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Cadmium exposure and risk of kidney effects and bone fractures: Population-based studies in England and Sweden.

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Abstract

Cadmium (Cd) is a toxic metal with no beneficial biological function. The dissemination of cadmium to the surface environment, by industrial and agricultural practices, has led to increased human exposure. Food is the main source of exposure in the general non-smoking population however in areas close to industrial sources, contact with contaminated environmental media may also be important. Previous studies have shown toxic effects of cadmium on the kidneys and bone, however, considerable uncertainty remains over the exposure levels at which these toxic effects may start to occur and the clinical relevance of the early effects observed following long-term, low-level cadmium exposure.

The aims of this thesis were: 1) To assess cadmium body burden and early signs of kidney dysfunction in a population exposed to industrial cadmium emissions and to develop and validate an air dispersion model of these emissions. 2) To identify urinary metabolites, associated with cadmium exposure, using metabolic profiling techniques. 3) To prospectively assess the association between validated estimates of dietary cadmium exposure and chronic kidney disease (CKD) incidence, kidney stone incidence, and fracture incidence, in two large population-based cohorts of men and women.

In a population-based sample of 180 subjects, living close to a zinc smelter in Avonmouth, Southwest England, urinary cadmium concentrations (median = 0.22 nmol Cd/mmol creatinine) were in the same range as those where associations with kidney and/or bone effects have been observed previously. Three percent had concentrations above 1nmol Cd/mmol creatinine (~1µg/g) – the point of departure for tubular proteinuria set by the European Food Safety Authority in 2009. Modelled air cadmium concentrations from the smelter were strongly correlated with those from air monitoring sites (R^2=0.84) and were a significant predictor of urinary cadmium (p=0.04). In a cross-sectional analysis, a significant dose-response relationship between urinary cadmium and one of the biomarkers of early tubular dysfunction (N-acetyl-β-d-glucosaminidase) was observed. Metabolic profiling identified six urinary metabolites, either related to mitochondrial metabolism or one carbon metabolism, associated with urinary cadmium.

Two large population-based cohorts of men and women from Central Sweden were used to investigate the association between dietary cadmium exposure and incidence of CKD, kidney stones and fractures. Median dietary cadmium exposure levels in our study populations were 19µg/day in men and 13µg/day women. During an average of 12 years of follow-up, we ascertained 599 incident cases of CKD among men (481,591 person-years) and 253 among women (415,432 person-years). We did not observe an association between dietary Cd and rate of CKD in men, hazard ratio (HR) 0.97 (95% CI 0.77-1.21) or women HR 0.74 (95% CI 0.53-1.04), either before or after adjustment for potential confounders. During an average of 13 years of follow-up, we ascertained 707 incident cases of kidney stone among men (421,611 person-years) and 290 among women (403,575 person-years). Likewise, we did not observe an association between dietary Cd and rate of kidney stones in men HR 0.97 (95% CI 0.77-1.23) or women HR 0.99 (95%CI 0.89-1.43), either before or after adjustment for potential confounders.

We ascertained 2,183 cases of any fracture and 374 cases of hip fracture, during a 10-year follow-up of 20,173 Swedish men. In the multivariable adjusted model, dietary cadmium was associated with a statistically significant 19% (HR: 1.19, 95%CI: 1.06-1.34) higher rate of any fracture, comparing highest tertile with lowest. Hip fracture rates were also higher in the highest tertile of cadmium exposure but only statistically significant among never smokers, with a 70% (HR: 1.70, 95%CI: 1.04-2.77) higher rate. This study provides the first data on hip fracture rates in relation to cadmium exposure and is the first to report an excess risk of any fracture associated with long-term low-level cadmium exposure in men.

The results of this thesis suggest that the adverse effects of cadmium exposure around the Avonmouth smelter may be detected in urinary biomarkers. In addition, the results of the prospective studies do not support a role of dietary cadmium exposure, at the level seen in the general population, in the development of CKD or kidney stones. However, the results do provide further evidence of increase fracture risk in relation to cadmium exposure. In conjunction with recent findings, the results of this thesis suggest that bone may be a more sensitive target of cadmium toxicity than the kidney, in terms of clinically relevant outcomes.

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