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Urinary Cadmium and Incident Heart Failure

A Case–Cohort Analysis Among Never-Smokers in Denmark

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Background: Epidemiologic studies suggest cadmium exposure is associated with cardiovascular disease risk, including heart failure. However, prior findings may be influenced by tobacco smoking, a dominant source of cadmium exposure and risk factor for heart failure. The present study leverages up to 20 years of follow-up in the Danish Diet, Cancer and Health cohort to examine the relationship between urinary cadmium and incident heart failure among people who never smoked.

Methods: Between 1993 and 1997, 19,394 never-smoking participants (ages 50–64 years) enrolled and provided a urine sample. From this sample, we randomly selected a subcohort of 600 men and 600 women and identified 958 incident heart failure cases occurring between baseline and 2015. Using a case–cohort approach, we estimated adjusted hazard ratios (aHR) for heart failure in Cox proportional hazards models with age as the time scale.

Results: Participants had relatively low concentrations of urinary cadmium, as expected for never smokers (median = 0.20; 25th, 75th = 0.13, 0.32 μg cadmium/g creatinine). In adjusted models, we found that higher urinary cadmium was associated with a higher rate of incident heart failure overall (aHR = 1.1 per interquartile range difference [95% CI = 1.0, 1.2). In sex-stratified analyses, the association seemed restricted to men (aHR = 1.5 [95% CI = 1.2, 1.9]).

Conclusions: In this cohort of people who never smoked tobacco, environmental cadmium was positively associated with incident heart failure, especially among men.

Keywords: cadmium, case–cohort study design, incident heart failure, urine biomarker.

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Cadmium is a naturally occurring, non-essential, toxic metal that is transferred into the environment from industrial and agricultural activities. Human exposure to cadmium through diet and inhalation is a public health concern given its documented associations with cancer, impaired renal function, and cardiovascular morbidity and mortality.[1–5] Three recent systematic reviews have concluded that cadmium exposure is a risk factor for cardiovascular disease,[6–8] especially coronary heart disease. However, there remains some concern that the associations observed in prior studies may be influenced by tobacco smoking, a dominant source of cadmium exposure and major risk factor for heart failure and cardiovascular disease.[9] Furthermore, a majority of the prior epidemiologic studies have evaluated composite cardiovascular disease outcomes, and the few studies that have considered incident heart failure were underpowered to evaluate this association independent of tobacco smoking.[10–12] These studies reported an association between higher concentrations of cadmium biomarkers and heart failure that decreased in precision when the analyses were limited to never smokers.

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The data underlying this article cannot be shared publicly for the privacy of individuals that participated in the study. The data underlying this article were provided by The Diet, Cancer and Health Cohort with permission for this article.

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Heart failure is a prevalent condition that is characterized by left ventricular dysfunction which progresses into alterations in cardiac structure and the development of clinical symptoms.[13] Previous research suggests that cadmium exposure may increase risk for heart failure by directly altering the myocardium and potentially contributing to systolic left ventricular dysfunction.[14–16] The association between cadmium and heart failure may also be mediated through secondary mechanisms including hypertension and kidney dysfunction.[17–19] Determining whether cadmium exposure is a risk factor for heart failure can inform policy-makers who are considering health-based regulations to limit environmental cadmium exposure among the general population.[5,20]

The objective of this study was to evaluate the relationship between urinary cadmium and heart failure in a prospective case–cohort study of people who never smoked tobacco. In our analyses, we adjusted for urinary cotinine concentrations, an indicator of secondhand tobacco smoke exposure. We conducted analyses in the full sample and separate sex strata. Our hypothesis was that higher urinary cadmium concentrations would be positively associated with incident heart failure. Furthermore, we hypothesized that this association may vary by sex due to potential differences in cadmium absorption and heart failure etiology.

Previously, we published analyses examining the association of urinary cadmium with acute myocardial infarction and stroke among participants who self-identified at baseline as never tobacco smokers in the Danish Diet, Cancer and Health (DCH) cohort.[21,22] In these analyses, we did not find strong evidence to suggest that low levels of cadmium exposure were associated with incident stroke or acute myocardial infarction.

METHODS

We used existing data and urine samples from the prospective DCH cohort to evaluate the relationship between urinary cadmium concentrations and incident heart failure among men and women who never smoked tobacco. Details of sampling, recruitment, and follow-up procedures for the DCH cohort are provided elsewhere[23] and in the supplemental material; http://links.lww.com/EDE/B878. Briefly, between December 1993 and May 1997, 57,053 individuals (ages 50–64 years) living in the area surrounding Copenhagen or Aarhus consented to participate. The DCH cohort was established in accordance with the Helsinki Declaration and approved by the local Ethics Committees. Written informed consent was provided by all participants.

Only participants who self-identified at baseline as never tobacco smokers (n = 19,394; n = 6,821 men and n = 12,573 women) were eligible to be included in this analysis. Among eligible participants, we identified incident heart failure cases (ICD-10 codes I50.0-I50.9 and I11.0) and date of diagnosis in the Danish National Patient Registry (NPR) by means of the civil registry number, a unique personal identification number for every Danish citizen.[24] We also used the Danish Cause of Death Registry to identify fatal heart failure cases that were not included in the NPR and occurred after enrollment through 2013. We included all incident cases recorded in the NPR that occurred through 31 December 2015. We subsequently created a referent subcohort, by randomly sampling 600 men and 600 women (total n = 1,200) from the 19,394 participants who were never smokers. Of the 958 cases of incident heart failure identified in the full cohort, 64 were from the referent subcohort. We censored participants at the emigration date recorded in the Danish Central Person Registry (n = 3), the date of death documented in the Danish Cause of Death Registry (n = 154), or 31 December 2015, whichever date occurred first.

At baseline, we collected spot urine samples using trace metal-free techniques as previously described.[23] Samples from cases and subcohort members were mixed and anonymized before shipment on dry ice to the Trace Metals Laboratory at RTI International (Research Triangle Park, NC). At RTI, we used an iCAP Q ICP-MS system (Thermo Scientific, Waltham, MA) equipped with a helium gas collision cell to quantify cadmium concentrations in urine samples (see eAppendix; http://links.lww.com/EDE/B878). Additionally, we quantified urinary creatinine colorimetrically by the Jaffe reaction with a Cayman Chemicals (Ann Arbor, MI) Creatinine Assay Kit following the manufacturer's instructions. We measured urinary osmolality by the freezing point depression method using a Model 3320 Micro-Osmometer by Advanced Instruments, Inc (Norwood, MA).

For the main analyses, we used the machine-read cadmium values for all participants including the 18 heart failure cases and 22 subcohort members with values below the limit of detection (LOD; median LOD [25^{th}, 75^{th}] = 0.003 [0.001, 0.003] μg/L). We calculated creatinine-standardized cadmium concentrations by dividing urinary cadmium concentrations (μg) by creatinine (g).

We used a cotinine ELISA bioassay kit (Abnova Corporation, Taipei, Taiwan) to measure urinary cotinine, an indicator of tobacco smoke exposure. Participants self-reported age, sex, education, and physical activity on questionnaires administered at baseline, as previously described.[23] Women reported menopausal status and parity. To be considered postmenopausal, women either had surgically removed ovaries, reported an age of menopause, or reported no natural menstruation during the last 12 months. We considered women who did not fulfill these criteria but reported sequential hormone replacement therapy as probably menopausal. Premenopausal women reported at least one menstruation within the 12 months before entry to the cohort and had no hormone replacement therapy use. At baseline, lab technicians also measured height and weight and calculated body mass index.

Statistical Analyses

We used a case–cohort approach to estimate the relationship between creatinine-standardized urinary cadmium concentrations and incident heart failure.[25] In this

time-to-event analysis, follow-up for subcohort members started at their age on the DCH cohort enrollment date and ran until the age on the date of heart failure diagnosis or the censoring date. Based on the Prentice method, we estimated hazard ratios and robust 95% confidence intervals (CIs) for an interquartile range difference in cadmium using Cox proportional hazards models with age as the time scale.[25] We used age as the time scale because age is strongly predictive of the outcome and using time-on-study may bias results when age is related to the outcome.[26] We selected covariates a priori[27] and examined minimally adjusted models including only sex, as well as fully adjusted models additionally including body mass index (continuous–linear term), education (categorical), and urinary cotinine concentrations (continuous–linear term). We considered quartiles of creatinine-standardized cadmium to assess the dose–response relationship and conducted a linear test for trend by assigning observations in each cadmium quartile the median concentration of the quartile, treating the variable as continuous, and assessing the *P* value for this term.[28] Moreover, we visually evaluated linearity of the dose–response relationship by modeling creatinine-standardized cadmium using a natural cubic spline with three degrees of freedom (knots at 33rd and 67th percentiles). We used analysis of variance to compare this spline model to the model with a linear term and assessed the *P* value as the non-linearity *P* value.

We added a sex by cadmium (continuous variable) product term to adjusted models, as well as estimated the association between creatinine-standardized urinary cadmium concentrations and heart failure in sex-stratified analyses. Among the strata of women, we included menopausal status as an additional covariate in all models. We repeated the main analyses using cadmium quartiles and splines to assess the dose–response relationship in each sex stratum. We also conducted secondary analyses examining the association between urinary cadmium and heart failure among postmenopausal women only.

We conducted a series of sensitivity analyses (see eAppendix; http://links.lww.com/EDE/B878). In these sensitivity analyses, we examined multiple statistical approaches with urinary creatinine and osmolality measures to account for differences in urine density. We conducted these analyses because it is important to account for urine density when using urinary biomarkers, but there is little consensus on the optimal approach. We also conducted a series of analyses adjusting models for or excluding participants with health conditions that could be risk factors for heart failure. We did not include hypertension, diabetes, or hypercholesterolemia as covariates in our main analyses because it is plausible that these conditions could be on the causal pathway between cadmium exposure and heart failure.[29] Since secondhand tobacco smoke exposure is a well-documented confounder, we also examined different approaches adjusting for cotinine concentrations and history of secondhand tobacco smoke exposure.

Lastly, we estimated the proportion of incident heart failure cases attributable to the highest quartile of urinary cadmium by calculating the relative measure of effect ([adjusted hazard ratio (aHR) comparing highest versus lowest cadmium quartile−1]/aHR comparing highest versus lowest cadmium quartile) and multiplying it by the proportion of heart failure cases in the highest cadmium quartile for the full study sample and each sex strata.[30] All analyses were conducted in R version 3.6.2 using the survival package and functions to account for the case–cohort study design.

RESULTS

Participants who developed heart failure tended to be older, more obese, and have fewer years of formal education compared with the summary characteristics for the subcohort (Table 1). Participants who developed heart failure also had a slightly higher median urinary cadmium concentration (0.22 [0.10, 0.41] μg/L) compared with the subcohort members (0.19 [0.09, 0.34] μg/L). Overall, women had higher median creatinine-standardized cadmium concentrations (0.30 [0.20, 0.44] μg/g) than men (0.16 [0.11, 0.23] μg/g; combined median = 0.20; 25th, 75th = 0.13, 0.32 μg/g; eTable 1; http://links.lww.com/EDE/B878]. Compared with the subcohort, a higher proportion of the female heart failure cases were among postmenopausal women. The median age at incident heart failure was similar among men (71 [66, 75]) and women (73 [68, 77] years).

We found a positive trend in the relationship between quartiles of urinary cadmium and incident heart failure (Table 2). Specifically, the fully aHR for heart failure was 1.3 (95% CI = 0.95, 1.8) comparing participants in the highest versus lowest quartile of creatinine-standardized cadmium concentrations, with no evidence of departure from linearity (linearity *P* = 0.66; eFigure 1; http://links.lww.com/EDE/B878). An interquartile range difference in urinary cadmium (interquartile range width [IQR_w] = 0.19 μg/g) yielded a fully aHR for heart failure of 1.1 (95% CI = 1.0, 1.2; Table 2).

We found strong evidence suggesting the association between cadmium and incident heart failure varied by sex (sex by cadmium product term *P* value = 0.012). In sex-stratified analyses, we found a positive trend in the relationship between urinary cadmium and incident heart failure among men. The fully aHR for heart failure was 2.0 (95% CI = 1.2, 3.2) comparing men in the highest versus lowest quartile of creatinine-standardized cadmium concentrations (Table 3). Using splines to model cadmium, we report slight evidence of a non-linear U-shape relationship among men (linearity *P* value = 0.16; eFigure 1; http://links.lww.com/EDE/B878). An interquartile range difference (IQRw = 0.19 μg/g) in cadmium was associated with a hazard ratio of 1.5 (95% CI = 1.2, 1.9) among men.

We did not find strong evidence to suggest a relationship between higher urinary cadmium and a higher rate of heart failure among women, with little indication of departure from linearity (linearity *P* = 0.27; eFigure 1; http://links.lww.com/

TABLE 1. Baseline Characteristics of Heart Failure Cases and Subcohort Members

Baseline Characteristics	Subcohort (n=1200)		HF Cases (n=958)	
	No (%)	Median (25th, 75th)	No (%)	Median (25th, 75th)
Age at enrollment (yrs)	1200	55.8 (52.5, 59.9)	958	58.7 (54.5, 61.9)
Sex				
Men	600 (50)		481 (50)	
Women	600 (50)		477 (50)	
Education				
Low (<8 years)	344 (29)		361 (38)	
Medium (8–10 years)	549 (46)		415 (43)	
High (>10 years)	307 (25)		182 (19)	
Parity (women only)				
0	77 (13)		68 (14)	
1 to 2	360 (60)		260 (55)	
3 to 8	163 (27)		149 (31)	
Menopausal status (women only)				
Postmenopausal	349 (58)		335 (70)	
Premenopausal	103 (17)		37 (8)	
Probably menopausal	148 (25)		105 (22)	
Cotinine concentration				
≤20 ng/mL	690 (58)		478 (50)	
>20 ng/ml – <50 ng/mL	354 (30)		303 (32)	
≥50 ng/mL – <200ng/mL	134 (11)		153 (16)	
≥200 ng/mL	22 (1)		24 (2)	
Body mass index				
< 25	479 (40)		240 (25)	
25 to < 30	523 (44)		397 (41)	
30 +	198 (16)		321 (34)	
Leisure-time physical activity				
No	465 (39)		444 (46)	
Yes	735 (61)		514 (54)	
Urine Cd concentration (μg/L)		0.19 (0.09, 0.34)		0.22 (0.10, 0.41)
Urine creatinine concentration (g/L)		0.99 (0.47, 1.64)		1.05 (0.49, 1.65)
Urine osmolality (mOsM)		583 (312, 784)		596 (325, 784)

Cd indicates cadmium; and HF, heart failure.

TABLE 2. Adjusted Hazard Ratio (HR) for Incident Heart Failure Per Interquartile Range Difference and Quartile of Urinary Cadmium Concentration (Creatinine Standardized)

U-Cd (μg/g Creatinine)	Total	Cases (n)	U-Cd, Median (μg/g Creatinine)	Minimally Adjusted, HR (95% CI)[a]	Fully Adjusted, HR (95% CI)[b]	Trend Test, *P* Value
Continuous[c]	2094	958		1.1 (1.0 – 1.2)	1.1 (1.0 – 1.2)	0.048
Quartile 1: ≤ 0.13	495	211	0.10	Ref	Ref	
Quartile 2: > 0.13 – 0.20	471	195	0.17	0.89 (0.69 – 1.2)	0.93 (0.70 – 1.2)	
Quartile 3: > 0.20 – 0.32	544	257	0.25	1.2 (0.90 – 1.5)	1.2 (0.93 – 1.6)	
Quartile 4: > 0.32	584	295	0.45	1.2 (0.92 – 1.6)	1.3 (0.95 – 1.8)	

U-Cd indicates urinary cadmium.
[a]Minimally adjusted model includes sex.
[b]Fully adjusted model includes: sex (categorical), BMI (continuous), education (categorical), and cotinine (continuous).
[c]Continuous HR for an IQR_w = 0.19 μg/g difference in creatinine-standardized urinary cadmium concentration.

EDE/B878). The fully aHR for heart failure was 1.1 (95% CI = 0.68, 1.8) comparing women in the highest versus lowest quartile of creatinine-standardized cadmium concentrations (Table 3). The results were not materially different when we limited the secondary analyses to women who were postmenopausal (eTable 5; http://links.lww.com/EDE/B878).

In sensitivity analyses, we found that these results were robust to a number of analytic choices. Specifically,

TABLE 3. Adjusted Hazard Ratio (HR) for Incident Heart Failure Per Interquartile Range Increase and Quartile of Urinary Cadmium Concentration in Sex-Stratified Analyses

	Men			Women		
U-Cd (µg/g Creatinine)	**Total (n)**	**Cases (n)**	**Fully Adjusted HR (95% CI)**	**Total (n)**	**Cases (n)**	**Fully Adjusted HR (95% CI)**
Continuous[a]	1041	481	1.5 (1.2 – 1.9)	1053	477	1.1 (0.97 – 1.2)
Quartile 1: ≤ 0.13	385	170	Ref	110	41	Ref
Quartile 2: > 0.13 – 0.20	313	134	0.93 (0.67 – 1.3)	158	61	0.93 (0.52 – 1.7)
Quartile 3: > 0.20 – 0.32	240	113	1.1 (0.79 – 1.6)	304	144	1.4 (0.81 – 2.3)
Quartile 4: > 0.32	103	64	2.0 (1.2 – 3.2)	481	231	1.1 (0.68 – 1.8)

Adjusted model includes: BMI (continuous-linear), education (categorical-linear), and cotinine (continuous-linear). Analysis among women is also adjusted for menopause status. *P* value for sex by cadmium product term in the main fully adjusted model: $P = 0.012$. U-Cd indicates urinary cadmium.

[a]Continuous HR for an $IQR_w = 0.19$ µg/g difference in creatinine-standardized urinary cadmium concentration.

both censoring values below the LOD and excluding participants beyond the 5th and 95th percentile of creatinine-standardized cadmium concentrations resulted in slightly higher fully aHR estimates and consistent exposure-response relationships compared with the main results (eTable 2; http://links.lww.com/EDE/B878). Furthermore, using creatinine adjustment, covariate adjusted creatinine standardization, osmolality adjustment, or osmolality standardization did not meaningfully alter our results (eTable 3; http://links.lww.com/EDE/B878). Using these different methods to account for urine dilution, the relationship between urinary cadmium and incident heart failure ranged from aHR = 1.1 per IQR_w (95% CI = 1.0, 1.2) to aHR = 1.2 per IQR_w (95% CI = 1.0, 1.3). In the sex-stratified analyses accounting for urine dilution with osmolality adjustment or standardization, we found similar, but less pronounced, patterns in the relationship between cadmium and incident heart failure compared with our main results (eTable 4; http://links.lww.com/EDE/B878). Our results were not materially different across other sensitivity analyses adjusting for diabetes, hypertension, and hypercholesteremia or excluding participants with high urinary cotinine (≥200 ng/ml) or extreme urinary creatinine levels (<0.03 g/L and >3 g/L) concentrations (eTable 6; http://links.lww.com/EDE/B878, eTable 7; http://links.lww.com/EDE/B878, and eTable 8; http://links.lww.com/EDE/B878). Moreover, the results were consistent across different approaches adjusting for tobacco smoke exposure (eTable 9; http://links.lww.com/EDE/B878).

To facilitate interpretation of our results, we estimated the proportion of total heart failure cases in this population that may have been attributable to the highest quartile of urinary cadmium (concentrations above 0.32 µg/g creatinine; Table 4). Approximately 6.9% (95% CI = −1.6 to 13) of all incident heart failure cases, and 6.6% (95% CI = 2.6, 9.1) of all cases among men, were attributable to the highest quartile of urinary cadmium. We did not find strong evidence that heart failure cases among women are attributable to the highest quartile of urinary cadmium 4.8% (95% CI, −23 to 22).

DISCUSSION

In this cohort of individuals who reported never-smoking tobacco, we found that higher urinary cadmium was associated with incident heart failure, primarily among men. We observed this positive association at levels of urinary cadmium quite common in the general population. Our results were robust across a variety of sensitivity analyses. These results differ from our prior studies in which we found no strong evidence of an association between higher urinary cadmium and acute myocardial infarction or stroke among self-reported nonsmokers in the DCH cohort.[21,22] However, our results are consistent with evidence suggesting that cadmium adversely impacts myocardial structure and function to plausibly increase the risk of heart failure.[14–16]

Heart failure is among the most prevalent and costly health conditions in middle- and high-income countries.[9,31,32] Given widespread cadmium exposure driven by a number of regulatable sources, the recognition of environmental cadmium as a risk factor for heart failure in the absence of tobacco use has potentially important public health implications.

People are primarily exposed to cadmium through diet and tobacco use, largely due to anthropogenic contamination of land.[5] While background levels of cadmium are naturally found in soil, agricultural application of phosphate fertilizers is a major driver of soil cadmium accumulation on croplands.[33,34] Additionally, emissions from industrial facilities, such as solid waste incinerators, iron and steel manufacturers, zinc mines, and metal finishing facilities, can contribute to cadmium emissions in the air and deposition on agricultural soils.[35–37] Cadmium that accumulates in the soil is subsequently taken up by vegetation, including tobacco plants and virtually all food crops—with about 80% of food cadmium coming from cereals, vegetables, and potatoes.[38] To protect human health and the environment, some European countries, including Denmark, have enacted national policies to limit cadmium levels in phosphate fertilizers. Furthermore, the European Union recently adopted regulations (effective in 2022) to expand similar protections across all member states.[39,40] Both regulatory approaches are more restrictive

TABLE 4. The Proportion of Total Heart Failure Cases That May Have Been Attributable to the Highest Quartile of Urinary Cadmium (>0.32 µg/g Creatinine)

	% of Heart Failure Cases (95% CI)
All Participants	6.9 (−1.6 to 13)
Men	6.6 (2.6 to 9.1)
Women	4.8 (−23 to 22)

than regulations in the United States that have only been implemented in 3 states.[5,20]

Cadmium exposure may directly contribute to left ventricular dysfunction, as well as indirectly impair cardiovascular health by disrupting the function of other organs, such as the kidneys.[14,16–19] Decades of experimental and observational research suggest that cadmium exposure can contribute to endothelial dysfunction, promote atherosclerosis, and disrupt cardiac function by inducing subtle alterations within cardiovascular tissue.[14,15,41–47] Cadmium exposure may be linked to cardiovascular disease risk through mechanisms involving inflammatory pathways, epigenetic modifications, and endocrine disruption.[7,45,48–50]

Our results are similar to, but more precise than, prior epidemiologic studies suggesting that cadmium exposure is associated with incident heart failure.[10–12] For example, in a study of tobacco smokers and nonsmokers, Tellez-Plaza et al. (2013) found a higher rate of heart failure among participants in the highest urinary cadmium quartile compared with the lowest quartile (aHR = 1.61 [95% CI = 1.10, 2.36]) while adjusting for tobacco use. However, since tobacco smoking is a major source of cadmium exposure, these studies report substantially higher concentrations of blood or urine cadmium for former and current tobacco users compared with nonusers, driving concerns that statistical adjustment may not sufficiently control for cardiovascular risk associated with tobacco use.[11,51,52] The prior studies that have estimated relationships between cadmium and incident heart failure among subgroups of never smokers report imprecise results.[10–12] For example, in the same study, Tellez-Plaza et al. (2013) report an attenuated relationship of cadmium concentrations with incident heart failure among never smokers (aHR = 1.18 comparing 80th and 20th percentiles of cadmium; [95% CI = 0.68, 2.05). The consistency of the results across these prior studies and our analysis suggests that the association between cadmium and heart failure is not due to residual confounding by tobacco smoking. Therefore, our results help to further establish environmental cadmium exposure, at the relatively low levels typically seen in nonsmoking individuals, as a risk factor for heart failure among the general population.

In general, risk factors for and incidence of heart failure, and its etiologic subtypes, have been found to vary by sex.[9,53–56] For example, among the Danish population less than age 74 years, the incidence of heart failure was higher among men than women between 1995 and 2012.[54] Studies across Europe and the United States also suggest that men have a higher risk specifically of heart failure with reduced ejection fraction, primarily due to artery disease and myocardial infarction, while women tend to have a higher risk of heart failure with preserved ejection fraction.[57]

Our sex-stratified analyses suggest that, among men, higher cadmium concentrations were associated with a higher rate of incident heart failure which is consistent with some prior research.[10] However, not all studies have shown sex differences in the relationship between cadmium and incident heart failure,[11,12] and this question remains unsettled. Compared with men, women tend to absorb cadmium at higher rates due to lower iron levels, primarily during reproductive ages; therefore, women may have higher cadmium concentrations in urine, blood, and the kidneys.[58,59] However, the sex-specific relations of cadmium with different health outcomes could vary based on the underlying physiology and etiological involvement of hormones.[60,61] Cadmium-associated heart failure risk, in particular, may vary by sex due to differences in heart failure etiology and pathophysiology, cardiac structure, and prevalent comorbidities.[53,55] Our results warrant further investigation with additional consideration of factors that may contribute to sex-specific confounding.

Our study population is predominantly non-Hispanic White. Therefore, our results may not be generalizable to other racial and ethnic groups who have different cadmium exposure patterns or risk factors for heart failure. We expect our results to be generalizable to other Scandinavian and non-Hispanic White populations of never smokers with similar cadmium exposure levels.

Our study has several additional limitations. First, although we restricted our study to self-reported never smokers and adjusted for several potential confounders, we cannot exclude the possibility of unmeasured confounding factors. For example, we did not adjust for potential confounding by dietary factors. However, it seems unlikely that diet is an important confounder since cadmium is found in a wide variety of foods, including many that are nutritionally beneficial for cardiovascular health. Residual confounding by income is also possible, and we did not consider other metal biomarkers that could be correlated with cadmium concentrations and associated with heart failure. We also were unable to control for chronic kidney disease or estimated glomerular filtration rate as a marker of progressive kidney disease, which may be potential confounders. It is possible that cadmium could impact renal function to subsequently increase cardiovascular disease risk, as well as affect urinary cadmium biomarker concentrations. However, our results were similar across sensitivity analyses accounting for several other related health conditions. Second, although the use of the Danish NPR for identification of heart failure cases is specific and has been shown to have a high positive predictive value,[62,63] we could have missed incident heart failure

cases during the follow-up period because our approach was less sensitive.[64] However, we do not expect this underreporting of heart failure cases to be related to cadmium exposure; therefore, we expect that if we included more cases with the same exposure distribution it would only increase the power and precision of the associations. Third, the lack of information extracted from the NPR on the pathophysiologic etiology limited our ability to evaluate sex-specific results in more detail. Among the women, we observed a small association with wide confidence intervals. Therefore, with a larger sample of women it is plausible that we would have made different inferences about the association. Fourth, we were unable to identify prevalent heart failure among subcohort members who did not have an additional diagnosis of heart failure in the NPR during the follow-up period. However, the prevalence of heart failure at baseline was less than 2%; therefore, the impact of this source of misclassification is likely to be small. Last, it is possible that for some participants in the subcohort and larger DCH cohort, death may have precluded development of clinically recognized heart failure, and therefore, could be considered a competing risk. However, we do not expect this to substantially impact our results since few subcohort members were censored due to death.

Our study has several notable strengths. First, we used data from a Danish prospective, population-based study with a long follow-up period for our analysis. Second, we quantified cadmium concentrations in urine samples collected at baseline, which is a proxy measure of long-term exposure. Urinary cadmium is considered a biomarker for long-term cadmium exposure because concentrations reflect the level of cadmium that has bioaccumulated in the kidney, where it has an estimated half-life of 10-30 years.[5,33] Third, we assessed both urinary creatinine and osmolality and showed little difference across methods accounting for urinary dilution.

In conclusion, our study suggests that higher urinary cadmium concentration, a biomarker of long-term exposure, is positively associated with incident heart failure, especially among men. Our results extend findings from prior epidemiologic studies by providing evidence of an association between environmental cadmium exposure and incident heart failure, independent of tobacco smoking. Assuming that the observed associations are causal and minimally biased, our results estimate that ≈6.9% of heart failure cases, primarily among men, were attributable to environmental cadmium exposure resulting in urinary concentrations greater than 0.32 µg/g creatinine. Our results increase confidence that exposure to environmental cadmium is a risk factor for heart failure.

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