Supplemental Material

Cadmium Exposure and Coronary Artery Atherosclerosis: A Cross-Sectional Population-Based Study of Swedish Middle-Aged Adults

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Figure S1. Adjusted PRs (solid line) with 95% CI (short dashed lines) for the relation between blood cadmium concentrations (μg/L) and CACS >0 (Model 2, Table S5, All individuals, but 52 individuals excluded). Prevalence ratios were modelled using unrestricted cubic splines with three knots (0.16, 0.24 and 0.38) at percentiles 25%, 50% and 75%, in a Poisson regression model adjusted for age, sex, smoking, hypertension, diabetes, family history, and LDL/HDL ratio. The reference value for blood cadmium was 0.12 μg/L (median for Q1). The histogram shows the frequency distribution of blood cadmium concentrations.

Figure S2. Adjusted PRs (solid line) with 95% CI (short dashed lines) for the relation between blood cadmium concentrations (μg/L) and CACS >0 among men (A) and women (B) (Model 2, Table S5, 52 individuals excluded). Prevalence ratios were modelled using unrestricted cubic splines with three knots (0.13, 0.19 and 0.30 for men, 0.20, 0.29, 0.44 for women) at percentiles 25%, 50% and 75%, in a Poisson regression model adjusted for age, sex, smoking, hypertension, diabetes, family history, and LDL/HDL ratio. The reference value for blood cadmium was 0.12 μg/L (median for Q1). The histogram shows the frequency distribution of blood cadmium concentrations.

Figure S3. Adjusted PRs (solid line) with 95% CI (short dashed lines) for the relation between blood cadmium concentrations (μg/L) and CACS ≥100 among men (A) and women (B) (Model 2, Table S5, 52 individuals excluded). Prevalence ratios were modelled using unrestricted cubic splines with three knots (0.13, 0.19 and 0.30 for men, 0.20, 0.29, 0.44 for women) at percentiles 25%, 50% and 75%, in a Poisson regression model adjusted for age, sex, smoking, hypertension, diabetes, family history, and LDL/HDL ratio. The reference value for blood cadmium was 0.12 μg/L (median for Q1). The histogram shows the frequency distribution of blood cadmium concentrations.

Figure S4. Adjusted PRs (solid line) with 95% CI (short dashed lines) for the relation between blood cadmium concentrations (μg/L) and CACS >0 among never-smokers (Model 2, Table 3, but 52 individuals excluded). Prevalence ratios were modelled using unrestricted cubic splines with three knots (0.14, 0.19 and 0.27) at percentiles 25%, 50% and 75%, in a Poisson regression model adjusted for age, sex, smoking, hypertension, diabetes, family history, and LDL/HDL ratio. The reference value for blood cadmium was 0.12 μg/L (median for Q1). The histogram shows the frequency distribution of blood cadmium concentrations.

Figure S5. Adjusted PRs (solid line) with 95% CI (short dashed lines) for the relation between blood cadmium concentrations (μg/L) and **CACS ≥100 among never-smokers** (Model 2, Table 3, but 52 individuals excluded). Prevalence ratios were modelled using unrestricted cubic splines with three knots (0.14, 0.19 and 0.27) at percentiles 25%, 50% and 75%, in a Poisson regression model adjusted for age, sex, smoking, hypertension, diabetes, family history, and LDL/HDL ratio. The reference value for blood cadmium was 0.12 μg/L (median for Q1). The histogram shows the frequency distribution of blood cadmium concentrations.

Supplemental material

Table S1. Results for analysis of cadmium in certified reference materials from Sero AS, Billingstad, Norway.

Laboratory	Seronorm Trace elements whole blood	Number of samples	Obtained concentration	Recommended concentration
Gothenburg	L-1, lot. 1103128	103	0.34±0.01	0.36±0.20
	L-2, lot. 1103129	103	5.8±0.17	5.8±0.20
Lund	L-1, lot. 1702821	48	0.28±0.01	0.28±0.06
	L-2, lot. 1702825	48	5.0±0.27	5.1±1.0

Table S2. Distribution of blood cadmium (B-Cd) overall, by gender, and in never-smokers.

B-Cd percentiles	All participants	All women	All men	All never-smokers	Female never-smokers	Male never-smokers
0.5	0.06	0.08	0.05	0.06	0.08	0.05
10	0.12	0.15	0.10	0.10	0.13	0.09
25	0.16	0.20	0.13	0.13	0.18	0.11
50	0.24	0.29	0.19	0.19	0.25	0.15
75	0.39	0.45	0.30	0.27	0.33	0.20
90	0.76	0.86	0.65	0.39	0.46	0.27
99.5	2.70	3.28	2.46	0.93	1.05	0.68

Table S3. Odds ratios (95% confidence intervals) for coronary artery calcium score (Agatston score) >0, and ≥100 by sex and blood cadmium concentration in a Swedish population-based cohort. Quartiles are mutually-exclusive, but cut-points in the columns are rounded.

Outcome, group, and model	Number of subjects/cases	OR per 1 µg/L	OR (95% CI) and number of cases/total number per quartile of blood cadmium (Q1 – Q4) in µg/L			
			1	**2**	**3**	4
			<0.16	0.16 – 0.24	0.24 – 0.39	0.39 – 8.5
Calcium score >0						
All						
Model 1 (age and sex)	2301/5627	1.2 (1.1 , 1.3)	1.0 (622/1407)	1.0 (0.9 , 1.2) (561/1406)	1.0 (0.8 , 1.2) (492/1407)	1.6 (1.4 , 1.9) 626/1407
Model 2[a]	2143/5295	1.5 (1.2 , 1.8)	1.0 (574/1329)	1.0 (0.8 , 1.2) (527/1342)	0.9 (0.8 , 1.1) (454/1320)	1.3 (1.1 , 1.6) (588/1304)
Women						
Model 1 (age)	781/2893	1.2 (1.1 , 1.4)	1.0 (82/355)	1.0 (0.7 , 1.4) (172/678)	0.9 (0.7 , 1.2) (222/939)	1.6 (1.2 , 2.1) (305/921)
Model 2[a]	735/2745	1.4 (1.1 , 1.8)	1.0 (73/338)	1.1 (0.8 , 1.5) (164/659)	0.9 (0.6 , 1.2) (206/883)	1.3 (0.9 , 1.7) (292/865)
Men						
Model 1 (age)	1520/2734	1.2 (1.1 , 1.2)	1.0 540/1042)	1.0 (0.8 , 1.2) 389/728	1.1 (0.9 , 1.4) 270/468	1.7 (1.3 , 2.1) 321/486
Model 2[a]	1408/2550	1.6 (1.1 , 2.2)	1.0 501/991	1.0 (0.8 , 1.2) 363/683	1.0 (0.8 , 1.3) 248/437	1.5 (1.1 , 2.1) 296/439
Calcium score ≥100						
All						
Model 1 (age and sex)	702/5627	1.9 (1.7 , 2.2)	1.0 163/1407	1.1 (0.9 , 1.4) 161/1406	1.2 (0.9 , 1.5) 138/1407	2.5 (2.0 , 3.1) 240/1407
Model 2[a]	654/5295	1.7 (14 , 2.1)	1.0 148/1329	1.1 (0.9 , 1.4) 152/1342	1.0 (0.8 , 1.4) 126/1320	1.9 (1.4 , 2.5) 228/1304
Women						
Model 1 (age)	181/2893	2.0 (1.6 , 2.5)	1.0 10/355	1.3 (0.6 , 2.8) 28/678	1.6 (0.8 , 3.3) 48/939	3.8 (1.9 , 7.4) 95/921
Model 2[a]	170/2745	1.9 (1.4 , 2.5)	1.0 8/338	1.4 (0.6 , 3.2) 27/659	1.6 (0.7 , 3.5) 45/883	2.9 (1.3 , 6.3) 90/865
Men						
Model 1 (age)	521/2734	1.8 (1.5 , 2.2)	1.0 153/1052	1.1 (0.9 , 1.5) 133/728	1.1 (0.8 , 1.5) 90/468	2.2 (1.7 , 2.9) 145/486
Model 2[a]	484/2550	1.5 (1.1 , 2.1)	1.0 140/991	1.2 (0.9 , 1.5) 125/683	1.0 (0.7 , 1.4) 81/437	1.8 (1.3 , 2.5) 138/439

[a]Model 2: Model 1 + smoking (never, former, current), hypertension, diabetes, family history, LDL/HDL ratio.

Table S4. Odds ratios (OR), with 95% confidence intervals (CI) for coronary artery calcium score (Agatston score) >0, and ≥100 by sex and blood cadmium concentration in never-smokers in a Swedish population-based cohort. Quartiles are mutually-exclusive, but cut-points in the columns are rounded.

Outcome, group, and model	Number of subjects/cases	OR per 1 µg/L	OR (95% CI) and number of cases/total number per quartile of blood cadmium (Q1 – Q4) in µg/L			
			Q1 <0.16	Q2 0.16 – 0.24	Q3 0.24 – 0.39	Q4 0.39 – 8.5
Calcium score >0						
All						
Model 1 (age and sex)	874/2520	1.1 (0.6 , 2.1)	1.0 395/950	1.0 (0.8 , 1.2) 251/727	0.9 (0.7 , 1.2) 163/589	1.1 (0.7 , 1.5) 65/254
Model 2[a]	848/2446	1.1 (0.5 , 2.1)	1.0 384/925	1.0 (0.8 , 1.3) 245/710	1.0 (0.8 , 1.3) 156/565	1.1 (0.8 , 1.6) 63/246
Women						
Model 1 (age)	1227/237	1.0 (0.4 , 2.4)	1.0 44/224	1.0 (0.6 , 1.5) 73/363	0.8 (0.5 , 1.2) 75/422	1.0 (0.6 , 1.6) 45/218
Model 2[a]	228/1193	0.8 (0.3 , 1.9)	1.0 42/216	1.0 (0.7 , 1.6) 72/359	0.9 (0.5 , 1.3) 71/406	1.0 (0.6 , 1.6) 43/212
Men						
Model 1 (age)	1293/637	1.2 (0.4 , 3.8)	1.0 351/726	0.9 (0.7 , 1.2) 178/364	1.0 (0.7 , 1.4) 88/167	1.1 (0.5 , 2.2) 20/36
Model 2[a]	620/1253	1.8 (0.6 , 6.0)	1.0 342/709	1.0 (0.8 , 1.3) 173/351	1.1 (0.8 , 1.6) 85/159	1.4 (0.7 , 2.8) 20/34
Calcium score ≥100						
All						
Model 1 (age and sex)	2520/208	2.5 (0.9 , 6.8)	1.0 96/950	0.9 (0.6 , 1.3) 55/727	1.1 (0.7 , 1.7) 40/589	1.7 (0.9 , 3.0) 17/254
Model 2[a]	200/2446	2.8 (1.0 , 7.5)	1.0 93/925	1.0 (0.7 , 1.4) 53/710	1.2 (0.8 , 1.9) 37/565	1.9 (1.0 , 3.6) 17/246
Women						
Model 1 (age)	1227/33	4.1 (1.3 ,13)	1.0 3/224	1.9 (0.5 , 7.2) 10/363	1.5 (0.4 , 5.5) 9/422	3.7 (1.0 , 13) 11/218
Model 2[a]	32/1193	3.4 (1.0 , 11)	1.0 3/216	2.0 (0.5 , 7.6) 10/359	1.5 (0.4 , 5.7) 8/406	3.6 (1.0 , 14) 11/212
Men						
Model 1 (age)	1293/175	1.3 (0.3 , 6.1)	1.0 93/726	0.9 (0.6 , 1.3) 45/364	1.2 (0.8 ,2.0) 31/167	1.0 (0.4 , 2.6) 6/36
Model 2[a]	168/1253	1.7 (0.3 , 8.7)	1.0 90/709	0.9 (0.6 , 1.3) 43/351	1.3 (0.8 , 2.1) 29/159	1.3 (0.5 , 3.4) 6/34

[a]Model 2: Model 1 + hypertension, diabetes, family history, LDL/HDL ratio

Table S5. Prevalence ratios (95% confidence intervals) for coronary artery calcium scores (Agatston score) >0 and ≥100, overall and by sex for sensitivity analyses with additional adjustment for cardiovascular risk factors, study site, and smoking pack-years, respectively, and after excluding participants with the highest (n = 26) and lowest (n = 26) exposures. Quartiles are mutually-exclusive, but cut points in the columns are rounded.

Outcome, group, and model	Number of cases/subjects	PR per 1 µg/L	PR (95% CI) and number of cases/total number per quartile of blood cadmium (Q1 – Q4) in µg/L			
			1	2	3	4
			<0.16	0.16 – 0.24	0.24 – 0.39	0.39 – 8.5
CACS >0: All						
Model 2[a]	2143/5295	1.1 (1.1, 1.2)	1.0 (574/1329)	1.0 (0.9, 1.1) (527/1342)	0.9 (0.9, 1.0) (454/1320)	1.1 (1.0, 1.3) (588/1304)
Model 2 + CVD risk factors[b]	2067/5162	1.1 (1.0, 1.2)	1.0 561/1307	1.0 (0.9, 1.1) 515/1319	0.9 (0.9, 1.0) 437/1287	1.1 (1.0, 1.2) 554/1249
Model 2 + site[c]	2143/5295	1.1 (1.1, 1.2)	1.0 (574/1329)	1.0 (0.9, 1.1) (527/1342)	0.9 (0.9, 1.0) (454/1320)	1.1 (1.0, 1.3) (588/1304)
Model 2 + pack-years[d]	2143/5295	1.1 (1.0, 1.2)	1.0 (574/1329)	1.0 (0.9, 1.1) (527/1342)	0.9 (0.8, 1.0) (454/1320)	1.1 (1.0, 1.2) (588/1304)
Model 2 excluding low + high B-Cd[e]	2112/5243	1.3 (1.1, 1.4)	1.0 (559/1303)	1.0 (0.9, 1.1) (527/1342)	0.9 (0.9, 1.0) (454/1320)	1.1 (1.0, 1.3) (572/1278)
CACS >0: Women						
Model 2[a]	735/2745	1.1 (1.0, 1.2)	1.0 (73/338)	1.0 (0.8, 1.3) (164/659)	0.9 (0.7, 1.2) (206/883)	1.2 (0.9, 1.5) (292/865)
Model 2 + CVD risk factors[b]	710/2686	1.0 (0.9, 1.2)	1.0 72/333	1.0 (0.8, 1.3) 160/648	0.9 (0.7, 1.1) 199/865	1.1 (0.9, 1.4) 279/840
Model 2 + site[c]	735/2745	1.1 (1.0 , 1.2)	1.0 (73/338)	1.1 (0.8 , 1.3) (164/659)	0.9 (0.7 , 1.2) (206/883)	1.2 (0.9 , 1.5) (292/865)
Model 2 + pack-years[d]	735/2745	1.0 (0.9 , 1.2)	1.0 (73/338)	1.0 (0.8 , 1.3) (164/659)	1.0 (0.9 , 1.1) (206/883)	1.1 (1.0 , 1.3) (292/865)
Model 2 excluding low + high B-Cd[e]	726/2725	1.4 (1.2 , 1.7)	1.0 (72/336)	1.1 (0.8 , 1.3) (164/659)	0.9 (0.7 , 1.2) (206/883)	1.2 (0.9 , 1.5) (284/847)
CACS >0: Men						
Model 2[a]	1408/2550	1.1 (1.0 , 1.2)	1.0 501/991	1.0 (0.9 , 1.1) 363/683	1.0 (0.9 , 1.1) 248/437	1.2 (1.0 , 1.3) 296/439
Model 2 + CVD risk factors[b]	1357/2476	1.1 (1.0 , 1.2)	1.0 489/974	1.0 (0.9 , 1.1) 355/671	1.0 (0.9 , 1.1) 238/422	1.2 (1.0 , 1.3) 275/409
Model 2 + site[c]	1408/2550	1.1 (1.0 , 1.2)	1.0 501/991	1.0 (0.9 , 1.1) 363/683	1.0 (0.9 , 1.1) 248/437	1.2 (1.0 , 1.3) 296/439
Model 2 + pack-years[d]	1408/2550	1.1 (1.0 , 1.2)	1.0 501/991	1.0 (0.9 , 1.1) 363/683	1.0 (0.9 , 1.1) 248/437	1.1 (1.0 , 1.3) 296/439
Model 2 excluding low + high B-Cd[e]	1386/2518	1.1 (1.0 , 1.3)	1.0 487/967	1.0 (0.9 , 1.1) 363/683	1.0 (0.9 , 1.1) 248/437	1.2 (1.0 , 1.3) 288/431
CACS >100: All						
Model 2[a]	654/5295	1.3 (1.1 , 1.4)	1.0 148/1329	1.1 (0.9 , 1.3) 152/1342	1.0 (0.8 , 1.3) 126/1320	1.6 (1.3 , 2.0) 228/1304
Model 2 + CVD risk factors[b]	620/5162	1.2 (1.1 , 1.3)	1.0 145/1307	1.0 (0.8 , 1.3) 144/1319	1.0 (0.8 , 1.3) 123/1287	1.5 (1.2 , 1.9) 208/1249
Model 2 + site[c]	654/5295	1.3 (1.1 , 1.4)	1.0 148/1329	1.1 (0.9 , 1.3) 152/1342	1.0 (0.8 , 1.3) 126/1320	1.6 (1.3 , 2.0) 228/1304
Model 2 + pack-years[d]	654/5295	1.2 (1.1 , 1.3)	1.0 148/1329	1.1 (0.9 , 1.3) 152/1342	1.0 (0.8 , 1.2) 126/1320	1.4 (1.1 , 1.7) 228/1304
Model 2 excluding low + high B-Cd[e]	642/5243	1.7 (1.4 , 2.0)	1.0 145/1303	1.1 (0.9 , 1.3) 152/1342	1.0 (0.8 , 1.3) 126/1320	1.6 (1.3 , 2.0) 219/1278

CACS >100: Women						
Model 2[a]	170/2745	1.2 (1.1 , 1.4)	1.0 8/338	1.4 (0.6 , 3.1) 27/659	1.6 (0.7 , 3.3) 45/883	2.6 (1.3 , 5.5) 90/865
Model 2 + CVD risk factors[b]	162/2686	1.2 (1.0 , 1.4)	1.0 8/333	1.3 (0.6 , 2.8) 25/648	1.5 (0.7 , 3.2) 44/865	2.4 (1.2 , 5.1) 85/840
Model 2 + site[c]	170/2745	1.1 (1.0 , 1.2)	1.0 8/338	1.4 (0.7 , 3.1) 27/659	1.6 (0.8 , 3.3) 45/883	2.6 (1.3 , 5.5) 90/865
Model 2 + pack-years[d]	170/2745	1.1 (0.9 , 1.3)	1.0 8/338	1.4 (0.6 , 3.1) 27/659	1.5 (0.7 , 3.1) 45/883	2.2 (1.0 , 4.6) 90/865
Model 2 excluding low + high B-Cd[e]	164/2725	2.6 (1.8 , 3.6)	1.0 7/336	1.6 (0.7 , 3.7) 27/659	1.8 (0.8 , 3.9) 45/883	3.0 (1.4 , 6.5) 85/847
CACS >100: Men						
Model 2[a]	484/2550	1.2 (1.1 , 1.4)	1.0 140/991	1.1 (0.9 , 1.4) 125/683	1.0 (0.8 , 1.3) 81/437	1.5 (1.1 , 1.9) 138/439
Model 2 + CVD risk factors[b]	458/2476	1.2 (1.0 , 1.4)	1.0 137/974	1.1 (0.9 , 1.3) 119/671	1.0 (0.8 , 1.3) 79/422	1.4 (1.1 , 1.8) 123/409
Model 2 + site[c]	484/2550	1.2 (1.0 , 1.4)	1.0 140/991	1.1 (0.9 , 1.4) 125/683	1.0 (0.8 , 1.3) 81/437	1.5 (1.1 , 1.9) 138/439
Model 2 + pack-years[d]	484/2550	1.2 (1.0 , 1.4)	1.0 140/991	1.1 (0.9 , 1.4) 125/683	1.0 (0.8 , 1.3) 81/437	1.3 (1.0 , 1.7) 138/439
Model 2 excluding low + high B-Cd[e]	478/2518	1.3 (1.1 , 1.7)	1.0 138/967	1.1 (0.9 , 1.4) 125/683	1.0 (0.8 , 1.3) 81/437	1.4 (1.1 , 1.8) 134/431

[a]Model 2 is adjusted for age, sex, smoking category (never, former, current), hypertension, diabetes, heredity, LDL/HDL ratio.

[b]Model 2 + lipid-lowering medications, waist circumference, education (3 categories), low physical activity, born outside Sweden, systolic blood pressure, log-transformed C-reactive protein.

[c]Model 2 + study site (Gothenburg or Malmo)

[d]Model 2 + smoking pack-years (continuous)

[e]Model 2 after excluding participants with B-Cd below the 0.5th percentile or above the 99.5th percentile for the study population as a whole.
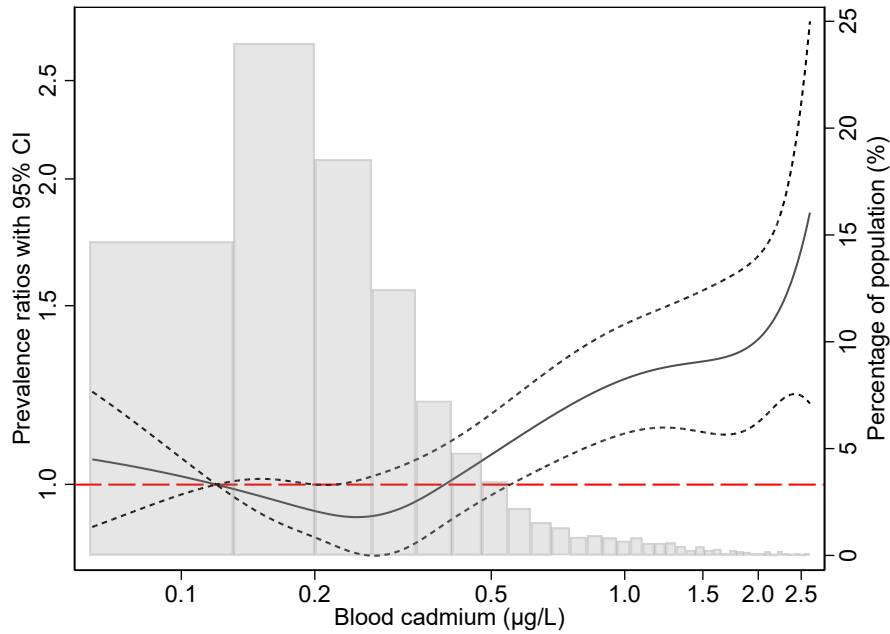
Figure S1. Adjusted PRs (solid line) with 95% CI (short dashed lines) for the relation between blood cadmium concentrations (µg/L) and CACS >0 (Model 2, Table S5, All individuals, but 52 individuals excluded). Prevalence ratios were modelled using unrestricted cubic splines with three knots (0.16, 0.24 and 0.38) at percentiles 25%, 50% and 75%, in a Poisson regression model adjusted for age, sex, smoking, hypertension, diabetes, family history, and LDL/HDL ratio. The reference value for blood cadmium was 0.12 µg/L (median for Q1). The histogram shows the frequency distribution of blood cadmium concentrations.
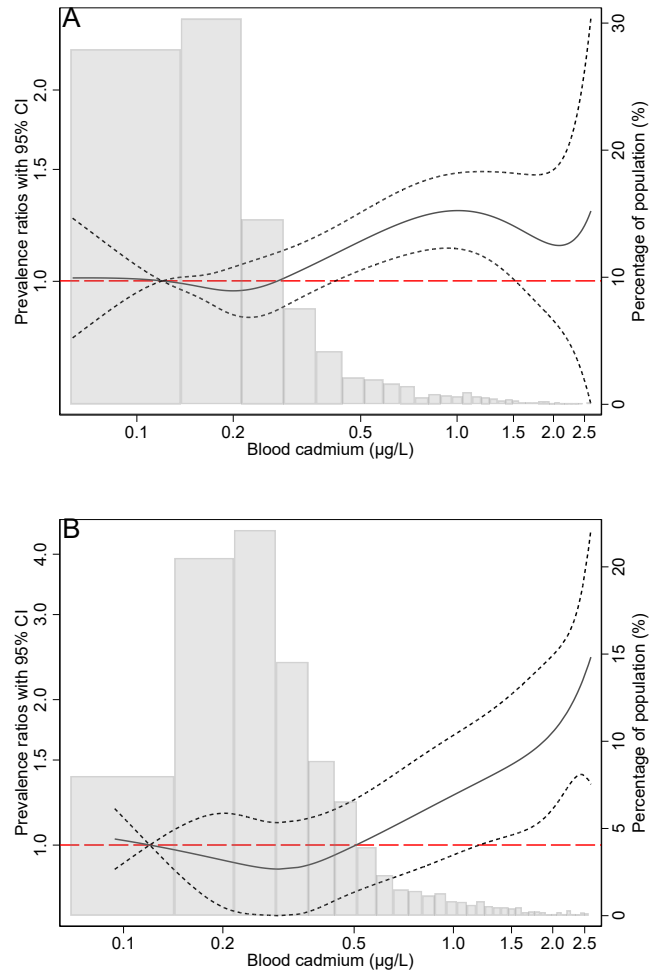
Figure S2. Adjusted PRs (solid line) with 95% CI (short dashed lines) for the relation between blood cadmium concentrations (µg/L) and CACS >0 among men (A) and women (B) (Model 2, Table S5, 52 individuals excluded). Prevalence ratios were modelled using unrestricted cubic splines with three knots (0.13, 0.19 and 0.30 for men, 0.20, 0.29, 0.44 for women) at percentiles 25%, 50% and 75%, in a Poisson regression model adjusted for age, sex, smoking, hypertension, diabetes, family history, and LDL/HDL ratio. The reference value for blood cadmium was 0.12 µg/L (median for Q1). The histogram shows the frequency distribution of blood cadmium concentrations.

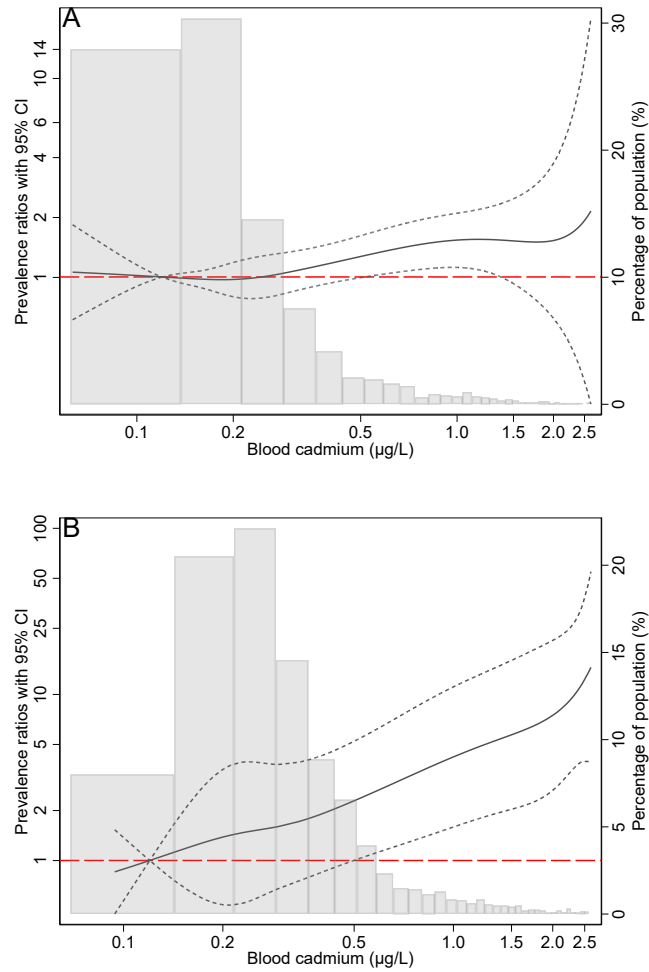**Figure S3.** Adjusted PRs (solid line) with 95% CI (short dashed lines) for the relation between blood cadmium concentrations (µg/L) and CACS ≥100 among men (A) and women (B) (Model 2, Table S5, 52 individuals excluded). Prevalence ratios were modelled using unrestricted cubic splines with three knots (0.13, 0.19 and 0.30 for men, 0.20, 0.29, 0.44 for women) at percentiles 25%, 50% and 75%, in a Poisson regression model adjusted for age, sex, smoking, hypertension, diabetes, family history, and LDL/HDL ratio. The reference value for blood cadmium was 0.12 µg/L (median for Q1). The histogram shows the frequency distribution of blood cadmium concentrations.

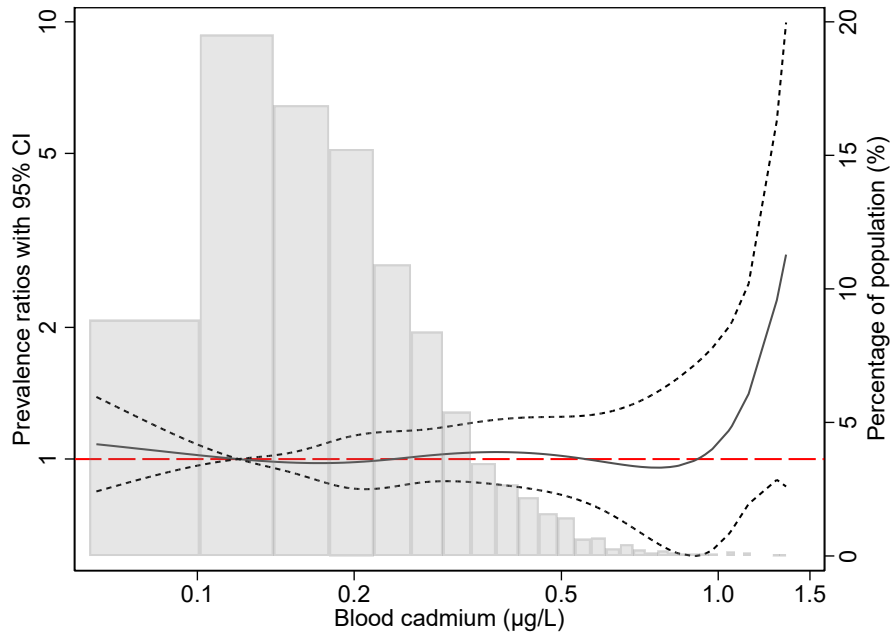**Figure S4.** Adjusted PRs (solid line) with 95% CI (short dashed lines) for the relation between blood cadmium concentrations (μg/L) and CACS >0 among never-smokers (Model 2, Table 3, but 52 individuals excluded). Prevalence ratios were modelled using unrestricted cubic splines with three knots (0.14, 0.19 and 0.27) at percentiles 25%, 50% and 75%, in a Poisson regression model adjusted for age, sex, smoking, hypertension, diabetes, family history, and LDL/HDL ratio. The reference value for blood cadmium was 0.12 μg/L (median for Q1). The histogram shows the frequency distribution of blood cadmium concentrations.
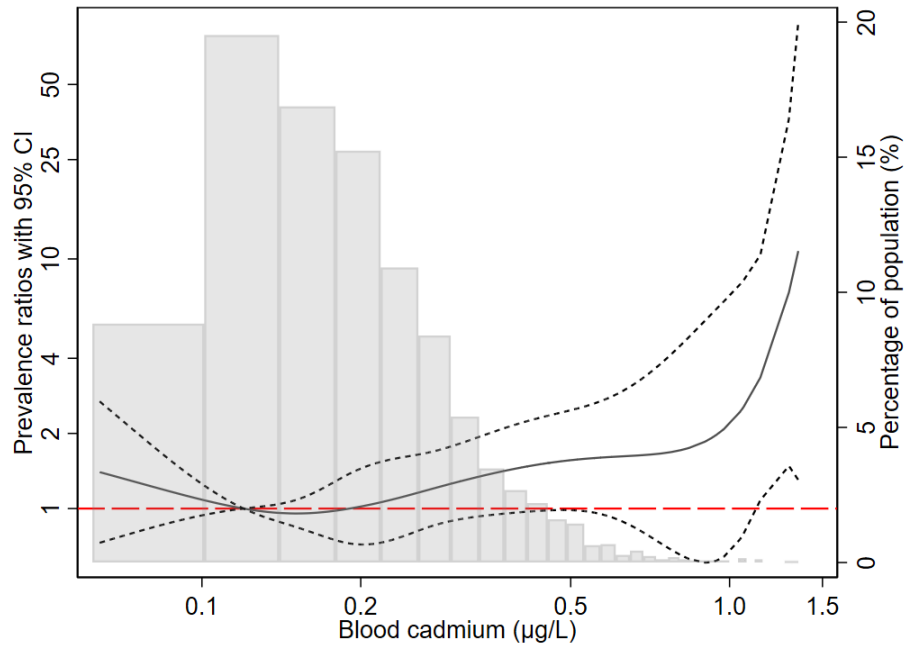
Figure S5. Adjusted PRs (solid line) with 95% CI (short dashed lines) for the relation between blood cadmium concentrations (µg/L) and **CACS ≥100 among never-smokers** (Model 2, Table 3, but 52 individuals excluded). Prevalence ratios were modelled using unrestricted cubic splines with three knots (0.14, 0.19 and 0.27) at percentiles 25%, 50% and 75%, in a Poisson regression model adjusted for age, sex, smoking, hypertension, diabetes, family history, and LDL/HDL ratio. The reference value for blood cadmium was 0.12 µg/L (median for Q1). The histogram shows the frequency distribution of blood cadmium concentrations.