



Early View

Research letter

The association between cadmium exposure and chronic airflow limitation and emphysema: The Swedish CARDioPulmonary BioImage Study (SCAPIS Pilot)

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The association between cadmium exposure and chronic airflow limitation and emphysema: The Swedish CARDIOpulmonary BioImage Study (SCAPIS Pilot)

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To the Editor:

Cadmium is a metal that is widely spread in the environment and human populations are exposed to it through food, mainly grains and vegetables. The tobacco plants accumulate cadmium, and tobacco smokers accumulate the cadmium in tobacco smoke, which is absorbed in the lungs (1). Occupational exposure to cadmium has been linked to the development of emphysema and impaired lung function (2, 3). Increased levels of blood cadmium (B-Cd) or urinary cadmium are associated with lower lung function, and it has been suggested that cadmium, also in the low-dose interval, is a risk factor for impaired lung function (1, 4).

The aim of this study was to examine whether cadmium exposure in the low dose interval was associated with increased prevalence of emphysema and impaired pulmonary function. The study population comprised randomly selected subjects (n=1,111) from the population in Gothenburg aged 50-64 years (5). All subjects answered a questionnaire and performed dynamic spirometry including forced expiratory volume in 1 second (FEV₁) and forced vital capacity (FVC). From diffusing capacity measurements for carbon monoxide, DL_{CO} (diffusing capacity) and K_{CO} (transfer coefficient) were obtained (6). A Jaeger Master Screen PFT (Vyaire, Mettawa, IL, US) was used for all measurements. Residual volume (RV) and total lung capacity (TLC) were measured using a body box. All procedures were performed after inhalation of 400 µg of salbutamol and according to American Thoracic Society (ATS)/European Respiratory Society (ERS) standards, as previously described (5). Predicted values (% predicted) and lower limits of normal (LLN) were based on published equations (7-10). Predicted values (FEV₁ and FVC) were based on recently developed equations from same source population (7). Cadmium (B-Cd) was analysed in whole blood as previously described (11). The pulmonary CT investigations were performed and assessed according to international guidelines (12).

Chronic airflow limitation according to Global Initiative for Obstructive Lung Disease (GOLD) (CAL_{GOLD}) was defined as an FEV₁/FVC ratio <0.7.

Chronic airflow limitation (CAL_{LLN}) was defined as an FEV₁/FVC ratio below the lower limit of normal (LLN).

Emphysema was defined as having at least mild emphysema in any zone of the lungs.

Centrilobular emphysema was defined as having centrilobular emphysema in any zone of the lungs.

Smoking was categorized as current smoker, former smoker or never-smokers. Pack-years (cumulative tobacco exposure) were calculated for all participants with a history of smoking. Never-smokers were assigned 0 (zero) pack-years.

Socioeconomic status (SES) was defined according to the highest level of education achieved.

Body mass index (BMI) was defined as measured weight/height² (kg/m²).

Occupational exposure to vapour, gas, dust or fumes (VGDF) was based on an affirmative answer to the item "Have you ever been exposed to vapor, gas, dust or fumes at your workplace?".

B-Cd was classified in quartiles; <0.16 µg/L, 0.16 - <0.23 µg/L, 0.23-<0.39 µg/L and 0.39 – 3.63 µg/L.

Correlations (Spearman, r_s) were analyzed between B-Cd and pack-years, and FEV₁, FEV₁/FVC, TLC, RV, TL_{CO} and K_{CO}. Associations between B-Cd quartiles and emphysema, centrilobular emphysema and CAL were analyzed using multiple logistic regression models and associations between B-Cd quartiles and continuous pulmonary function variables using multiple linear regression models. All models were adjusted for age, socioeconomic status, occupational exposure, and smoking. In model 1 the smoking adjustments included current smoking and former smoking vs. never smoking and in model 2 the smoking adjustment included pack-years. All calculations were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA). P-values<0.05 were considered significant.

Of the 1,111 subjects, complete data on lung CT, lung function and B-Cd was obtained for 741 individuals, 381 men and 360 women, mean age 57.1 years. From the lowest to the highest B-Cd quartile the mean age was 56.4, 57.1, 57.7 and 57.0 years, respectively. The study population consisted of 45.3% (n=336) never-smokers and 17.4% current smokers (n=129), with mean 16.7 pack-years for former smokers and mean 20.5 pack-years for current smokers. From the lowest to the highest B-Cd quartile the means were 3.3, 5.4, 7.9 and 18.9 packyears, respectively. Among all individuals the mean B-Cd concentration was 0.38 µg/L, median 0.24 µg/L. Never-smokers had significantly lower B-Cd, (mean 0.22 µg/L, median 0.19 µg/L), compared with current smokers, (mean 1.02 µg/L, median 0.85 µg/L). The correlation (r_s) between B-Cd and pack-years was 0.48 (p<0.0001), among individuals with emphysema it was $r_s=0.42$ (p<0.001) and among those with no emphysema it was $r_s=0.37$ (p<0.001). For all individuals, there were significant negative correlations between B-Cd and FEV₁/FVC ($r_s=-0.08$), TLC ($r_s=-0.25$), DL_{CO} ($r_s=-0.39$) and K_{CO} ($r_s=-0.31$).

The multivariate results are presented in the Table. There were increased odds for emphysema (odds ratio (OR) 5.5; 95% confidence interval (CI) 1.4 – 21.0), CAL_{GOLD} (OR 2.8; 95% CI 1.02 – 7.5) and CAL_{LLN} (OR 3.1; 95% CI 1.1 – 8.4) in the highest quartile of B-Cd versus the lowest quartile. The OR for

emphysema was still elevated (OR 4.6; 95% CI 1.3 – 16.9) in the third B-Cd quartile. In the models current smoking were associated with emphysema (OR 11.0, 95% CI 3.9 – 30.7) and CAL_{GOLD} (OR 2.8, 95% CI 1.2-6.5). When adjusting for cumulative tobacco exposure, the results were similar.

Regarding centrilobular emphysema, we found a significantly increased OR in the highest (OR 12.4; 95% CI 1.5 – 102.2) as well as in the third B-Cd quartile (OR 8.8; 95% CI 1.1 – 71.2). When adjusting for the cumulative tobacco exposure we found similar results. There was decreased DL_{CO}, but not K_{CO}, in the highest B-Cd quartile compared to the lowest.

The most important findings were the increased prevalence of emphysema in the two upper quartiles of B-Cd (median 0.29 and 0.71 µg/L) compared with the lowest quartile of B-Cd (median 0.13 µg/L). Further supporting the link between emphysema and B-Cd, DL_{CO} was decreased in the highest B-Cd quartile. The B-Cd levels in the upper quartile are common in many countries, and our results indicate that cadmium at these levels may be an important risk factor for emphysema (13).

The results are in line with previous papers describing increased risk to develop emphysema in workers occupationally exposed to cadmium (2, 3). Rats exposed to cadmium chloride have been reported to develop lesions that resemble centrilobular emphysema (14).

The analyses were adjusted for either smoking categories or cumulative dose of tobacco (pack-years). We consider the cumulative model the most adequate, as the risk for emphysema is more related to the cumulative exposure than to the timing of the exposure (current vs former smoking). There is, however, a strong relation between emphysema and tobacco smoking, and, hence, residual confounding by smoking cannot be excluded.

The main strength of the present study is the use of low-dose CT of the lungs to assess emphysema in combination with lung function. The main limitation of this study is the small sample. Smoking habits were based on self-reported data, and studies have indicated that some ever-smokers may tend to over classify themselves as never-smoker (15). If this is the case in our study population, it may mean that a small proportion of never-smokers in the current study indeed may indeed be misclassified smokers.

In conclusion, we suggest that cadmium exposure, also in the low dose range, is a risk factor for emphysema. We have controlled for smoking, but there is a need for further general population studies in never smokers.

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Competing interests.

All authors have completed the Unified Competing Interest form at www.icmje/coi_disclosure.pdf (available in request from the corresponding author): KT, ACO, GB, ÅJ, NF, GS and LB do not have any conflict of interest to report. JV reports personal fees from Boehringer Ingelheim outside the submitted work.

Ethical approval

The study was approved by the Regional Committee of Ethics in Umeå, 2010/228-31, and all included subjects gave their written consent to participate in the study.

Data sharing

The study is based on random population sample, which needs a Swedish ethical application to be analyzed.

The lead author (KT) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Table. The associations between quartiles of blood cadmium (B-Cd) and emphysema, and chronic airflow limitation (CAL). The regression models are adjusted for age, former smoking, current smoking, socioeconomic status and occupational exposure. Model 2 adjusted for age, socioeconomic status, occupational exposure and pack-years.

Dependent Variables (outcomes)	B-Cd		
	Multiple logistic regression models Odds ratios and 95% confidence intervals		
	Quartile 2 ¹ 0.16 - <0.23 µg/L	Quartile 3 ¹ 0.23-<0.39 µg/L	Quartile 4 ¹ 0.39 – 3.63 µg/L
Model 1			
Emphysema n=71	1.09 (0.2-5.1)	4.6 (1.3-16.9)	5.5 (1.4-21.0)
Centrilobular emphysema n=49	0.7 (0.05-12.0)	8.8 (1.1-71.2)	12.4 (1.5-102.2)
CAL _{GOLD} (n=71)	2.1 (0.8-5.1)	1.7 (0.7-4.3)	2.8 (1.02-7.5)
CAL _{LLN} (n=66)	1.8 (0.7-4.6)	1.7 (0.7-4.4)	3.1 (1.1-8.4)
Model 2			
Emphysema (n=71)	1.1 (0.2-5.1)	5.3 (1.5-19.3)	8.6(2.4-30.8)
Centrilobular emphysema N=49	0.70 (0.04-11.7)	9.2 (1.1-74.3)	16.0 (2.0-127.3)
CAL _{GOLD} (n=71)	2.1 (0.8-5.1)	1.7 (0.7-4.3)	3.2 (1.3-8.1)
CAL _{LLN} (n=66)	1.8 (0.7-4.5)	1.6 (0.6-4.2)	3.1 (1.2-7.8)
Multiple linear regression models Estimates (µg/L) and p-values			
	Quartile 2 ¹ 0.16 - <0.23 µg/L	Quartile 3 ¹ 0.23-<0.39 µg/L	Quartile 4 ¹ 0.39 – 3.63 µg/L
Model 1			
DL _{CO} , % pred	1.5 (N.S.)	-2.0 (N.S.)	-7.4 (p<0.0001)
K _{CO} , % pred	2.2 (N.S.)	3.7 (N.S.)	-4.0 (N.S.)
TLC, % pred	2.4 (N.S.)	0.48 (N.S.)	0.002 (N.S.)
RV, % pred	-0.60 (N.S.)	-0.38 (N.S.)	-2.6 (N.S.)
Model 2			
DL _{CO} , % pred	1.7 (N.S.)	-1.8 (N.S.)	-7.9 (p<0.001)
K _{CO} , % pred	2.3 (N.S.)	3.8 (N.S.)	-3.6 (N.S.)
TLC, % pred	2.8 p<0.05)	1.1 (N.S.)	1.3 (N.S.)
RV, % pred	0.17 (N.S.)	0.73 (N.S.)	-0.83 (N.S.)

1. Compared with quartile 1 (<0.16 µg/L). 95% CI = 95% confidence interval; OR = odds ratio;