Supplemental Material

Blood Cadmium Levels and Incident Cardiovascular Events during Follow-up in a Population-Based Cohort of Swedish Adults: The Malmö Diet and Cancer Study

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Table S1. Mortality and first incident cardiovascular events (*n*) during follow-up from baseline to 2010. Number of person-years (rounded) given for each analysis.

Event	Total	Women	Men
All-cause mortality	882	417	465
Person-years	81400		
Cardiovascular mortality[a]	257	113	144
Person-years	81400		
Acute coronary event	377	146	231
Person-years	78500		
Acute AMI	344	136	208
Death in IHD	33	10	23
Stroke (N)	336	170	166
Person-years	79100		
Ischemic	278	138	140
Other or unspecified	58	32	26
Major adverse cardiac event[b]	479	180	299
Person-years	77400		
CABG	162	59	103
PCI	52	17	35

An individual could contribute to AMI as well as to stroke, and to incident disease as well as to mortality. **a)** ICD9: 390 – 459 or ICD10: I00 –I99 **b)** Acute MI, death in IHD, coronary artery bypass graft (CABG), percutaneous coronary intervention (PCI). Only the first major adverse cardiac event was considered here.

Table S2. Stratified hazard ratios (95% confidence intervals) for acute coronary event comparing the 4th quartile of B-Cd with the first quartile.[a]

Subgroup	n events/ N participants	HR (95% CI
Age		
>60 years	187/1615	1.8 (1.1 , 3.1)
≤60 years	141/2752	1.9 (0.98 , 3.6)
Sex		
Women	128/2628	1.7 (0.8 , 3.5)
Men	200/1739	1.9 (1.1 , 3.2)
Smoking		
Never	111/1782	2.3 (1.01 , 5.1)
Former	110/1463	2.1 (1.01 , 4.2)
Current	107/1122	2.3 (0.6 , 9.3)
Education		
<9 years	200/1974	1.8 (1.04 , 3.1)
≥9 years	128/2393	2.0 (1.03 , 3.8)
Waist circumference (cm)		
>85 cm	201/1812	1.9 (1.1 , 3.1)
≤85 cm	127/2555	1.8 (0.8 , 3.6)
Antihypertensive medication		
Yes	80/665	1.7 (0.8 , 3.8)
No	248/3702	1.9 (1.2 , 3.2)
Diabetes		
Yes	58/333	2.1 (0.8 , 5.7)
No	270/4034	1.8 (1.1 , 2.9)

a) Time scale is age, and the model is adjusted for sex, smoking, waist circumference, low education, low physical activity, alcohol intake, serum triglycerides, HbA1c, and CRP (=Model 2 in main Table 2).

Table S3. Hazard ratios (95% CI) for first incident cardiovascular disease event by quartiles of cadmium concentration in blood **in women and men**[a]. Quartiles of blood cadmium are based on the total data set including both men and women. The number of events (n) is given for each outcome.

	Quartiles of blood cadmium				P for inter-action
	1	**2**	**3**	**4**	
Acute coronary event (AMI + death in IHD					0.84
Women (n=128)	1.0	1.2 (0.7 , 2.1)	1.3 (0.7 , 2.3)	1.7 (0.8 , 3.5)	
Men (n=200)	1.0	1.1 (0.8 , 1.8)	1.4 (0.9 , 2.1)	1.9 (1.1 , 3.2)	
Acute myocardial infarction					0.85
Women (n=121)	1.0	1.2 (0.7 , 2.3)	1.3 (0.7 , 2.3)	1.6 (0.8 , 3.4)	
Men (n=184)	1.0	1.2 (0.7 , 1.8)	1.3 (0.9 , 2.1)	1.8 (1.1 , 3.2)	
Major adverse cardiac event					0.51
Women (n=161)	1.0	1.5 (0.8 , 2.6)	1.9 (1.1 , 3.3)	2.3 (1.2 , 4.5)	
Men (n=261)	1.0	1.2 (0.8 , 1.7)	1.4 (0.97 , 2.0)	1.7 (1.1 , 2.7)	
Any stroke					0.02
Women (n=147)	1.0	1.0 (0.6 , 1.9)	1.5 (0.9 , 2.5)	2.8 (1.5 , 5.4)	
Men (n=147)	1.0	1.0 (0.6 , 1.6)	0.7 (0.4 , 1.2)	1.5 (0.8 , 2.8)	
Ischemic stroke					0.007
Women (n=117)	1.0	1.1 (0.6 , 2.2)	1.7 (0.9 , 3.2)	3.1 (1.5 , 6.5)	
Men (n=123)	1.0	0.9 (0.6 , 1.5)	0.6 (0.3 , 1.04)	1.6 (0.8 , 3.0)	
All-cause mortality					0.68
Women (n=364)	1.0	1.0 (0.7 , 1.4)	1.0 (0.7 , 1.4)	1.8 (1.2 , 2.7)	
Men (n=407)	1.0	1.0 (0.7 , 1.4)	1.1 (0.8 , 1.5)	1.5 (1.03 , 2.1)	
Cardiovascular mortality					0.06
Women (n=95)	1.0	1.0 (0.5 , 1.9)	1.1 (0.5 , 2.1)	2.6 (1.2 , 5.7)	
Men (n=120)	1.0	1.5 (0.9 , 2.7)	1.8 (1.05 , 3.1)	1.6 (0.8 , 3.1)	

a) Model adjusted for smoking, waist circumference, low education, low physical activity, alcohol intake, serum triglycerides, HbA1c, CRP (=Model 2 in main Table 2).

Table S4. Hazard ratios (95% CI) for first incident cardiovascular disease event by quartiles of cadmium concentration in blood (time scale=age). Model 1 and 2 as in main Table 2, but **including only those with data for all covariates in Model 3, thus resulting in the same individuals in all three models (N=4045).** The number of events (n) is given for each outcome.

	Quartiles of blood cadmium			
	1	2	3	4
Acute coronary event				
(AMI + death in IHD)				
Model 1 (n=306)	1.0	1.0 (0.7 , 1.4)	1.2 (0.9 , 1.7)	2.1 (1.5 , 2.8)
Model 2 (n=306)	1.0	1.0 (0.7 , 1.4)	1.2 (0.8 , 1.7)	1.9 (1.2 , 2.8)
Model 3 (n=306)	1.0	1.0 (0.7 , 1.4)	1.2 (0.8 , 1.6)	1.9 (1.2 , 2.9)
Acute myocardial infarction				
Model 1 (n=283)	1.0	1.0 (0.7 , 1.4)	1.2 (0.8 , 1.6)	2.0 (1.4 , 2.7)
Model 2 (n=283)	1.0	1.0 (0.7 , 1.5)	1.1 (0.8 , 1.7)	2.0 (1.3 , 2.9)
Model 3 (n=283)	1.0	1.0 (0.7 , 1.5)	1.1 (0.8 , 1.6)	1.8 (1.2 , 2.8)
Major adverse cardiac event				
Model 1 (n=394)	1.0	1.1 (0.8 , 1.5)	1.4 (1.04 , 1.9)	2.1 (1.6 , 2.8)
Model 2 (n=394)	1.0	1.1 (0.8 , 1.5)	1.4 (1.03 , 1.9)	1.9 (1.3 , 2.8)
Model 3 (n=394)	1.0	1.1 (0.9 , 1.5)	1.4 (1.04 , 1.9)	1.9 (1.3 , 2.8)
Any stroke				
Model 1 (n=271)	1.0	0.9 (0.6 , 1.2)	1.0 (0.7 , 1.4)	1.9 (1.4 , 2.7)
Model 2 (n=271)	1.0	0.9 (0.6 , 1.3)	1.0 (0.7 , 1.4)	2.1 (1.3 , 3.2)
Model 3 (n=271)	1.0	0.8 (0.6 , 1.2))	0.9 (0.7 , 1.4)	2.1 (1.3 , 3.2)
Ischemic stroke				
Model 1 (n=224)	1.0	0.9 (0.6 , 1.3)	0.9 (0.6 , 1.3)	2.0 (1.4 , 2.8)
Model 2 (n=224)	1.0	0.9 (0.6 , 1.3)	0.9 (0.6 , 1.4)	2.1 (1.3 , 3.3)
Model 3 (n=224)	1.0	0.8 (0.6 , 1.2))	0.9 (0.6 , 1.4)	2.1 (1.3 , 3.3)
All-cause mortality				
Model 1 (n=718)	1.0	1.0 (0.8 , 1.3)	1.1 (0.9 , 1.4)	2.2 (1.8 , 2.7)
Model 2 (n=718)	1.0	1.0 (0.8 , 1.3)	1.0 (0.8 , 1.3)	1.7 (1.3 , 2.2)
Model 3 (n=718)	1.0	1.0 (0.8 , 1.3)	1.0 (0.8 , 1.3)	1.6 (1.3 , 2.2)
Cardiovascular mortality				
Model 1 (n=206)	1.0	1.3 (0.8 , 2.0)	1.5 (0.97 , 2.3)	2.5 (1.7 , 2.8)
Model 2 (n=206)	1.0	1.3 (0.8 , 2.0)	1.4 (0.9 , 2.2)	1.9 (1.1 , 3.2)
Model 3 (n=206)	1.0	1.2 (0.8 , 1.9)	1.3 (0.9 , 2.1)	1.9 (1.1 , 3.2)

Table S5. Hazard ratios (95% CI) for first incident cardiovascular disease event by quartiles of **erythrocyte cadmium (µg/L) instead of blood cadmium in Model 2.[a]** The number of events (n) is given for each outcome.

	Quartiles of erythrocyte cadmium			
	1	**2**	**3**	**4**
Mean	0.31	0.52	0.85	2.8
Range	0.06 – 0.414	>0.41 – 0.633	>0.633 – 1.21	>1.21 – 11.3
Acute coronary event[b] (n=328, sample 4367) (AMI + death in IHD)	1.0	1.1 (0.8 , 1.5)	1.5 (1.04 , 2.1)	1.8 (1.2 , 2.7)
Acute myocardial infarction (n=305, sample 4367)	1.0	1.1 (0.8 , 1.6)	1.5 (1.04 , 2.1)	1.7 (1.1 , 2.7)
Major adverse cardiac event (n=422, sample 4350)	1.0	1.2 (0.9 , 1.6)	1.6 (1.2 , 2.2)	1.7 (1.2 , 2.5)
Any stroke (n=294, sample 4404)	1.0	0.8 (0.6 , 1.2)	0.9 (0.6 , 1.2)	1.8 (1.2 , 2.7)
Ischemic stroke (n=240, sample size 4416)	1.0	0.8 (0.5 , 1.2)	0.8 (0.6 , 1.2)	1.8 (1.1 , 2.8)
All-cause mortality (n=771, sample size 4437)	1.0	0.9 (0.7 , 1.1)	1.0 (0.8 , 1.2)	1.5 (1.2 , 1.9)
Cardiovascular mortality (n=215, sample size 4437)	1.0	1.0 (0.7 , 1.6)	1.3 (0.9 , 1.9)	1.5 (0.9 , 2.5)

a) Model adjusted for sex, smoking, waist circumference, low education, low physical activity, alcohol intake, serum triglycerides, HbA1c, and CRP (=Model 2 in main Table 2).
b) ICD9: 410, 412, or 414 or ICD10: I21, I22, I23, or I25.

Table S6. Hazard ratios (95% CI) for first incident cardiovascular disease event by quartiles of cadmium concentration in blood.[a)] Model **additionally number of pack-years[b)] in participants with such data available (N=3938 out of 4819)**.
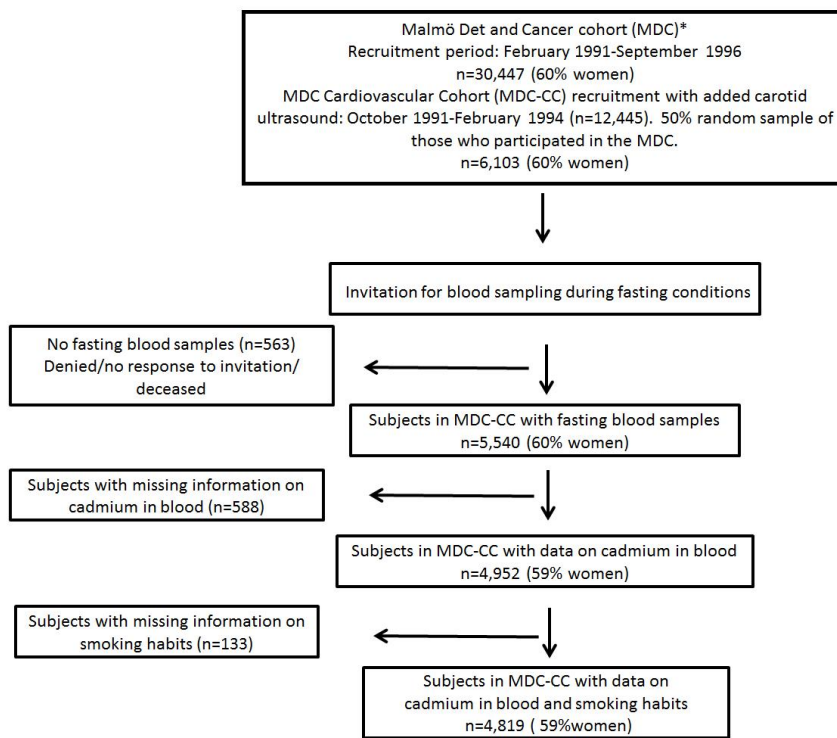
	Quartiles of blood cadmium			
	1	**2**	**3**	**4**
Acute coronary event (n=253) (AMI + death in IHD)[c)]	1.0	1.0 (0.7 , 1.5)	1.2 (0.8 , 1.8)	1.8 (1.1, 2.9)
Acute myocardial infarction (n=238)	1.0	1.1 (0.7 , 1.6)	1.2 (0.8 , 1.8)	1.8 (1.1 , 3.1)
Major adverse cardiac event (n=332)	1.0	1.1 (0.8 , 1.6)	1.4 (0.99 , 2.0)	1.8 (1.1 , 2.7)
Any stroke (n=232)	1.0	0.9 (0.6 , 1.3)	1.1 (0.7 , 1.6)	2.0 (1.2 , 3.4)
Ischemic stroke (n=187)	1.0	0.8 (0.5 , 1.3)	1.0 (0.6 , 1.5)	2.0 (1.1 , 3.6)
All-cause mortality (n=506)	1.0	1.0 (0.7 , 1.3)	0.9 (0.7 , 1.3)	1.5 (1.01 ,2.1)
Cardiovascular mortality (n=140)	1.0	1.1 (0.7 , 2.0)	1.1 (0.6 , 1.9)	1.9 (0.9 , 3.8)

a) Model adjusted for sex, smoking, waist circumference, low education, low physical activity, alcohol intake, serum triglycerides, HbA1c, CRP (=Model 2 in main Table 2), and pack-years.
b) Pack-years were categorized in five categories, one for never-smokers and four based on quartiles among ever-smokers. Category 1: 0 pack-years, Category 2: >0 but <7.5 pack-years, Category 3: ≥7.5 but <17 pack-years, Category 4: ≥17 but <30 pack-years, and Category 5: ≥30 pack-years.
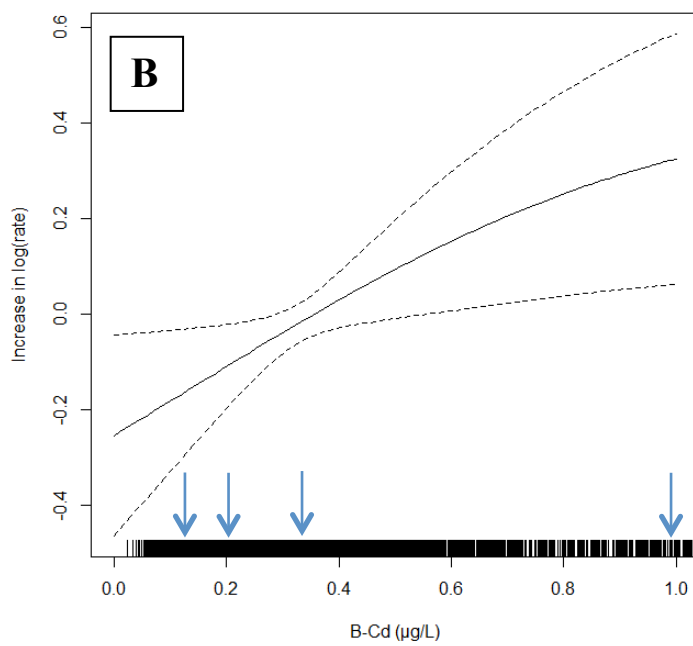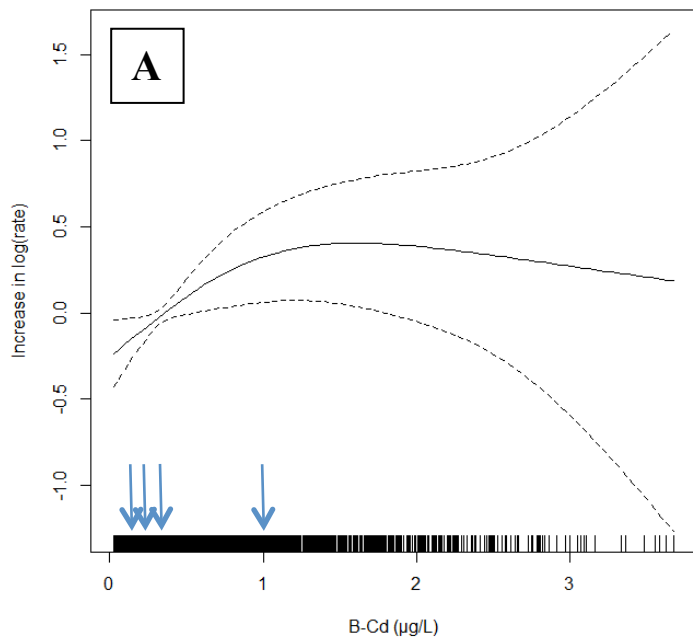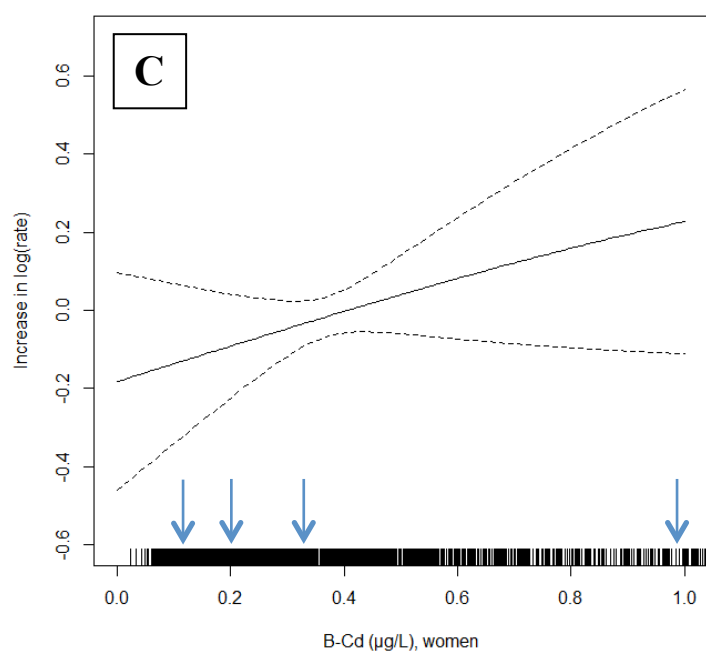**c)** ICD9: 410, 412, or 414 or ICD10: I21, I22, I23, or I25.

Figure S1. Flow chart showing the recruitment of the MDC cardiovascular cohort and the study participants of the present study.

Figure S2. Smooth function (with 95% confidence interval) describing the impact of B-Cd on the risk of acute coronary event, in a model adjusted for age, gender, smoking, waist, education, physical activity, alcohol, triglycerides, HbA1c, and C-reactive protein (=Model 2 in Table 2 + age). Graph A shows results up to B-Cd 4 µg/L Graph B shows results up to B-Cd 1 µg/L. Graph C shows results up to B-Cd 1 µg/L in women and graph D in men. Arrows indicate medians of B-Cd within quartiles.