PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Cadmium exposure and incidence of heart failure and atrial fibrillation - a population-based prospective cohort study
AUTHORS	Borné, Yan; Barregard, Lars; Persson, Margaretha; Hedblad, Bo; Fagerberg, Björn; Engström, Gunnar

VERSION 1 - REVIEW

REVIEWER	Tubek Slawomir Department of Internal Diseases, Voivdeship Hospital, Opole, Poland
REVIEW RETURNED	31-Jan-2015

GENERAL COMMENTS	Action of Cd is element of Zn intracellular metabolism disturbances and may lead to chronic myocardial damage.

REVIEWER	Laura Zheng Johns Hopkins University, USA
REVIEW RETURNED	25-Feb-2015

GENERAL COMMENTS	Borne et al's paper "Cadmium exposure and incidence of heart failure and atrial fibrillation – Results from the Malmo Diet and Cancer Study" is a good paper looking at the association between cadmium and HF and AF. The methods are solid, and the discussion is thorough. I would recommend this paper for publication with some minor revisions below: Please provide some background on the levels of cadmium and the primary routes of cadmium exposure in the Swedish population in either the discussion or the introduction section. Methods: Diabetes mellitus was defined as self-reported physician's diagnosis, use of anti-diabetic medication, or fasting whole blood glucose≥109 mg/dL (≥6.1 mmol/L). This range includes pre-diabetes. The fasting whole blood glucose cutoff should be set at ≥126 mg/dL. Cadmium levels were measured in erythrocytes. If you are reporting erythrocyte cadmium, it would be more descriptive to call it "erythrocyte cadmium" instead of "blood cadmium." Also, please present your analysis adjusted, and unadjusted for hematocrit in a sensitivity analysis. In your statistical analysis, you specify that they were followed from baseline to emigration, death, or December 31, 2010. Does this refer to emigration from the city of Malmo or from Sweden? Also do not specify what percent of your population is lost to follow-up. It would be nice to know how much loss to follow-up this study has. You adjust for smoking status (never, former, current) but this may not be enough. You will need to additionally adjust for pack-years of

	cigarettes smoked. We also suggest that you perform additional sensitivity analyses without the use of sex specific cutoffs for cadmium and for tertiles/quartiles of baseline age. Table 1: Please add a column in the tables for baseline characteristics overall. Figure 1: Please present the figure stratified by smoking status (a plot for never smokers, a plot for former smokers, and a plot for current smokers) Figure 2: Cubic spline models for hazard ratios should also include adjustment for smoking status.

VERSION 1 – AUTHOR RESPONSE

Reviewer Name Tubek Slawomir
Institution and Country Department of Internal Diseases, Voivdeship Hospital, Opole, Poland
Please state any competing interests or state 'None declared': zinc, zinc transporters

Please leave your comments for the authors below
Action of Cd is element of Zn intracellular metabolism disturbances and may lead to chronic myocardial damage.

Response: Thanks for this comment. Following text with reference "Cadmium could potentially replace and interact with the homeostasis of several essential metals, such as zinc, iron and calcium [33]." was inserted in discussion part on page 12.

Reviewer Name Laura Zheng
Institution and Country Johns Hopkins University, USA
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
Borne et al's paper "Cadmium exposure and incidence of heart failure and atrial fibrillation – Results from the Malmo Diet and Cancer Study" is a good paper looking at the association between cadmium and HF and AF. The methods are solid, and the discussion is thorough. I would recommend this paper for publication with some minor revisions below:

Please provide some background on the levels of cadmium and the primary routes of cadmium exposure in the Swedish population in either the discussion or the introduction section.

Response: Please see revised introduction.

Methods: Diabetes mellitus was defined as self-reported physician's diagnosis, use of anti-diabetic medication, or fasting whole blood glucose≥109 mg/dL (≥6.1 mmol/L). This range includes pre-diabetes. The fasting whole blood glucose cutoff should be set at ≥126 mg/dL.

Response: Yes, diabetes mellitus is usually defined by fasting plasma blood glucose (fpGlc), which has a cutoff at ≥126 mg/dL. However, in our study, we used the fasting whole blood glucose (fbGlc). A fpGlc of 126 mg/L corresponds to fbGlc of 109 mg/dL (≥6.1 mmol/L). (Alberti KG and Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med. 1998 Jul;15(7):539-53.). To clarify, we add the reference 28 in the manuscript on page 5.

Cadmium levels were measured in erythrocytes. If you are reporting erythrocyte cadmium, it would be more descriptive to call it “erythrocyte cadmium” instead of “blood cadmium.”
Also, please present your analysis adjusted, and unadjusted for hematocrit in a sensitivity analysis.

Response: blood cadmium concentrations in the paper were calculated as Ery-Cd x hematocrit (%). We did a sensitivity analysis using erythrocyte cadmium instead of blood cadmium; the results are listed in supplement table 1. We also inserted text on page 9, “We also did a sensitivity analysis using erythrocyte cadmium instead of Blood cadmium, and the results are listed in supplement table 1.”

In your statistical analysis, you specify that they were followed from baseline to emigration, death, or December 31, 2010. Does this refer to emigration from the city of Malmo or from Sweden? Also do not specify what percent of your population is lost to follow-up. It would be nice to know how much loss to follow-up this study has.

Response: This refers to emigration from Sweden; those who moved to other areas in Sweden can be followed in patient registers with national coverage. Thirty participants (0.7 %) were censored due to emigration out of Sweden. “from Sweden,” and “A total of 30 (0.7%) participants emigrated from Sweden during the follow-up.” were inserted on page 7.

You adjust for smoking status (never, former, current) but this may not be enough. You will need to additionally adjust for pack-years of cigarettes smoked.

Response: We do not have complete data for pack-years. However, we ran an analysis for HF with additional adjustment for pack-years. The result was similar. The following text was inserted on page 9: “We ran a sensitivity analysis with additional adjustment for pack-years, the result was similar. Subjects in the 4th compared to the 1st quartile of blood cadmium had a significantly higher risk for incident HF (HR: 1.98: 1.04-3.78, p=0.038).”

We also suggest that you perform additional sensitivity analyses without the use of sex specific cutoffs for cadmium and for tertiles/quartiles of baseline age.

Response: We ran additional analysis and added this information in the result part on page 9: “In addition, we analysed the association between blood cadmium and HF using quartile limits based on the entire sample instead of sex specific cutoffs. The HR (Q4 vs Q1) was 1.83(1.00-3.36, p=0.052) for the adjusted model when sex was added to the covariates. The relationship between cadmium and HF was only observed in subjects above 57 years of age. HR for Q4 vs Q1 for sex-specific quartiles cadmium was 1.11 (0.26-4.73, p=0.888) among 46-57 years old and 2.20 (1.07-4.50, p=0.031) among above 57 to 67 years old. However, only 24 HF cases occurred in subjects 46-57 years.”

Table 1: Please add a column in the tables for baseline characteristics overall.

Response: We inserted a column in the table 1 for overall baseline characteristics.

Figure 1: Please present the figure stratified by smoking status (a plot for never smokers, a plot for former smokers, and a plot for current smokers)

Response: Thanks for this suggestion. However, we think the number of HF cases is too small to subdivide into three plots, so we would prefer to keep one plot and present never smokers in a separate table.

Figure 2: Cubic spline models for hazard ratios should also include adjustment for smoking status.

Response: A new Cubic spline models adjusted for age, sex and smoking status replaced the old figure 2.

VERSION 2 – REVIEW

REVIEWER	Laura Zheng Johns Hopkins Bloomberg School of Public Health
REVIEW RETURNED	31-Mar-2015

GENERAL COMMENTS	To the authors: great job on revisions. I would accept for publication. However, please clarify in your materials and methods section that a fasting plasma blood glucose cutoff of >=126 mg/dL is equal to a fasting whole blood glucose cutoff of 109 mg/dL.