, the proportions of at-risk subpopulations are concerning.

Effects of environmental exposure to Cd on blood pressure has been well documented in studies of the general populations of the U.S. [15–17], Canada [18], China [19–21], Korea [22,23], and Japan [24]. For non-occupationally exposed populations, diet is the main source of Cd exposure, other than through passive and active smoking [25–28]. The intestinal absorption rate of Cd can be as high as 45% [29,30] as Cd can be absorbed through several metal transporters for metal nutrients, iron, zinc, copper, and calcium (Fe, Zn, Cu and Ca) [31,32]. Furthermore, Cd complexed with metallothionein (MT) and phytochelatin (PC), as CdMT and CdPC, can be absorbed through transcytosis as well as receptor-mediated endocytosis [33–35]. Notably, however, there are no physiologic mechanisms for Cd elimination. Continued exposure will lead to its accumulation in tissues and organs throughout the body, notably in the kidneys, where it promoted the progression of kidney disease to kidney failure, especially in diabetics [36].

The kidneys play an indispensable role in long-term blood pressure regulation [2], and the principal site of Cd toxicity due to a preferential accumulation of Cd in the proximal tubular epithelium [37,38]. As these cells die, CdMT is released into tubular lumen and is excreted in urine [39]. Most or all excreted Cd originates from injured or dying kidney tubular epithelial cells, thus the excretion of Cd itself indicates the severity of the kidney injury at the present time [39]. A correlation between kidney accumulation and urinary Cd concentration also forms the basis for urinary Cd as an indicator of long-term exposure to Cd or its body burden [40].

The deleterious effects of Cd exposure on the kidneys have been investigated extensively in workplace and non-workplace exposure settings [41]. However, a few studies have explored the mechanism by which Cd raises blood pressure. The present study aimed to test the hypothesis that an increase in blood pressure is the result of kidney tubular cell damage by Cd. Because a reduction in the glomerular filtration rate (GFR) is a common sequela of ischemic acute tubular necrosis, and acute and chronic tubulointerstitial fibrosis, all of which create impediments to filtration [42,43], we quantified tubular cell damage, tubular proteinuria, systolic, and diastolic blood pressures (SBP and DBP) according to the estimated GFR (eGFR) and Cd exposure levels in those diagnosed with and without hypertension. Urinary excretion of Cd (E_{Cd}) and blood Cd concentrations ($[Cd]_b$) were used as measures of exposure levels. Urinary excretion of β_2-microglobulin (β_2M) and N-acetyl-β-D-glucosaminidase (NAG) were used to assess tubular proteinuria and damage to the kidney tubular cells, respectively [41].

2. Results

2.1. Demographic and Biologic Characteristics of Participants

A total of 447 persons (333 women and 114 men) with a mean age of 51.1 years, were recruited to this study (Table 1).

Overall mean $[Cd]_u$ and $[Cd]_b$ values were 4.23 and 2.75 μg/L, respectively. Participants were grouped by the tertile of the Cd excretion rate $[(E_{Cd}/C_{cr}) \times 100]$. Corresponding mean $(E_{Cd}/C_{cr}) \times 100$ values in the low, middle, and high tertile groups were 0.38, 2.28 and 6.89 μg/L filtrate, equivalent to E_{Cd}/E_{cr} of 0.48, 3.07 and 8.48 μg/g creatinine. Mean blood Cd concentration $[Cd]_b$ values in the low, middle and high tertiles of Cd burden were 0.72, 2.37, and 5.14 μg/L, respectively.

Table 1. Descriptive characteristics of study subjects according to cadmium burden tertiles.

Parameters	All, *n* = 447	Cd Burden Tertiles			*p*
		Low, *n* = 148	Middle, *n* = 149	High, *n* = 150	
Age, years	51.1 ± 8.6	56.6 ± 9.7	48.1 ± 6.9	48.7 ± 6.1	<0.001
Age range, years	33–80	37–80	33–78	36–73	
BMI, kg/m^2	24.8 ± 4.0	25.5 ± 4.5	24.8 ± 3.8	24.0 ± 3.4	0.006
eGFR [a], mL/min/1.73 m^2	90 ± 18	84 ± 18	96 ± 17	91 ± 18	<0.001
% eGFR ≤ 60 mL/min/1.73 m^2	6.9	10.3	1.3	8.7	0.005
% Hypertension	48.8	51.4	46.3	48.7	0.685
% Smoking	31.1	16.2	34.9	42.7	<0.001
% Diabetes	15.4	39.2	3.4	4.0	<0.001
Tubular proteinuria					
% Moderate	58.8	58.8	52.3	65.3	0.074
% Severe	23.9	25.7	14.8	31.3	0.027
Systolic blood pressure, mmHg	128 ± 17	134 ± 17	126 ± 16	126 ± 16	<0.001
Diastolic blood pressure, mmHg	81 ± 10	83 ± 10	80 ± 10	80 ± 11	0.019
$[cr]_p$, mg/dL	0.82 ± 0.22	0.86 ± 0.25	0.77 ± 0.17	0.83 ± 0.23	0.001
$[cr]_u$, mg/dL	114 ± 74	113 ± 72	131 ± 72	99 ± 75	<0.001
$[Cd]_b$, µg/L	2.75 ± 3.19	0.72 ± 0.83	2.37 ± 2.06	5.14 ± 3.95	<0.001
$[Cd]_u$, µg/L	4.23 ± 5.68	0.71 ± 1.20	3.91 ± 2.50	8.03 ± 7.86	<0.001
Normalized to E_{cr} (E_{Cd}/E_{cr}) [b]					
E_{Cd}/E_{cr}, µg/g creatinine	4.03 ± 4.42	0.48 ± 0.62	3.07 ± 0.93	8.48 ± 4.87	<0.001
$E_{\beta 2M}/E_{cr}$, µg/g creatinine	3223 ± 21,872	1115 ± 1791	1186 ± 3108	7328 ± 37,331	0.001
E_{NAG}/E_{cr}, units/g creatinine	13.25 ± 11.43	8.85 ± 3.18	11.81 ± 6.43	15.80 ± 15.42	<0.001
Normalized to C_{cr}, (E_{Cd}/C_{cr}) [c]					
(E_{Cd}/C_{cr}) × 100, µg/L filtrate	3.20 ± 3.73	0.38 ± 0.46	2.28 ± 0.56	6.89 ± 4.31	<0.001
($E_{\beta 2M}/C_{cr}$) × 100, µg/L filtrate	3845 ± 30,456	1117 ± 2352	1105 ± 3657	9257 ± 52,090	<0.001
(E_{NAG}/C_{cr}) × 100, µg/L filtrate	10.79 ± 12.20	6.78 ± 2.46	9.13 ± 6.71	13.46 ± 16.60	<0.001

n, number of subjects; BMI, body mass index; eGFR, estimated glomerular filtration rate; cr, creatinine; alb, albumin; Cd, cadmium. [a] eGFR was determined using the CKD-EPI equations [44]. [b] $E_{Cd}/E_{cr} = [Cd]_u/[cr]_u$. [c] $E_{Cd}/C_{cr} = [Cd]_u[cr]_p/[cr]_u$ [45]. SBP and DBP data were from 445 subjects. Data on E_{NAG}/E_{cr} and (E_{NAG}/C_{cr}) × 100 were from 308 subjects. All other data were from 447 subjects. Arithmetic mean ± standard deviation (SD) values are provided for all continuous variables. $p \leq 0.05$ identifies statistical significance.

$[Cd]_u$ and $[Cd]_b$ correlated strongly with each other in both women and men with respective Pearson's correlation coefficients of 0.688 and 0.615. After controlling for age, $[Cd]_u$ and $[Cd]_b$ correlations remained with partial *r* values of 0.584 and 0.658 in women and men, respectively.

The percentages (%) of smoking in the top (42.7%) and middle (34.9%) E_{Cd}/C_{cr} tertile groups were higher than the low (16.2%) tertile group. The % hypertension were similar across E_{Cd}/C_{cr} tertiles, but diabetes was more prevalent in the low tertile (39.2%) compared with the middle (3.4%) and high (4.0%) tertile groups. In parallel, low eGFR was more prevalent in the low tertile (10.3%) than in the middle (1.3%) and top (8.7%) tertiles.

More than half (58.8%) of participants had moderate proteinuria, and 23.9% had severe proteinuria. The % severe tubular proteinuria rose to 31.3% in the top E_{Cd}/C_{cr} tertile, compared with 14.8% in the middle tertile group.

Mean age (56.6 years), mean BMI (25.5 kg/m^2), mean SBP (134 mmHg), and mean DBP (83 mmHg) in the low tertile group were all statistically higher than the middle and top E_{Cd}/C_{cr} tertile groups. The mean eGFR of 84 mL/min/1.73 m^2 in the low tertile was 7–12 mL/min/1.73 m^2 below the mean eGFR values in the middle and top tertiles.

2.2. Cadmium, Hypertension, Low eGFR and Tubular Proteinuria

We used logistic regression to evaluate associations of age, BMI, gender, smoking, diabetes, and Cd burden with prevalence odds ratios (POR) for hypertension (Table 2).

Table 2. Effects of cadmium burden on prevalence odds ratios for hypertension.

Independent Variables/Factors	Hypertension				
	β Coefficients (SE)	POR	95% CI Lower	95% CI Upper	*p*
Age, years	0.023 (0.014)	1.024	0.997	1.051	0.085
BMI, kg/m^2	0.079 (0.027)	1.082	1.027	1.140	0.003
Gender	0.070 (0.260)	0.932	0.560	1.551	0.788
Smoking	0.444 (0.250)	0.642	0.393	1.048	0.076
Diabetes	0.575 (0.329)	1.777	0.932	3.388	0.081
Cd burden [a]					
Mild	Referent				
Moderate	0.748	2.114	1.049	4.260	0.036
Heavy	0.504	1.655	0.921	2.973	0.092

POR, prevalence odds ratio; CI, confidence interval; β, regression coefficient; SE, standard error of mean; BMI, body mass index. [a] Mild, moderate, and heavy Cd burdens were defined, respectively, as $(E_{Cd}/C_{cr}) \times 100 < 1$, 1–4.99 and ≥5 μg/L filtrate. Arithmetic means (SD) of $(E_{Cd}/C_{cr}) \times 100$ in the low, medium, and high Cd burden groups were 0.20 (0.26), 2.69 (1.08), and 9.11 (4.72) μg/L filtrate, respectively. Corresponding numbers of subjects in these Cd burden groups were 123, 241, and 83. For all tests, *p*-values ≤ 0.05 indicate a statistical significance.

The prevalence odds ratio (POR) for hypertension rose with BMI (POR 1.082, 95% CI: 1.027–1.140) and Cd burden at a medium level (POR 2.114, 95% CI: 1.049–4.260). An increase in POR for hypertension was statistically insignificantly in the heavy Cd burden group ($p = 0.092$).

Results of an analogous analysis with $[Cd]_b$ can be found in Table 3.

Table 3. Prevalence odds ratios for hypertension in relation to blood cadmium quartiles.

Independent Variables/Factors	Hypertension				
	β Coefficients (SE)	POR	95% CI Lower	95% CI Upper	*p*
Age, years	0.018 (0.012)	1.018	0.994	1.042	0.148
BMI, kg/m^2	0.080 (0.026)	1.083	1.029	1.140	0.002
Gender	0.050 (0.254)	0.951	0.578	1.565	0.844
Smoking	0.433 (0.255)	0.649	0.394	1.069	0.089
Diabetes	0.422 (0.294)	1.526	0.858	2.713	0.150
Quartile of $[Cd]_b$, μg/L					
Q1: <0.60	Referent				
Q2: 0.61–1.69	0.748 (0.293)	2.113	1.191	3.749	0.011
Q3: 1.70–3.38	0.606 (0.309)	1.833	1.000	3.360	0.050
Q4: >3.38	0.587 (0.337)	1.798	0.928	3.482	0.082

POR, prevalence odds ratio; CI, confidence interval; β, regression coefficient; SE, standard error of mean; BMI, body mass index. Arithmetic means (SD) of $[Cd]_b$ quartiles 1, 2, 3, and 4 were 0.21 (0.22), 1.11 (0.30), 2.44 (0.52), and 6.72 (3.72) μg/L, respectively. Corresponding numbers of subjects in $[Cd]_b$ quartiles 1, 2, 3, and 4 quartile groups were 126, 117, 119, and 120. For all tests, *p*-values ≤ 0.05 indicate a statistical significance.

Per every 1 kg/m^2 increase in BMI, the POR for hypertension rose 8.3% (95% CI: 2.9–14.0). Compared with $[Cd]_b < 0.60$ μg/L, the POR for hypertension increased to 2.113 (95% CI: 1.191–3.749) and 1.833 (95% CI: 1.000–3.360) in those with $[Cd]_b$ of 0.61–1.69, and 1.70–3.38 μg/L, respectively. An increment of the POR for hypertension in the top $[Cd]_b$ quartile ($[Cd]_b > 6.92$ μg/L) was statistically insignificant ($p = 0.082$).

To evaluate the effects of Cd on the prevalence of low eGFR and tubular proteinuria, three more logistic regression models were conducted (Table 4).

For every one-year older, the POR for low eGFR, moderate, and severe tubular proteinuria rose 14.6%, 3.7%, and 6.4%, while doubling of body burden of Cd was associated with 41%, 23%, and 48% increases in the POR for low eGFR, moderate, and severe tubular proteinuria, respectively. Among diabetics, there were 4.3-fold, 5.5-fold, and 13.4-fold increases in the POR for low eGFR, moderate, and severe tubular proteinuria, respectively.

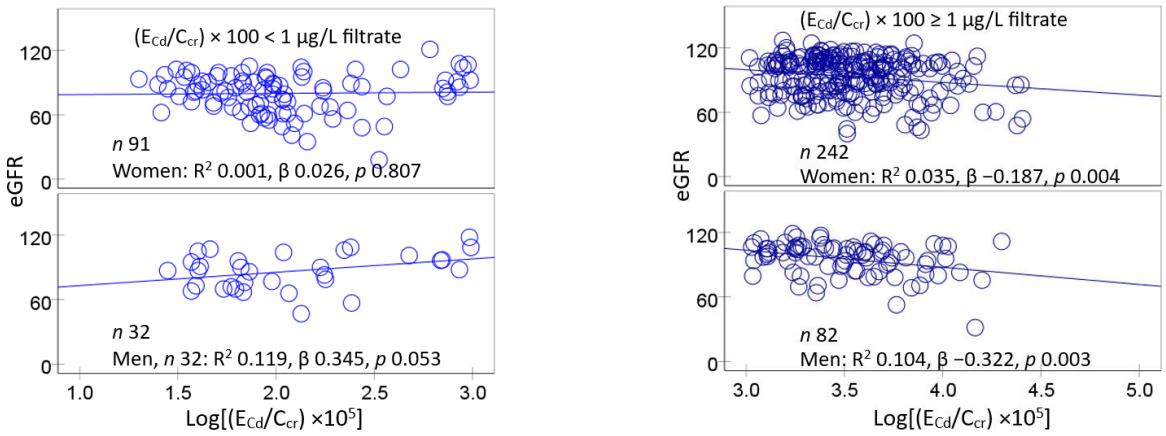
Table 4. Prevalence odds ratios for low eGFR and tubular proteinuria in relation to cadmium body burden and other independent variables.

Independent Variables/Factors	Low eGFR [a]		Moderate Proteinuria [b]		Severe Proteinuria [c]	
	POR (95% CI)	*p*	POR (95% CI)	*p*	POR (95% CI)	*p*
Age, years	1.146 (1.087, 1.209)	<0.001	1.037 (1.007, 1.067)	0.014	1.064 (1.029,1.100)	<0.001
BMI, kg/m^2	1.023 (0.926, 1.129)	0.659	0.972 (0.921, 1.026)	0.299	0.964 (0.903,1.030)	0.283
$Log_2[(E_{Cd}/C_{cr}) \times 10^5]$, µg/L filtrate	1.417 (1.247, 1.750)	0.001	1.230 (1.101, 1.374)	<0.001	1.480 (1.271,1.724)	<0.001
Gender	1.701 (0.479, 6.043)	0.412	1.395 (0.828, 2.349)	0.211	1.250 (0.663,2.357)	0.490
Smoking	0.814 (0.263, 2.521)	0.721	0.942 (0.579, 1.566)	0.815	0.757 (0.418,1.370)	0.358
Diabetes	4.262 (1.532, 12.86)	0.005	5.485 (2.614, 11.51)	<0.001	13.37 (5.698,31.36)	<0.001

POR, prevalence odds ratio; CI, confidence interval; BMI, body mass index; eGFR, estimated glomerular filtration rate. [a] Low eGFR was defined as eGFR ≤ 60 mL/min/1.73 m^2. [b] Moderate tubular proteinuria was indicated by $(E_{\beta 2M}/C_{cr}) \times 100 \geq 300$ µg/L filtrate. [c] Severe tubular proteinuria was indicated by $(E_{\beta 2M}/C_{cr}) \times 100 \geq 1000$ µg/L filtrate. For all tests, *p*-values ≤ 0.05 indicate a statistical significance.

2.3. Comparing Effects of Cadmium on eGFR in Women and Men

Scatterplots that related eGFR to the Cd excretion rates Cd in women and men are presented in Figure 1.



(**a**) (**b**)

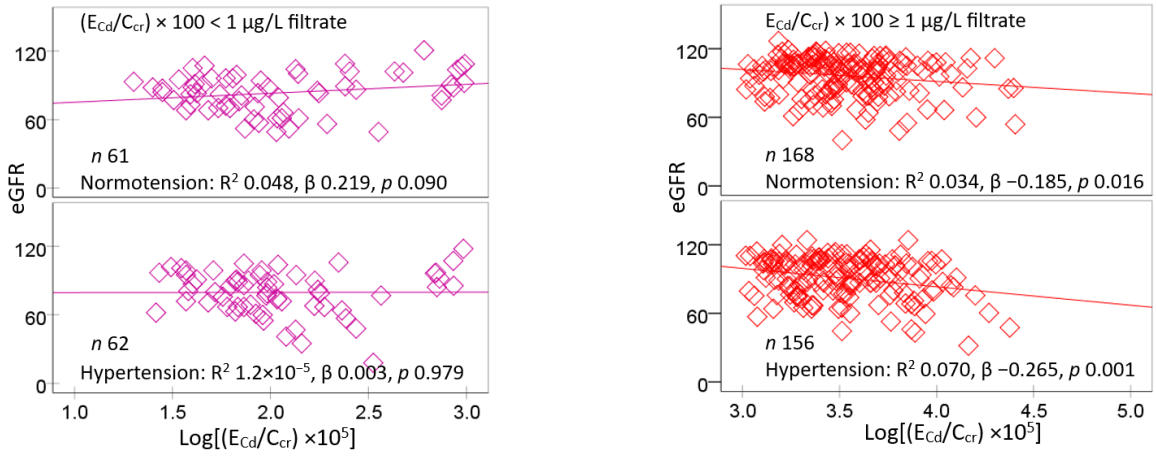
Figure 1. Comparing cadmium effects on GFR in women and men. Scatterplots relate eGFR to $\log[(E_{Cd}/C_{cr}) \times 10^5]$ in women and men with $(E_{Cd}/C_{cr}) \times 100 < 1$ µg/L filtrate (**a**) and $E_{Cd}/C_{cr}) \times 100 \geq 1$ µg/L filtrate (**b**). Coefficients of determination (R^2) and standardized β-coefficients for all scatterplots, numbers of subjects in subgroups, and *p*-values are provided.

A significant inverse dose–response relationship was observed between eGFR and E_{Cd}/C_{cr} in women (β = −0.187) and men (β = −0.322) who had medium plus heavy Cd burdens (Figure 1b), but not in those with a mild Cd burden (Figure 1a).

2.4. Comparing Effects of Cadmium on eGFR in the Normotensive and Hypertensive Groups

Scatterplots that related eGFR to the excretion rate of Cd in the normotensive and hypertensive groups are presented in Figure 2.

Lower eGFR values were associated with higher E_{Cd}/C_{cr} values in both normotensive (β = −0.034) and hypertensive groups (β = −0.070) who had medium plus heavy Cd burdens (Figure 2b). In comparison, eGFR and E_{Cd}/C_{cr} were not corelated with each other in the groups with a mild Cd burden, regardless of blood pressure status (Figure 2a).



(**a**) (**b**)

Figure 2. Comparing the effects of cadmium on GFR in the normotensive and hypertensive groups. Scatterplots relate eGFR to log[(ECd/Ccr) × 105] in normotensive and hypertensive with $(E_{Cd}/C_{cr}) \times 100 < 1$ µg/L filtrate (**a**) and $E_{Cd}/C_{cr}) \times 100 \geq 1$ µg/L filtrate (**b**). Coefficients of determination (R2) and standardized β-coefficients for all scatterplots, numbers of subjects in subgroups, and *p*-values are provided.

In a multiple regression of eGFR, age, BMI, $\log_2[(E_{Cd}/C_{cr}) \times 10^5]$, gender, hypertension, smoking, and diabetes contributed, respectively, to 27.9%, 24.8%, 31.8%, and 24.2% of the variation in eGFR in women and men, and in the normotensive and hypertensive groups (Table 5).

Table 5. Comparing inverse associations of eGFR with the cadmium excretion rate in subjects grouped by gender and blood pressure status.

Independent Variables/ Factors	eGFR, mL/min/1.73 m²							
	Women, *n* = 333		Men, *n* = 114		Normotension, *n* = 229		Hypertension, *n* = 218	
	β	*p*	β	*p*	β	*p*	β	*p*
Age, years	−0.528	<0.001	−0.505	<0.001	−0.559	<0.001	−0.517	<0.001
BMI, kg/m²	−0.050	0.308	−0.136	0.122	−0.037	0.532	−0.077	0.216
$\log_2[(E_{Cd}/C_{cr}) \times 10^5]$, µg/L filtrate	−0.121	0.051	−0.077	0.463	−0.056	0.440	−0.177	0.023
Gender	–	–	–	–	−0.017	0.787	−0.012	0.870
Hypertension	−0.045	0.344	−0.203	0.018	–	–	–	–
Smoking	0.031	0.533	0.043	0.624	0.152	0.020	−0.098	0.178
Diabetes	−0.133	0.016	−0.018	0.854	−0.049	0.445	−0.175	0.012
Adjusted R^2	0.279	<0.001	0.248	<0.001	0.318	<0.001	0.242	<0.001

n, number of subjects; eGFR, estimated glomerular filtration rate; β, standardized regression coefficient; BMI, body mass index; adjusted R^2, coefficient of determination. β indicates strength of association of eGFR with seven independent variables (first column). Adjusted R^2 indicates the proportion of eGFR variation explained by all independent variables. *p*-values ≤ 0.05 indicate statistically significant associations of independent variables and eGFR.

In women, lower eGFR values were associated with older age (β = −0.528) higher E_{Cd}/C_{cr} (β = −0.121), and diabetes (β = −0.133). In men, lower eGFR values were associated with older age (β = −0.505) and hypertension (β = −0.203). In the normotensive group, eGFR was inversely associated with age (β = −0.559) while showing a positive association with smoking. In the hypertensive group, eGFR was inversely associated with age (β = −0.517), E_{Cd}/C_{cr} (β = −0.177), and diabetes (β = −0.175).

2.5. Inverse Relationships between Blood Pressure and eGFR

Scatterplots relating blood pressure levels to eGFR can be found in Figure 3.

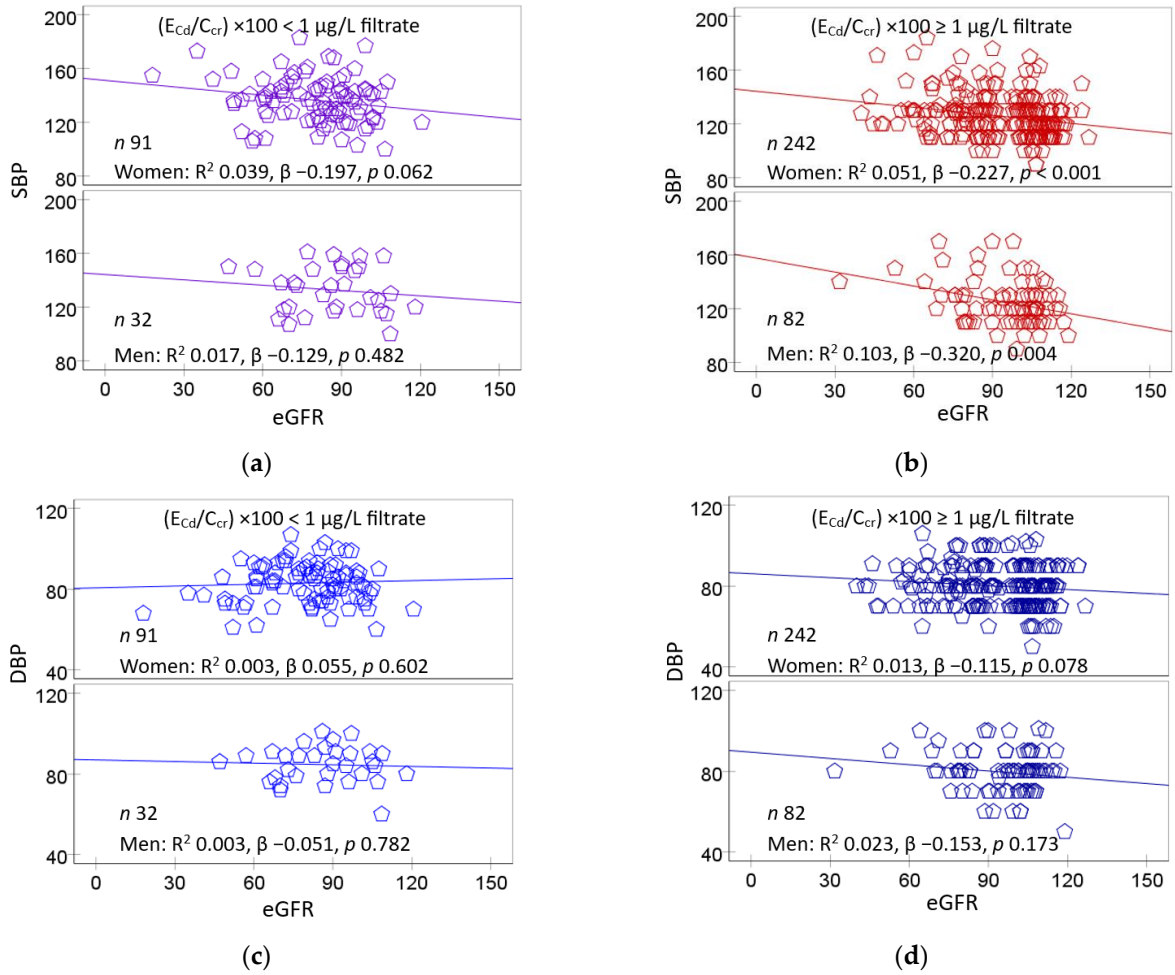


Figure 3. Cadmium and eGFR as predictors of blood pressure increases. Scatterplots relate SBP (**a**,**b**) and DBP (**c**,**d**) to eGFR in women and men with $(E_{Cd}/C_{cr}) \times 100$ of <1 and ≥ 1 µg/L filtrate. Coefficients of determination (R^2) and standardized β-coefficients for all scatterplots, numbers of participants in subgroups, and *p*-values are provided.

A significant inverse dose–response relationship was evident between SBP and eGFR in women (β = −0.227) and men (β = −0.320) of the medium plus heavy Cd burden group (Figure 3b), but not a mild Cd burden group (Figure 3a). In comparison, DBP did not significantly correlate with eGFR in women or men at any Cd burden (Figure 3c,d).

2.6. Regression Model Analysis of SBP and DBP

Results of an evaluation of the independent effect of GFR and diabetes on SBP and DBP are presented in Table 6.

Age, BMI, $\log_2[(E_{Cd}/C_{cr}) \times 10^5]$, eGFR, gender, hypertension, smoking, and diabetes together contributed, respectively, to 19.9%, 15.7%, and 15.0% of the variation in SBP in all subjects, the mild Cd burden, and medium plus heavy Cd burden groups. The fractional DBP variation explained by these independent variables in the mild Cd burden, and medium plus heavy Cd burden groups, were 4.6%, 0%, and 5.8%, respectively.

Table 6. Multiple linear regression analysis to evaluate association of systolic and diastolic blood pressures with cadmium, eGFR, and other variables.

Independent Variables/Factors	SBP or DBP					
	All, n = 447		Mild Cd Burden [a] n = 123		Medium + Heavy n = 324	
	β	p	β	p	β	p
Model 1: SBP						
Age, years	0.243	<0.001	0.395	<0.001	0.091	0.143
BMI, kg/m^2	0.113	0.013	0.081	0.361	0.097	0.084
$Log_2[(E_{Cd}/C_{cr}) \times 10^5]$, µg/L filtrate	0.027	0.624	0.080	0.372	−0.051	0.352
eGFR, mL/min/1.73 m^2	−0.106	0.036	0.011	0.907	−0.176	0.004
Gender	−0.044	0.378	−0.096	0.360	−0.024	0.688
Smoking	−0.075	0.145	−0.176	0.093	−0.031	0.600
Diabetes	0.216	<0.001	0.202	0.020	0.265	<0.001
Adjusted R^2	0.199	<0.001	0.157	<0.001	0.150	<0.001
Model 2: DBP						
Age, years	−0.028	0.650	0.036	0.739	−0.081	0.213
BMI, kg/m^2	0.123	0.013	0.069	0.475	0.123	0.037
$Log_2[(E_{Cd}/C_{cr}) \times 10^5]$, µg/L filtrate	−0.069	0.255	−0.059	0.546	−0.025	0.660
eGFR, mL/min/1.73 m^2	−0.085	0.123	0.057	0.582	−0.130	0.041
Gender	−0.055	0.314	−0.207	0.074	−0.003	0.968
Smoking	−0.050	0.373	−0.209	0.068	0.008	0.897
Diabetes	0.102	0.064	0.027	0.775	0.193	0.001
Adjusted R^2	0.046	<0.001	−0.005	0.498	0.058	0.001

[a] Mild, medium plus heavy Cd burdens were defined as $(E_{Cd}/C_{cr}) \times 100 < 1$ and ≥ 1 µg/L, respectively. eGFR, estimated glomerular filtration rate; β, standardized regression coefficient; adjusted R^2, coefficient of determination. β indicates strength of association of eGFR with seven independent variables (first column). Adjusted R^2 indicates the fraction of SBP and DBP variability that all independent variables explained. p-values ≤ 0.05 indicate statistically significant associations of independent variables and blood pressure.

In an inclusive analysis, higher SBP values were associated with older age (β = 0.243), higher BMI (β = 0.113), lower eGFR (β = −0.106), and diabetes (β = 0.216). In the mild Cd burden group, SBP showed positive associations with BMI (β = 0.395) and diabetes (β = 0.202). In the medium plus high Cd burden group, SBP showed a significant association with diabetes (β = 0.265), while showing an inverse association with eGFR (β = −0.176).

In an equivalent inclusive analysis, higher DBP values were associated only with higher BMI values (β = 0.123). In the medium plus high Cd burden group only, higher DBP values were associated with higher BMI (β = 0.123), lower eGFR (β = −0.130), and diabetes (β = 0.193).

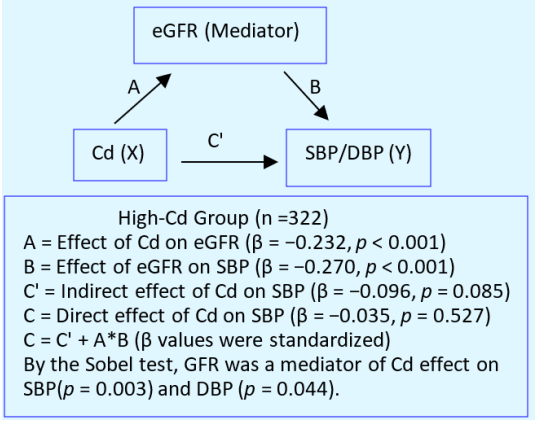
2.7. Mediation Analysis

We employed a simple mediation model analysis to explore whether Cd increased blood pressure through its effect on GFR. In this analysis, eGFR was a single mediator, while E_{Cd}/C_{cr} was an independent variable, and SBP or DBP was a dependent variable). Results for those with $(E_{Cd}/C_{cr}) \times 100 \geq 1$ µg/L filtrate (the high Cd-group, n = 322) can be found in Figure 4.

In the high-Cd group, Cd did not affect SBP or DBP directly, but through its effect on GFR. GFR was a full mediator of the increment of both SBP and DBP in Cd exposed persons with $(E_{Cd}/C_{cr}) \times 100 \geq 1$ µg/L filtrate.

An equivalent mediation analysis was undertaken for those with $(E_{Cd}/C_{cr}) \times 100 < 1$ µg/L filtrate (the low-Cd burden group, n = 123), and results are provided in Figure 5.

In the low-Cd group (Figure 5), an effect of eGFR on SBP was statistically significant (standardized β = −0.186, p = 0.041). However, the Sobel test result (A*B) indicated that eGFR was not a mediator of the effect of Cd on SBP (p = 0.309) or DBP (p = 0.595).



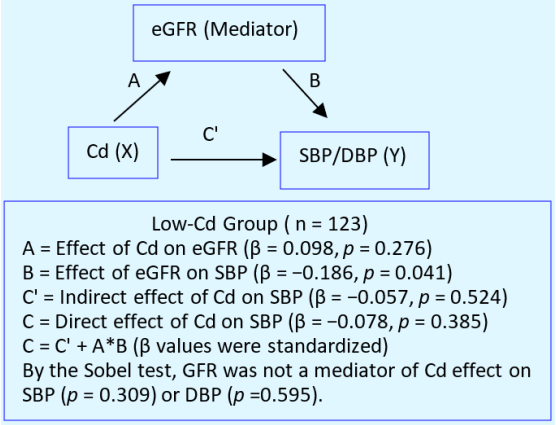
(**a**)

The Sobel Test			
SBP	β (SE)	95% CI of β	*p*-value
A	−13.79 (3.628.)	−21.00, −6.148	<0.001
B	−0.249 (0.052)	−0.351, −0.156	0.001
A*B	4.433	–	0.003
C	−1.934 (2.651)	−7.119, 3.488	0.470
C'	−5.227 (2.633)	−10.62, −0.172	0.055
DBP	β (SE)	95% CI of β	*p*-value
A	−13.37 (3.640)	−21.69, −5.591	0.001
B	−0.080 (0.033)	−0.147, −0.020	0.022
A*B	1.70	–	0.044
C	−0.570 (1.675)	−3.773, 2.655	0.727
C'	−1.623 (1.734)	−5.037, 1.519	0.363

SE, standard error of mean; CI, confidence interval. β and 95% CI values were unstandardized, obtained by bootstrapping.

(**b**)

Figure 4. Mediation analysis of the effect of cadmium on blood pressure in the high-exposure group. (**a**) A model depicts eGFR as a mediator of the effect of Cd on blood pressure increases and standardized β values (**b**) The Sobel test of unstandardized β coefficients describing relationships of Cd with eGFR (A), eGFR with blood pressure (B), and Cd with blood pressure (C′).



(**a**)

The Sobel Test			
SBP	β (SE)	95% CI of β	*p*-value
A	4.048 (3.488)	−3.459, 10.48	0.231
B	−0.176 (0.083)	−0.334, 0.007	0.036
A*B	0.172	–	0.309
C	−3.074 (3.486)	−10.20, 4.038	0.389
C'	−2.234 (3.335)	−9.149, 4.768	0.502
DBP	β (SE)	95% CI of β	*p*-value
A	4.861 (3.677)	−2.004, 11.38.	0.183
B	0.029 (0.050)	−0.066, 0.121	0.570
A*B	0.140	–	0.595
C	−2.089 (2.134)	−6.027, 2.069	0.313
C'	−2.222 (2.122)	−6.174, 2.001	0.294

SE, standard error of mean; CI, confidence interval. β and 95% CI values were unstandardized, obtained by bootstrapping.

(**b**)

Figure 5. Mediation analysis of the effect of cadmium on blood pressure in the low-exposure group. (**a**) A model depicts eGFR as a mediator of the effect of Cd on blood pressure increases and standardized β values. (**b**) The Sobel test of unstandardized β coefficients describing relationships of Cd with eGFR (A), eGFR with blood pressure (B), and Cd with blood pressure (C′).

3. Discussion

In this Thai cohort of 447 adults, the overall mean Cd excretion rate was 0.003 µg/L filtrate, corresponding to 4.03 µg/g creatinine. The mean blood and urinary Cd concentrations were 2.75 and 4.23 µg/L, respectively. Nearly half (48.8%) of the cohort's participants had hypertension, while 15.4% and 6.9% had diabetes and low eGFR, respectively. Similarly, a study from Bangladesh reported that half of those aged ≥ 60 years had hypertension [46]. The prevalence of low eGFR in our study was in line with the figure of 6.3% found in the Taiwanese general population [47]. However, the % of hypertension and diabetes in the present study were higher than those recorded in studies from the U.S., where hypertension and diabetes were 39% and 10.3–13%, respectively [48,49].

The high prevalence of hypertension in this cohort was its strength as it meant that even a modest sample size (n < 1000) could offer a sufficient number of cases from which a reliable conclusion could be drawn. Previously, an effect of smoking on the risk of CVD had been found to be partially mediated by Cd [50,51]. An inclusion of smokers and diabetics was an additional strength as they enabled an adjustment for their effects in

realistic population situations. Another strength was that Cd exposure was assessed with blood and urinary Cd levels.

The limitations of the study are acknowledged. They include a one-time-only assessment of Cd exposure and its effects, and the heterogeneity in the hormonal status of women; both menopausal and post-menopausal women were included [52–56], and there was a small number of men (n = 114) in the study cohort; this meant that definitive conclusions about gender disparity in the prevalence, severity, and adverse outcomes of Cd-induced hypertension could not be made [53–56].

3.1. A Rise in Blood Pressure at Low Levels of Cadmium Exposure

An increased risk of hypertension was associated with both urinary and blood Cd levels (Tables 2 and 3). POR for hypertension rose two-fold in the medium burden group and in those with the blood Cd quartiles 2 and 3. However, the increases in POR for hypertension in those with a heavy burden of Cd (POR 1.66) and those with the top blood Cd quartile (POR 1.80) were not statistically significant. Thus, Cd effects on blood pressure appeared to be particularly strong in low-dose exposure conditions as detailed below.

In a Chinese case-control study, a 1.33-fold increase in the risk of hypertension was associated with urinary Cd levels > 1.07 μg/L [20]. In the present study, a two-fold rise in POR for hypertension was observed in the medium burden group with urinary Cd levels > 0.57 μg/L (Table 2). A 2.6-fold increase in risk of hypertension was seen in white and Mexican-American women who had blood Cd levels ≥ 0.4 μg/L [15]. In the present study, an increase in POR for hypertension was found in those who had blood Cd of 0.61–3.38 μg/L (Table 3).

In a study from Korea, increases in prevalence of pre-hypertension and hypertension were associated with doubling blood Cd from 0.62 to 1.33 μg/L in men, and from 0.73 to 1.57 μg/L in women [22]. In a study of residents in a Cd-polluted area of China, increased risk of hypertension was associated with blood Cd of 1–1.7 μg/L [19].

In a Canadian study, SBP and DBP were positively associated with blood Cd, but the risk of hypertension fell 52% in women who were current smokers and had a very high blood Cd level [18]. In the Canadian health measure survey, the mean values for blood and urinary excretion of Cd in current smokers were 1.64 μg/L and 0.58 μg/g creatinine, respectively [57]. A similar observation was made in a U.S. population study, where associations between blood pressure measurements and blood Cd were particularly strong in non-smokers, moderate in former smokers, and weak or negligible in current smokers [15].

3.2. Different Susceptibility to Cadmium-Induced Hypertension

The urinary and blood Cd levels found to be associated with a significant increase in risk of hypertension varied among populations. This may be due to different susceptibility to hypertension or some protective factors. For instance, white and Mexican-American women were found to be more susceptible to Cd-induced blood pressure increases than black women; an increased risk of hypertension was seen in Caucasian (OR 1.54) and Mexican-American women (OR 2.38) who had blood Cd as little as 0.4 μg/L, but not in black women or white, black, or Mexican-American men [16].

Male–female differences were evident from a regression model analysis (Table 5), where an inverse association of eGFR and Cd burden was found only in women ($\beta = -0.121$, $p = 0.051$). In comparison, male eGFR did not show a significant association with Cd burden ($\beta = -0.077$, $p = 0.463$). In a Taiwanese study, an association of urinary Cd and a tubular damage marker (urinary NAG) was found in women only [58]. In a Thai population study, the risk of hypertension rose 20% in Cd-exposed subjects with kidney tubular damage, assessed with urinary NAG excretion [59].

People with diabetes were more susceptible to adverse kidney effects of Cd than their non-diabetic counterparts. In a Dutch cross-sectional study, including 231 patients with type 2 diabetes, Cd exposure increased the risk of diabetic kidney disease [60]. In a

six-year median follow-up of these diabetic patients, a progressive reduction of eGFR was attributable to Cd exposure [36].

In a prospective cohort study, a 49% increase in all-cause mortality among the diabetics was associated with urinary Cd levels > 0.60 μg/L [61]. In the present study, the risk of having low eGFR, moderate, and severe tubular proteinuria among diabetics rose 4.3-fold, 5.5-fold, and 13.4-fold, respectively (Table 4). Both SBP (β = 0.265) and DBP (β = 0.193) rose significantly among diabetics with $(E_{Cd}/C_{cr}) \times 100 \geq 1$ μg/L filtrate (Table 6). This Cd-induced SBP and DBP increment may promote kidney disease development in Cd-exposed diabetics given that hypertension is a strong independent risk factor for the development and progression of CKD [3,62]. A 1.76-fold increase in death from CVD among U.S. citizens with hypertension was associated with elevated Cd exposure, indicated by blood Cd levels ≥ 0.80 μg/L [63]. At the same Cd exposure level, the risk of death from CVD rose 2.12-fold among non-smokers who had hypertension [63].

3.3. A Rise of Blood Pressure Due to Tubular Damage and GFR Loss

To the best of our knowledge, the present study has provided, for the first time, evidence linking Cd-induced eGFR reduction to a rise in blood pressure (Figure 3). SBP was inversely associated with eGFR in women (β = −0.227) and men (β = −0.320) who had medium plus heavy Cd burdens, $(E_{Cd}/C_{cr}) \times 100 \geq 1$ μg/L filtrate. DBP showed a weak inverse association with eGFR (Figure 3a,b vs. Figure 3c,d). By multiple regression analysis (Table 6), an independent effect of eGFR reduction on a rise of SBP was found in the medium plus heavy Cd burden group (β = −0.176). Using the mediation analysis, GFR reduction was a full mediator of Cd effect on blood pressure increases in the high-exposure group (Figure 4). Our observation that blood pressure rises as GFR falls helps to explain why patients with CKD have hypertension almost universally.

The doubling of the body burden of Cd was associated, respectively, with increases of 41%, 23%, and 48% in the POR values for low eGFR, moderate, and severe tubular proteinuria, evident from increased β_2M excretion levels (Table 4). In Japanese population studies, increased β_2M excretion levels were associated with enhanced risks of hypertension and a large decline in eGFR (10 mL/min/1.73 m^2) over a five-year observation period [64,65]. Thus, an increased risk of hypertension among study subjects could be attributed to Cd-induced tubular damage and GFR loss.

In summary, we have shown that increases in blood pressure may be a consequence of a decrease in GFR induced by Cd. The indispensable role of the kidneys in long-term blood pressure regulation is well established [2]. As their function declines (indicated by low eGFR), the kidneys eliminate less water and sodium, which may increase blood pressure. Rats with Cd-induced hypertension showed increased sodium retention and reduced sodium excretion [66–68]. Thus, increased tubular avidity for filtered sodium appeared to be a possible mechanism by which lifelong, low-dose Cd intake caused hypertension.

CKD has now reached epidemic proportions and is predicted to become an even greater health problem in years to come as its major risk factors—obesity, diabetes, hypertension, and non-alcoholic fatty liver—continue to rise. Given the immense financial and community burden, developing strategies to reduce its progression to kidney failure is of vital importance. Cd excretion corresponding to a discernible GFR decline at E_{Cd}/C_{cr} of 0.01 μg/L filtrate is extremely low.

4. Materials and Methods

4.1. Participants

This study was conducted following the principles outlined in the Declaration of Helsinki. Participants were recruited from Nakhon Si Thammarat Province in the south and Mae Sot District in the northwest of Thailand [69,70]. Previous studies suggest female preponderance effects Cd exposure [9,12]. Thus, more women were recruited to maximize the likelihood of finding an effect of Cd in a modest sample size (n = 447).

All participants gave informed consent prior to participation. They had been living at their current addresses for at least 30 years. Exclusion criteria were pregnancy, breast-feeding, a history of metal work, and a hospital record or physician's diagnosis of an advanced chronic disease. All subjects were provided with details of study objectives, study procedures, benefits, and potential risks, and they all provided their written informed consent prior to participation.

The Office of the Human Research Ethics Committee of Walailak University approved the study protocol for the Nakhon Si Thammarat group (Approval number WUEC-20-132-01, 28 May 2020) [69]. The study protocol for the Mae Sot group was approved by the Institutional Ethical Committees of Chiang Mai University and the Mae Sot Hospital (Approval No. 142/2544, 5 October 2001) [70].

Levels of various contaminants, including arsenic, chromium, lead, and Cd in samples of soils and food crops in Nakhon Si Thammarat were within permissible ranges [68], and no association was found between water arsenic concentration and the risk of diabetes [71,72]. In comparison, the Cd concentration of the paddy soil samples from the Mae Sot district exceeded the standard of 0.15 mg/kg, and the rice samples collected from household storage contained four times the amount of the permissible Cd level of 0.1 mg/kg [73]. In a health survey of residents of the Mae Sot District (n = 5273), urinary Cd excretion levels correlated with hypertension and diabetes [74].

4.2. Blood Pressure and Cadmium Exposure Ascertainment

Our study design was population-based and recruited participants from their communities. This precluded a 24 h measurement, and more visits to communities for a second measurement. The one-time measurement of SBP/DBP was the average of 3 repeated measurements. The diagnosis of hypertension relied primarily on the assessment made by the presiding physician and the recorded use of anti-hypertensive medication. Of 233 subjects included as hypertensive cases in our study, 220 (94.4%) were being treated and 13 hypertensive cases were identified during our visit.

Cd exposure was based on urinary Cd excretion (E_{Cd}) and blood Cd concentration ($[Cd]_b$). Simultaneous urine and whole blood sampling were undertaken after an overnight fast. Aliquots of blood and urine samples were stored at −80 °C for later analysis. Atomic absorption spectrophotometry was used to determine urinary and blood levels of $[Cd]_u$ and $[Cd]_b$ using multi-element standards (Merck KGaA, Darmstadt, Germany) for instrument calibration. For quality control and assurance purposes, blood and urine samples from subjects, blood control samples (ClinChek, Munich, Germany), and the reference urine metal controls (Lyphocheck, Bio-Rad, Hercules, CA, USA) were simultaneously analyzed.

The limit of detection (LOD) for Cd in blood or urine was 0.3 µg/L for $[Cd]_b$ and 0.1 µg/L for $[Cd]_u$. The Cd concentration assigned to a sample that contained Cd below its LOD was assigned a value of the LOD divided by the square root of 2 [75].

4.3. Normalization of Cadmium Excretion Rate

E_{Cd} was normalized to creatinine clearance (C_{cr}) as $E_{Cd}/C_{cr} = [Cd]_u[cr]_p/[cr]_u$, where $[Cd]_u$ = urine concentration of Cd (mass/volume); $[cr]_p$ = plasma creatinine concentration (mg/dL); and $[cr]_u$ = urine creatinine concentration (mg/dL). E_{Cd}/C_{cr} was expressed as an amount of Cd excreted per volume of the glomerular filtrate. C_{cr}-normalization corrects for urine dilution and number of functioning nephrons [45].

E_{Cd} was normalized to E_{cr} as $[Cd]_u/[cr]_u$, where $[Cd]_u$ = urine concentration of Cd (mass/volume) and $[cr]_u$ = urine creatinine concentration (mg/dL). E_{Cd}/E_{cr} was expressed in µg/g creatinine. E_{cr}-normalization corrects for urine dilution, but it is influenced by muscle mass. The effect of Cd exposure on GFR was obscure, when E_{Cd} was normalized to E_{cr} [76].

4.4. Estimated Glomerular Filtration Rate (eGFR)

We used the GFR estimating equations, established by the chronic kidney disease epidemiology collaboration (CKD–EPI) to compute the estimated GFR (eGFR) [44]. The CKD–EPI equations have been validated with inulin clearance [77].

Male eGFR = $141 \times [cr]_p/0.9^Y \times 0.993^{age}$, where Y = -0.411 if $[cr]_p \leq 0.9$ mg/dL and Y = -1.209 if $[cr]_p > 0.9$ mg/dL.

Female eGFR = $144 \times [cr]_p/0.7^Y \times 0.993^{age}$, where Y = -0.329 if $[cr]_p \leq 0.7$ mg/dL and Y = -1.209 if $[cr]_p > 0.7$ mg/dL.

4.5. Statistical Analysis

Data were analyzed with IBM SPSS Statistics 21 (IBM Inc., New York, NY, USA). The Kruskal-Wallis test was used to assess differences in means across tertiles of Cd burden, and the Pearson chi-squared test was used to assess differences in percentages. Distribution of continuous variables was assessed by the one-sample Kolmogorov–Smirnov test. A logarithmic transformation was applied to variables that showed rightward skewing. A simple mediation model with a single mediator was used in the mediation analysis [78,79]

Prevalence Odds Ratio (POR) for hypertension, which was defined as SBP $\geq$ 140 mmHg or DBP $\geq$ 90 mmHg [1], was determined by logistic regression. Multiple linear regression was used to identify variables affecting eGFR, SBP, and DBP. For all tests, p-values ≤ 0.05 were considered as statistically significant.

5. Conclusions

By mediation analysis, an increase in SBP was attributable totally to Cd-induced GFR loss. Cd appeared to influence SBP more markedly than DBP. A two-fold increased risk of hypertension was associated with urinary Cd excretion of 0.98 μg/g creatinine and a blood Cd level of 0.61 μg/L. As these are levels that are reported widely in studies of non-occupationally exposed populations from across the world, it is imperative that authorities monitor the environmental levels of Cd closely, especially in staple foods.

Author Contributions: Conceptualization, S.S., D.A.V. and A.B.Đ.; methodology, S.Y., T.K. and P.P.; formal analysis, S.S. and A.B.Đ.; investigation, S.S., S.Y., T.K. and P.P.; resources, D.A.V., S.Y. and A.B.Đ.; data curation, S.S. and S.Y.; writing—original draft preparation, S.S.; writing—review and editing, S.S., D.A.V. and A.B.Đ.; project administration, S.S. and S.Y. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: This is not applicable for the present study, which used archived data [69,70].

Informed Consent Statement: Written informed consent was obtained from study subjects.

Data Availability Statement: All data are contained within this article.

Acknowledgments: This work was supported by resources from the Centre for Kidney Disease Research, Translational Research Institute, the Department of Kidney and Transplant Services, Princess Alexandra Hospital, the Department of Toxicology, Faculty of Pharmacy, University of Belgrade, Serbia.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Bloch, M.J.; Basile, J.N. Review of recent literature in hypertension: Updated clinical practice guidelines for chronic kidney disease now include albuminuria in the classification system. *J. Clin. Hypertens.* **2013**, *15*, 865–867. [CrossRef] [PubMed]
2. Crowley, S.D.; Coffman, T.M. The inextricable role of the kidney in hypertension. *J. Clin. Investig.* **2014**, *124*, 2341–2347.
3. Kalantar-Zadeh, K.; Jafar, T.H.; Nitsch, D.; Neuen, B.L.; Perkovic, V. Chronic kidney disease. *Lancet* **2021**, *398*, 786–802. [CrossRef] [PubMed]
4. Foreman, K.J.; Marquez, N.; Dolgert, A.; Fukutaki, K.; Fullman, N.; McGaughey, M.; Pletcher, M.A.; Smith, A.E.; Tang, K.; Yuan, C.W.; et al. Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: Reference and alternative scenarios for 2016-40 for 195 countries and territories. *Lancet* **2018**, *392*, 2052–2090. [CrossRef] [PubMed]

5. GBD 2021 Forecasting Collaborators. Burden of disease scenarios for 204 countries and territories, 2022–2050: A forecasting analysis for the Global Burden of Disease Study 2021. *Lancet* **2024**, *403*, 2204–2256. [CrossRef]
6. Verzelloni, P.; Urbano, T.; Wise, L.A.; Vinceti, M.; Filippini, T. Cadmium exposure and cardiovascular disease risk: A systematic review and dose-response meta-analysis. *Environ. Pollut.* **2024**, *345*, 123462. [CrossRef] [PubMed]
7. Doccioli, C.; Sera, F.; Francavilla, A.; Cupisti, A.; Biggeri, A. Association of cadmium environmental exposure with chronic kidney disease: A systematic review and meta-analysis. *Sci. Total Environ.* **2024**, *906*, 167165. [CrossRef] [PubMed]
8. Zhang, J.; Wang, X.; Ma, Z.; Dang, Y.; Yang, Y.; Cao, S.; Ouyang, C.; Shi, X.; Pan, J.; Hu, X. Associations of urinary and blood cadmium concentrations with all-cause mortality in US adults with chronic kidney disease: A prospective cohort study. *Environ. Sci. Pollut. Res. Int.* **2023**, *30*, 61659–61671. [CrossRef]
9. Nishijo, M.; Satarug, S.; Honda, R.; Tsuritani, I.; Aoshima, K. The gender differences in health effects of environmental cadmium exposure and potential mechanisms. *Mol. Cell. Biochem.* **2004**, *255*, 87–92. [CrossRef]
10. Trzcinka-Ochocka, M.; Jakubowski, M.; Szymczak, W.; Janasik, B.; Brodzka, R. The effects of low environmental cadmium exposure on bone density. *Environ. Res.* **2010**, *110*, 286–293. [CrossRef]
11. Nishijo, M.; Nambunmee, K.; Suvagandha, D.; Swaddiwudhipong, W.; Ruangyuttikarn, W.; Nishino, Y. Gender-specific impact of cadmium exposure on bone metabolism in older people living in a cadmium-polluted area in Thailand. *Int. J. Environ. Res. Public Health* **2017**, *14*, 401. [CrossRef] [PubMed]
12. Madrigal, J.M.; Ricardo, A.C.; Persky, V.; Turyk, M. Associations between blood cadmium concentration and kidney function in the U.S. population: Impact of sex, diabetes and hypertension. *Environ. Res.* **2018**, *169*, 180–188. [CrossRef] [PubMed]
13. Mortensen, M.E.; Wong, L.Y.; Osterloh, J.D. Smoking status and urine cadmium above levels associated with subclinical renal effects in U.S. adults without chronic kidney disease. *Int. J. Hyg. Environ. Health* **2011**, *214*, 305–310. [CrossRef] [PubMed]
14. Satarug, S.; Ujjin, P.; Vanavanitkun, Y.; Baker, J.R.; Moore, M.R. Influence of body iron store status and cigarette smoking on cadmium body burden of healthy Thai women and men. *Toxicol. Lett.* **2004**, *148*, 177–185. [CrossRef] [PubMed]
15. Tellez-Plaza, M.; Navas-Acien, A.; Crainiceanu, C.M.; Guallar, E. Cadmium exposure and hypertension in the 1999–2004 National Health and Nutrition Examination Survey (NHANES). *Environ. Health Perspect.* **2008**, *116*, 51–56. [CrossRef] [PubMed]
16. Scinicariello, F.; Abadin, H.G.; Murray, H.E. Association of low-level blood lead and blood pressure in NHANES 1999–2006. *Environ. Res.* **2011**, *111*, 1249–1257. [CrossRef]
17. Oliver-Williams, C.; Howard, A.G.; Navas-Acien, A.; Howard, B.V.; Tellez-Plaza, M.; Franceschini, N. Cadmium body burden, hypertension, and changes in blood pressure over time: Results from a prospective cohort study in American Indians. *J. Am. Soc. Hypertens.* **2018**, *12*, 426–437.e9. [CrossRef]
18. Garner, R.E.; Levallois, P. Associations between cadmium levels in blood and urine, blood pressure and hypertension among Canadian adults. *Environ. Res.* **2017**, *155*, 64–72. [CrossRef]
19. Chen, X.; Wang, Z.; Zhu, G.; Liang, Y.; Jin, T. Benchmark dose estimation of cadmium reference level for hypertension in a Chinese population. *Environ. Toxicol. Pharmacol.* **2015**, *39*, 208–212. [CrossRef]
20. Wu, W.; Liu, D.; Jiang, S.; Zhang, K.; Zhou, H.; Lu, Q. Polymorphisms in gene MMP-2 modify the association of cadmium exposure with hypertension risk. *Environ. Int.* **2019**, *124*, 441–447. [CrossRef]
21. Zhong, Q.; Wu, H.B.; Niu, Q.S.; Jia, P.P.; Qin, Q.R.; Wang, X.D.; He, J.L.; Yang, W.J.; Huang, F. Exposure to multiple metals and the risk of hypertension in adults: A prospective cohort study in a local area on the Yangtze River, China. *Environ. Int.* **2021**, *153*, 106538. [CrossRef] [PubMed]
22. Lee, B.K.; Kim, Y. Association of blood cadmium with hypertension in the Korean general population: Analysis of the 2008–2010 Korean National Health and Nutrition Examination Survey data. *Am. J. Ind. Med.* **2012**, *55*, 1060–1067. [CrossRef] [PubMed]
23. Kwon, J.A.; Park, E.; Kim, S.; Kim, B. Influence of serum ferritin combined with blood cadmium concentrations on blood pressure and hypertension: From the Korean National Health and Nutrition Examination Survey. *Chemosphere* **2022**, *288*, 132469. [CrossRef] [PubMed]
24. Kaneda, M.; Wai, K.M.; Kanda, A.; Ando, M.; Murashita, K.; Nakaji, S.; Ihara, K. Low level of serum cadmium in relation to blood pressures among Japanese general population. *Biol. Trace Element Res.* **2021**, *200*, 67–75. [CrossRef] [PubMed]
25. Watanabe, T.; Kataoka, Y.; Hayashi, K.; Matsuda, R.; Uneyama, C. Dietary exposure of the Japanese general population to elements: Total diet study 2013–2018. *Food Saf.* **2022**, *10*, 83–101. [CrossRef]
26. Almerud, P.; Zamaratskaia, G.; Lindroos, A.K.; Bjermo, H.; Andersson, E.M.; Lundh, T.; Ankarberg, E.H.; Lignell, S. Cadmium, total mercury, and lead in blood and associations with diet, sociodemographic factors, and smoking in Swedish adolescents. *Environ. Res.* **2021**, *197*, 110991. [CrossRef] [PubMed]
27. Kim, J.; Song, H.; Lee, J.; Kim, Y.J.; Chung, H.S.; Yu, J.M.; Jang, G.; Park, R.; Chung, W.; Oh, C.M.; et al. Smoking and passive smoking increases mortality through mediation effect of cadmium exposure in the United States. *Sci. Rep.* **2023**, *13*, 3878. [CrossRef]
28. Hill, D.T.; Jandev, V.; Petroni, M.; Atallah-Yunes, N.; Bendinskas, K.; Brann, L.S.; Heffernan, K.; Larsen, D.A.; MacKenzie, J.A.; Palmer, C.D.; et al. Airborne levels of cadmium are correlated with urinary cadmium concentrations among young children living in the New York state city of Syracuse, USA. *Environ. Res.* **2023**, *223*, 115450. [CrossRef] [PubMed]
29. Kikuchi, Y.; Nomiyama, T.; Kumagai, N.; Dekio, F.; Uemura, T.; Takebayashi, T.; Nishiwaki, Y.; Matsumoto, Y.; Sano, Y.; Hosoda, K.; et al. Uptake of cadmium in meals from the digestive tract of young non-smoking Japanese female volunteers. *J. Occup. Health* **2003**, *45*, 43–52. [CrossRef]

30. Horiguchi, H.; Oguma, E.; Sasaki, S.; Miyamoto, K.; Ikeda, Y.; Machida, M.; Kayama, F. Comprehensive study of the effects of age, iron deficiency, diabetes mellitus, and cadmium burden on dietary cadmium absorption in cadmium-exposed female Japanese farmers. *Toxicol. Appl. Pharmacol.* **2004**, *196*, 114–123. [CrossRef]
31. Satarug, S.; Phelps, K.R. Chapter 14: Cadmium Exposure and Toxicity. In *Metal Toxicology Handbook*; Bagchi, D., Bagchi, M., Eds.; CRC Press: Boca Raton, FL, USA, 2021; pp. 219–274.
32. Satarug, S.; Vesey, D.A.; Gobe, G.C.; Phelps, K.R. Estimation of health risks associated with dietary cadmium exposure. *Arch. Toxicol.* **2023**, *97*, 329–358. [CrossRef] [PubMed]
33. Fujita, Y.; el Belbasi, H.I.; Min, K.S.; Onosaka, S.; Okada, Y.; Matsumoto, Y.; Mutoh, N.; Tanaka, K. Fate of cadmium bound to phytochelatin in rats. *Res. Commun. Chem. Pathol. Pharmacol.* **1993**, *82*, 357–365. [PubMed]
34. Langelueddecke, C.; Roussa, E.; Fenton, R.A.; Thévenod, F. Expression and function of the lipocalin-2 (24p3/NGAL) receptor in rodent and human intestinal epithelia. *PLoS ONE* **2013**, *8*, e71586. [CrossRef] [PubMed]
35. Langelueddecke, C.; Lee, W.K.; Thévenod, F. Differential transcytosis and toxicity of the hNGAL receptor ligands cadmium-metallothionein and cadmium-phytochelatin in colon-like Caco-2 cells: Implications for in vivo cadmium toxicity. *Toxicol. Lett.* **2014**, *226*, 228–235. [CrossRef] [PubMed]
36. Oosterwijk, M.M.; Hagedoorn, I.J.M.; Maatman, R.G.H.J.; Bakker, S.J.L.; Navis, G.; Laverman, G.D. Cadmium, active smoking and renal function deterioration in patients with type 2 diabetes. *Nephrol. Dial. Transplant.* **2023**, *38*, 876–883. [CrossRef] [PubMed]
37. Satarug, S.; Baker, J.R.; Reilly, P.E.; Moore, M.R.; Williams, D.J. Cadmium levels in the lung, liver, kidney cortex, and urine samples from Australians without occupational exposure to metals. *Arch. Environ. Health* **2002**, *57*, 69–77. [CrossRef]
38. Barregard, L.; Sallsten, G.; Lundh, T.; Mölne, J. Low-level exposure to lead, cadmium and mercury, and histopathological findings in kidney biopsies. *Environ. Res.* **2022**, *211*, 113119. [CrossRef]
39. Satarug, S.; Vesey, D.A.; Ruangyuttikarn, W.; Nishijo, M.; Gobe, G.C.; Phelps, K.R. The source and pathophysiologic significance of excreted cadmium. *Toxics* **2019**, *7*, 55. [CrossRef] [PubMed]
40. Akerstrom, M.; Barregard, L.; Lundh, T.; Sallsten, G. The relationship between cadmium in kidney and cadmium in urine and blood in an environmentally exposed population. *Toxicol. Appl. Pharmacol.* **2013**, *268*, 286–293. [CrossRef] [PubMed]
41. Johri, N.; Jacquillet, G.; Unwin, R. Heavy metal poisoning: The effects of cadmium on the kidney. *Biometals* **2010**, *23*, 783–792. [CrossRef]
42. Satarug, S.; Gobe, G.C.; Vesey, D.A.; Phelps, K.R. Cadmium and lead exposure, nephrotoxicity, and mortality. *Toxics* **2020**, *8*, 86. [CrossRef] [PubMed]
43. Lang, S.M.; Schiffl, H. Smoking status, cadmium, and chronic kidney disease. *Ren. Replace Ther.* **2024**, *10*, 17. [CrossRef]
44. Levey, A.S.; Stevens, L.A.; Scmid, C.H.; Zhang, Y.; Castro, A.F., III; Feldman, H.I.; Kusek, J.W.; Eggers, P.; Van Lente, F.; Greene, T.; et al. A new equation to estimate glomerular filtration rate. *Ann. Intern. Med.* **2009**, *150*, 604–612. [CrossRef]
45. Phelps, K.R.; Gosmanova, E.O. A generic method for analysis of plasma concentrations. *Clin. Nephrol.* **2020**, *94*, 43–49. [CrossRef] [PubMed]
46. Hanif, A.A.M.; Shamim, A.A.; Hossain, M.M.; Hasan, M.; Khan, M.S.A.; Hossaine, M.; Ullah, M.A.; Sarker, S.K.; Rahman, S.M.M.; Mitra, D.K.; et al. Gender-specific prevalence and associated factors of hypertension among elderly Bangladeshi people: Findings from a nationally representative cross-sectional survey. *BMJ Open* **2021**, *11*, e038326. [CrossRef] [PubMed]
47. Tsai, H.J.; Hung, C.H.; Wang, C.W.; Tu, H.P.; Li, C.H.; Tsai, C.C.; Lin, W.Y.; Chen, S.C.; Kuo, C.H. Associations among heavy metals and proteinuria and chronic kidney disease. *Diagnostics* **2021**, *11*, 282. [CrossRef] [PubMed]
48. Shi, P.; Yan, H.; Fan, X.; Xi, S. A benchmark dose analysis for urinary cadmium and type 2 diabetes mellitus. *Environ. Pollut.* **2021**, *273*, 116519. [CrossRef] [PubMed]
49. Lee, J.; Oh, S.; Kang, H.; Kim, S.; Lee, G.; Li, L.; Kim, C.T.; An, J.N.; Oh, Y.K.; Lim, C.S.; et al. Environment-wide association study of CKD. *Clin. J. Am. Soc. Nephrol.* **2020**, *15*, 766–775. [CrossRef]
50. Li, H.; Fagerberg, B.; Sallsten, G.; Borné, Y.; Hedblad, B.; Engström, G.; Barregard, L.; Andersson, E.M. Smoking-induced risk of future cardiovascular disease is partly mediated by cadmium in tobacco: Malmö Diet and Cancer Cohort Study. *Environ. Health* **2019**, *18*, 56. [CrossRef]
51. Hecht, E.M.; Landy, D.C.; Ahn, S.; Hlaing, W.M.; Hennekens, C.H. Hypothesis: Cadmium explains, in part, why smoking increases the risk of cardiovascular disease. *J. Cardiovasc. Pharmacol. Ther.* **2013**, *18*, 550–554. [CrossRef]
52. Vahter, M.; Berglund, M.; Akesson, A. Toxic metals and the menopause. *J. Br. Menopause Soc.* **2004**, *10*, 60–64. [CrossRef] [PubMed]
53. Reckelhoff, J.F. Gender differences in the regulation of blood pressure. *Hypertension* **2001**, *37*, 1199–1208. [CrossRef] [PubMed]
54. Reckelhoff, J.F. Mechanisms of sex and gender differences in hypertension. *J. Hum. Hypertens.* **2023**, *37*, 596–601. [CrossRef] [PubMed]
55. Connelly, P.J.; Currie, G.; Delles, C. Sex differences in the prevalence, outcomes and management of hypertension. *Curr. Hypertens. Rep.* **2022**, *24*, 185–192. [CrossRef] [PubMed]
56. Choi, H.M.; Kim, H.C.; Kang, D.R. Sex differences in hypertension prevalence and control: Analysis of the 2010–2014 Korea National Health and Nutrition Examination Survey. *PLoS ONE* **2017**, *12*, e0178334. [CrossRef] [PubMed]
57. Garner, R.; Levallois, P. Cadmium levels and sources of exposure among Canadian adults. *Health Reports* **2016**, *27*, 10–18. [PubMed]
58. Liao, K.W.; Chien, L.C.; Chen, Y.C.; Kao, H.C. Sex-specific differences in early renal impairment associated with arsenic, lead, and cadmium exposure among young adults in Taiwan. *Environ. Sci. Pollut. Res. Int.* **2022**, *29*, 52655–52664. [CrossRef] [PubMed]

59. Satarug, S.; Nishijo, M.; Ujjin, P.; Vanavanitkun, Y.; Moore, M.R. Cadmium-induced nephropathy in the development of high blood pressure. *Toxicol. Lett.* **2005**, *157*, 57–68. [CrossRef] [PubMed]
60. Hagedoorn, I.J.M.; Gant, C.M.; Huizen, S.V.; Maatman, R.G.H.J.; Navis, G.; Bakker, S.J.L.; Laverman, G.D. Lifestyle-related exposure to cadmium and lead is associated with diabetic kidney disease. *J. Clin. Med.* **2020**, *9*, 2432. [CrossRef]
61. Liu, Y.; Yang, D.; Shi, F.; Wang, F.; Liu, X.; Wen, H.; Mubarik, S.; Yu, C. Association of serum 25(OH)D, cadmium, CRP with all-cause, cause-specific mortality: A prospective cohort study. *Front. Nutr.* **2022**, *9*, 803985. [CrossRef]
62. Mayne, K.J.; Sullivan, M.K.; Lees, J.S. Sex and gender differences in the management of chronic kidney disease and hypertension. *J. Hum. Hypertens.* **2023**, *37*, 649–653. [CrossRef] [PubMed]
63. Chen, S.; Shen, R.; Shen, J.; Lyu, L.; Wei, T. Association of blood cadmium with all-cause and cause-specific mortality in patients with hypertension. *Front. Public Health* **2023**, *11*, 1106732. [CrossRef] [PubMed]
64. Mashima, Y.; Konta, T.; Kudo, K.; Takasaki, S.; Ichikawa, K.; Suzuki, K.; Shibata, Y.; Watanabe, T.; Kato, T.; Kawata, S.; et al. Increases in urinary albumin and beta2-microglobulin are independently associated with blood pressure in the Japanese general population: The Takahata Study. *Hypertens. Res.* **2011**, *34*, 831–835. [CrossRef] [PubMed]
65. Kudo, K.; Konta, T.; Mashima, Y.; Ichikawa, K.; Takasaki, S.; Ikeda, A.; Hoshikawa, M.; Suzuki, K.; Shibata, Y.; Watanabe, T.; et al. The association between renal tubular damage and rapid renal deterioration in the Japanese population: The Takahata study. *Clin. Exp. Nephrol.* **2011**, *15*, 235–241. [CrossRef] [PubMed]
66. Perry, H.M.; Erlanger, M.; Perry, E.F. Increase in the systolic pressure of rats chronically fed cadmium. *Environ. Health Perspect.* **1979**, *28*, 251–260. [CrossRef] [PubMed]
67. Perry, H.M., Jr.; Erlanger, M.W. Sodium retention in rats with cadmium-induced hypertension. *Sci. Total Environ.* **1981**, *22*, 31–38. [CrossRef] [PubMed]
68. Peña, A.; Iturri, S.J. Cadmium as hypertensive agent. Effect on ion excretion in rats. *Comp. Biochem. Physiol. C Comp. Pharmacol. Toxicol.* **1993**, *106*, 315–319. [CrossRef]
69. Yimthiang, S.; Pouyfung, P.; Khamphaya, T.; Kuraeiad, S.; Wongrith, P.; Vesey, D.A.; Gobe, G.C.; Satarug, S. Effects of environmental exposure to cadmium and lead on the risks of diabetes and kidney dysfunction. *Int. J. Environ. Res. Public Health* **2022**, *19*, 2259. [CrossRef] [PubMed]
70. Satarug, S.; Swaddiwudhipong, W.; Ruangyuttikarn, W.; Nishijo, M.; Ruiz, P. Modeling cadmium exposures in low- and high-exposure areas in Thailand. *Environ. Health Perspect.* **2013**, *121*, 531–536. [CrossRef]
71. Zarcinas, B.A.; Pongsakul, P.; McLaughlin, M.J.; Cozens, G. Heavy metals in soils and crops in Southeast Asia. 2. Thailand. *Environ. Geochem. Health* **2004**, *26*, 359–371. [CrossRef]
72. Sripaoraya, K.; Siriwong, W.; Pavittranon, S.; Chapman, R.S. Environmental arsenic exposure and risk of diabetes type 2 in Ron Phibun subdistrict, Nakhon Si Thammarat Province, Thailand: Unmatched and matched case-control studies. *Risk Manag Healthc. Policy* **2017**, *10*, 41–48. [CrossRef]
73. Suwatvitayakorn, P.; Ko, M.S.; Kim, K.W.; Chanpiwat, P. Human health risk assessment of cadmium exposure through rice consumption in cadmium-contaminated areas of the Mae Tao sub-district, Tak, Thailand. *Environ. Geochem. Health* **2020**, *42*, 2331–2344. [CrossRef] [PubMed]
74. Swaddiwudhipong, W.; Mahasakpan, P.; Limpatanachote, P.; Krintratun, S. Correlations of urinary cadmium with hypertension and diabetes in persons living in cadmium-contaminated villages in northwestern Thailand: A population study. *Environ. Res.* **2010**, *110*, 612–616. [CrossRef] [PubMed]
75. Hornung, R.W.; Reed, L.D. Estimation of average concentration in the presence of nondetectable values. *Appl. Occup. Environ. Hyg.* **1990**, *5*, 46–51. [CrossRef]
76. Satarug, S.; Vesey, D.A.; Nishijo, M.; Ruangyuttikarn, W.; Gobe, G.C.; Phelps, K.R. The effect of cadmium on GFR is clarified by normalization of excretion rates to creatinine clearance. *Int. J. Mol. Sci.* **2021**, *22*, 1762. [CrossRef] [PubMed]
77. White, C.A.; Allen, C.M.; Akbari, A.; Collier, C.P.; Holland, D.C.; Day, A.G.; Knoll, G.A. Comparison of the new and traditional CKD-EPI GFR estimation equations with urinary inulin clearance: A study of equation performance. *Clin. Chim. Acta* **2019**, *488*, 189–195. [CrossRef] [PubMed]
78. MacKinnon, D.P.; Warsi, G.; Dwyer, J.H. A simulation study of mediated effect measures. *Multiv. Behav. Res.* **1995**, *30*, 41–62. [CrossRef] [PubMed]
79. Preacher, K.J.; Hayes, A.F. SPSS and SAS procedures for estimating indirect effects in simple mediation models. *Behav. Res. Meth. Instrum. Comput.* **2004**, *36*, 717–731. [CrossRef]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.