Reviewer’s report

Title: Bone resorption and environmental exposure to cadmium in children

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Reviewer: Yasushi Suwazono

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The aim of this study was to investigate the association between markers of bone demineralization [urinary calcium (U-Ca) and deoxypyridinoline (U-DPD) excretion] and urinary cadmium (U-Cd) excretion (as an index of lifetime body burden). However, the measured U-DPD and U-Ca seemed to be much lower than the normal levels reported in previous studies. The association between U-Ca, U-DPD and U-Cd suggested in this child population seems to be so interesting and valuable that the present measurement should be carefully checked and revised adequately. Those estimates make a very important contribution to the international discussion on the risk assessment of environmental cadmium exposure in the general child population. Therefore, I recommend the authors to resubmit after careful revision of this manuscript.

Major Compulsory Revisions
1. Abstract: The authors noted that “A doubling of urinary Cd was associated with a 71% (p<0.0001) increase in urinary DPD and, a 33% (p=0.0006) increase in urinary Ca.” However, these values were different from those in table 2.
2. Methods: Please clarify whether the measured U-DPD was ‘free’ U-DPD or ‘total’ U-DPD.
3. Methods: Gender difference existed for U-Cd and U-DPD. I recommend the authors to divide the subjects into two groups according to gender, in order to make easier to interpret the results and to apply the results to actual population.
4. Results (page 8, lines 17-18): The authors noted “each doubling of urinary Cd was associated with an increase in urinary DPD of 1.86 ng/g creatinine (95% CI: 1.52 to 2.29; p: <0.0001).” These values were different from those in table 2.
5. Results (page 8, lines 17-18), Table 2: The authors reported that doubling of U-Cd may yield very small increase (1.86 ng/g creatinine) in U-DPD compared to the median level of 337 ng/g creatinine. As the authors estimated regression coefficient for each doubling of U-Cd, I guess the authors adopted 2 as the base of log-transformation of U-Cd, U-Ca and U-DPD. Based on this assumption, these regression coefficients can be presented as the anti-logarithm of these values and interpreted as doubling of U-Cd was associated with increase in U-DPD by 3.32(2^1.86) times. Another interpretation is that the presented values such as 1.86 were already converted as the anti-logarithm of obtained regression coefficients. The unit (ng/g creatinine and mg/g creatinine) should be deleted to avoid misinterpretation.
6. Table 1: The median of U-Ca (3.56 mg/g creatinine) seemed to be very small compared to the mean U-Ca (0.155 g/g creatinine=155mg/g creatinine) in primary school children in north of Iran. (http://www.ncbi.nlm.nih.gov/pubmed/16388158) The measurement of U-Ca should be checked carefully and revised adequately.

7. Table 1: The median of U-DPD (337ng/g creatinine) seemed to be very small compared to the median of free U-DPD (14-21 nmol/mmol creatinine) in primary school children in United Kingdom. (http://www.ncbi.nlm.nih.gov/pubmed/10086947) Based on the molecular weight of DPD (413g/mol) and creatinine (113g/mol), 337ng/g creatinine of U-DPD corresponds to 0.092 nmol/mmol creatinine. The measurement of U-DPD should be checked carefully and revised adequately. Furthermore, the unit should be converted to “nmol/mmol creatinine” for U-DPD.

8. Table 2 “Calcium, mg/g crtb”: In this model, U-Ca was adjusted to estimate regression coefficient for U-Ca. This is incorrect calculation. This line should be deleted.

9. Discussion (page 10, line 3): The authors should add at least one citation for “Children take up Cd more readily than adults due to lower iron stores.”

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I have no conflict of interest regarding this manuscript.