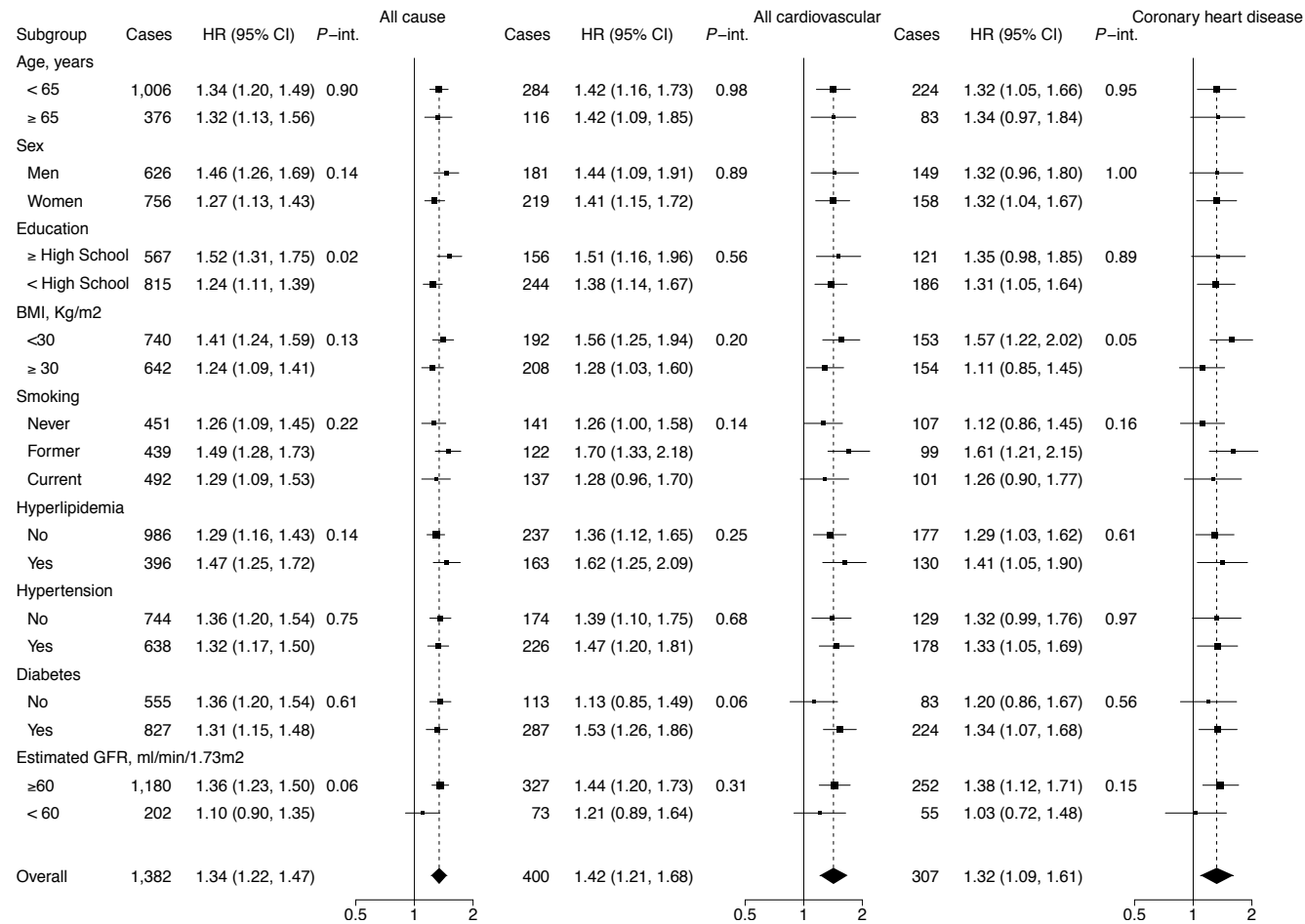**ONLINE-ONLY MATERIAL**

TITLE: Cadmium Exposure and Incident Cardiovascular Disease: A Population-Based Prospective Cohort Study

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eFigure 1. Hazard ratios (95% confidence interval) for cardiovascular disease mortality comparing the 80th versus the 20th percentiles of the urine cadmium distribution by participants characteristics at baseline (N=3,348)
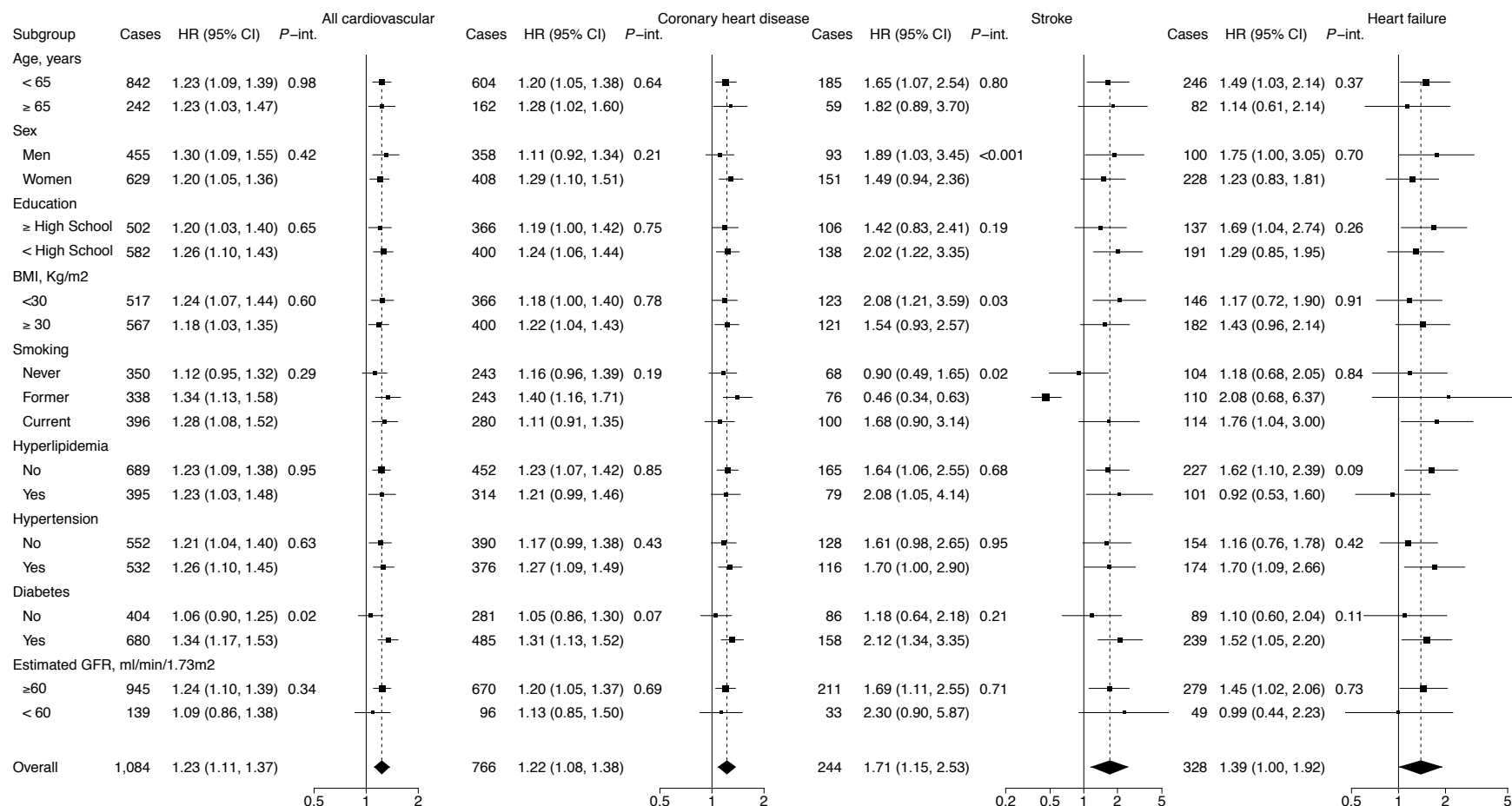
eFigure 2. Hazard ratios (95% confidence interval) for cardiovascular disease incidence comparing the 80th versus the 20th percentiles of the urine cadmium distribution by participants characteristics at baseline (N=3,348)

eFigure 1. Hazard ratios (95% confidence interval) for cardiovascular disease mortality comparing the 80th versus the 20th percentiles of the urine cadmium distribution by participants characteristics at baseline (N=3,348)

Subgroup	Cases	HR (95% CI)	*P*–int.	All cause	Cases	HR (95% CI)	*P*–int.	All cardiovascular	Cases	HR (95% CI)	*P*–int.	Coronary heart disease
Age, years												
< 65	1,006	1.34 (1.20, 1.49)	0.90		284	1.42 (1.16, 1.73)	0.98		224	1.32 (1.05, 1.66)	0.95	
≥ 65	376	1.32 (1.13, 1.56)			116	1.42 (1.09, 1.85)			83	1.34 (0.97, 1.84)		
Sex												
Men	626	1.46 (1.26, 1.69)	0.14		181	1.44 (1.09, 1.91)	0.89		149	1.32 (0.96, 1.80)	1.00	
Women	756	1.27 (1.13, 1.43)			219	1.41 (1.15, 1.72)			158	1.32 (1.04, 1.67)		
Education												
≥ High School	567	1.52 (1.31, 1.75)	0.02		156	1.51 (1.16, 1.96)	0.56		121	1.35 (0.98, 1.85)	0.89	
< High School	815	1.24 (1.11, 1.39)			244	1.38 (1.14, 1.67)			186	1.31 (1.05, 1.64)		
BMI, Kg/m2												
<30	740	1.41 (1.24, 1.59)	0.13		192	1.56 (1.25, 1.94)	0.20		153	1.57 (1.22, 2.02)	0.05	
≥ 30	642	1.24 (1.09, 1.41)			208	1.28 (1.03, 1.60)			154	1.11 (0.85, 1.45)		
Smoking												
Never	451	1.26 (1.09, 1.45)	0.22		141	1.26 (1.00, 1.58)	0.14		107	1.12 (0.86, 1.45)	0.16	
Former	439	1.49 (1.28, 1.73)			122	1.70 (1.33, 2.18)			99	1.61 (1.21, 2.15)		
Current	492	1.29 (1.09, 1.53)			137	1.28 (0.96, 1.70)			101	1.26 (0.90, 1.77)		
Hyperlipidemia												
No	986	1.29 (1.16, 1.43)	0.14		237	1.36 (1.12, 1.65)	0.25		177	1.29 (1.03, 1.62)	0.61	
Yes	396	1.47 (1.25, 1.72)			163	1.62 (1.25, 2.09)			130	1.41 (1.05, 1.90)		
Hypertension												
No	744	1.36 (1.20, 1.54)	0.75		174	1.39 (1.10, 1.75)	0.68		129	1.32 (0.99, 1.76)	0.97	
Yes	638	1.32 (1.17, 1.50)			226	1.47 (1.20, 1.81)			178	1.33 (1.05, 1.69)		
Diabetes												
No	555	1.36 (1.20, 1.54)	0.61		113	1.13 (0.85, 1.49)	0.06		83	1.20 (0.86, 1.67)	0.56	
Yes	827	1.31 (1.15, 1.48)			287	1.53 (1.26, 1.86)			224	1.34 (1.07, 1.68)		
Estimated GFR, ml/min/1.73m2												
≥60	1,180	1.36 (1.23, 1.50)	0.06		327	1.44 (1.20, 1.73)	0.31		252	1.38 (1.12, 1.71)	0.15	
< 60	202	1.10 (0.90, 1.35)			73	1.21 (0.89, 1.64)			55	1.03 (0.72, 1.48)		
Overall	1,382	1.34 (1.22, 1.47)			400	1.42 (1.21, 1.68)			307	1.32 (1.09, 1.61)		

The 80th and 20th percentiles of the urine cadmium distribution were 1.62 and 0.55 μg/g creatinine, respectively. Hazard ratios for the subgroups of interest and associated P for interaction were obtained from Cox proportional hazards models with log-transformed cadmium as a continuous variable. Models were adjusted for sex, post-menopausal status for women (yes, no), education (< high school, ≥ high school), body mass index (kg/m^2), total cholesterol (mg/dL), estimated LDL- cholesterol (mg/dL), hypertension (yes, no), diabetes (yes, no), and estimated glomerular filtration rate (ml/min/1.73m^2), smoking status (never, former, current) and cumulative smoking dose (pack-years modeled as restricted cubic splines with knots at 10, 20 and 30 pack-years).

eFigure 2. Hazard ratios (95% confidence interval) for cardiovascular disease incidence comparing the 80th versus the 20th percentiles of the urine cadmium distribution by participants characteristics at baseline (N=3,348)

Subgroup	All cardiovascular			Coronary heart disease			Stroke			Heart failure		
	Cases	HR (95% CI)	P−int.	Cases	HR (95% CI)	P−int.	Cases	HR (95% CI)	P−int.	Cases	HR (95% CI)	P−int.
Age, years												
< 65	842	1.23 (1.09, 1.39)	0.98	604	1.20 (1.05, 1.38)	0.64	185	1.65 (1.07, 2.54)	0.80	246	1.49 (1.03, 2.14)	0.37
≥ 65	242	1.23 (1.03, 1.47)		162	1.28 (1.02, 1.60)		59	1.82 (0.89, 3.70)		82	1.14 (0.61, 2.14)	
Sex												
Men	455	1.30 (1.09, 1.55)	0.42	358	1.11 (0.92, 1.34)	0.21	93	1.89 (1.03, 3.45)	<0.001	100	1.75 (1.00, 3.05)	0.70
Women	629	1.20 (1.05, 1.36)		408	1.29 (1.10, 1.51)		151	1.49 (0.94, 2.36)		228	1.23 (0.83, 1.81)	
Education												
≥ High School	502	1.20 (1.03, 1.40)	0.65	366	1.19 (1.00, 1.42)	0.75	106	1.42 (0.83, 2.41)	0.19	137	1.69 (1.04, 2.74)	0.26
< High School	582	1.26 (1.10, 1.43)		400	1.24 (1.06, 1.44)		138	2.02 (1.22, 3.35)		191	1.29 (0.85, 1.95)	
BMI, Kg/m2												
<30	517	1.24 (1.07, 1.44)	0.60	366	1.18 (1.00, 1.40)	0.78	123	2.08 (1.21, 3.59)	0.03	146	1.17 (0.72, 1.90)	0.91
≥ 30	567	1.18 (1.03, 1.35)		400	1.22 (1.04, 1.43)		121	1.54 (0.93, 2.57)		182	1.43 (0.96, 2.14)	
Smoking												
Never	350	1.12 (0.95, 1.32)	0.29	243	1.16 (0.96, 1.39)	0.19	68	0.90 (0.49, 1.65)	0.02	104	1.18 (0.68, 2.05)	0.84
Former	338	1.34 (1.13, 1.58)		243	1.40 (1.16, 1.71)		76	0.46 (0.34, 0.63)		110	2.08 (0.68, 6.37)	
Current	396	1.28 (1.08, 1.52)		280	1.11 (0.91, 1.35)		100	1.68 (0.90, 3.14)		114	1.76 (1.04, 3.00)	
Hyperlipidemia												
No	689	1.23 (1.09, 1.38)	0.95	452	1.23 (1.07, 1.42)	0.85	165	1.64 (1.06, 2.55)	0.68	227	1.62 (1.10, 2.39)	0.09
Yes	395	1.23 (1.03, 1.48)		314	1.21 (0.99, 1.46)		79	2.08 (1.05, 4.14)		101	0.92 (0.53, 1.60)	
Hypertension												
No	552	1.21 (1.04, 1.40)	0.63	390	1.17 (0.99, 1.38)	0.43	128	1.61 (0.98, 2.65)	0.95	154	1.16 (0.76, 1.78)	0.42
Yes	532	1.26 (1.10, 1.45)		376	1.27 (1.09, 1.49)		116	1.70 (1.00, 2.90)		174	1.70 (1.09, 2.66)	
Diabetes												
No	404	1.06 (0.90, 1.25)	0.02	281	1.05 (0.86, 1.30)	0.07	86	1.18 (0.64, 2.18)	0.21	89	1.10 (0.60, 2.04)	0.11
Yes	680	1.34 (1.17, 1.53)		485	1.31 (1.13, 1.52)		158	2.12 (1.34, 3.35)		239	1.52 (1.05, 2.20)	
Estimated GFR, ml/min/1.73m2												
≥60	945	1.24 (1.10, 1.39)	0.34	670	1.20 (1.05, 1.37)	0.69	211	1.69 (1.11, 2.55)	0.71	279	1.45 (1.02, 2.06)	0.73
< 60	139	1.09 (0.86, 1.38)		96	1.13 (0.85, 1.50)		33	2.30 (0.90, 5.87)		49	0.99 (0.44, 2.23)	
Overall	1,084	1.23 (1.11, 1.37)		766	1.22 (1.08, 1.38)		244	1.71 (1.15, 2.53)		328	1.39 (1.00, 1.92)	

The 80th and 20th percentiles of the urine cadmium distribution were 1.62 and 0.55 µg/g creatinine, respectively. Hazard ratios for the subgroups of interest and associated P for interaction were obtained from Cox proportional hazards models with log-transformed cadmium as a continuous variable, except for stroke and heart failure where cadmium was introduced as restricted quadratic splines with knots at percentiles 10th, 50th and 90th. Models were adjusted for sex, post-menopausal status for women (yes, no), education (< high school, ≥ high school), body mass index (kg/m^2), total cholesterol (mg/dL), estimated LDL- cholesterol (mg/dL), hypertension (yes, no), diabetes (yes, no), and estimated glomerular filtration rate (ml/min/1.73m^2), smoking status (never, former, current) and cumulative smoking dose (pack-years modeled as restricted cubic splines with knots at 10, 20 and 30 pack-years).