PERSISTENT ORGANOCHLORINE POLLUTANTS AND RISK FOR SKELETAL FRACTURES AND IMPAIRED BONE MINERAL DENSITY IN HUMANS – RESULTS FROM THE "COMPARE" PROJECT

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Introduction

Persistent organochlorine pollutants (POP) have, in animal studies, impaired normal bone metabolism and resulted in increased bone fragility.[1-3] Especially considering the dramatical increase in osteoporotic fractures in western societies during the last decades,[4] it is a pertinent question whether a high dietary intake of POP might pose a risk for deteriorated bone quality in humans. This problem has been assessed as a part of the collaborative project "COMPARE", funded by European Commission RD Life Science Program. As a study base we have used cohorts of Swedish fishermen's families. We have earlier shown that fishermen living at the east coast of Sweden, have a high consumption of contaminated fatty fish from the Baltic Sea and consequently relatively high exposure levels for various POPs, also compared with fishermen from the Swedish west coast.[5] Such a discrepancy was also found for fishermen's wives.

The aim of the project was to assess in epidemiological studies whether a high dietary intake of POP through fatty fish from the Baltic may result in an increased incidence of osteoporotic fractures or decreased bone mineral density (BMD). We give here an overview of the results.

Methods and Materials

Fracture incidence studies

Two methods were applied for assessing the association between POP exposure and fracture incidence in the Swedish fishermen's populations.

First, information on vital status and hospitalization of persons with fractures from 1987 to 1996 was retrieved through linkage with the Swedish inpatient ward register for 5572 fishermen from the west coast, 2385 fishermen from the east coast, 5166 fishermen's wives from the west coast, and 1859 fishermen's wives from the east coast.[6,7] The impact of cohort affiliation (east versus west coast) on fracture incidence was assessed by Poisson regression models for each gender, with age and calendar year taken into account.

Second, a postal questionnaire was sent to 2096 fishermen and 1602 fishermen's wives from the Swedish east coast, and 4584 fishermen and 4217 fishermen's wives from the west coasts.[8,9] Self reported fractures together with specified current fish consumption and information about potential confounders were registered. The response rates varied between 50 and 59 %. The non-responders had almost identical age distributions as the responders. Hip, vertebral, and wrist fractures were classified as osteoporotic fractures. The fracture incidence rates for specific skeletal localizations were based on allocated fractures and person-years under risk from age 25 until time of fracture or end of follow-up, and the impact of exposure variables (cohort affiliation and within the east coast cohort the consumption of fatty fish from the Baltic Sea) was assessed by Poisson regression models, adjusting for potential confounders.

POP exposure and bone mineral density

In a field study BMD was measured by DXA technique (wrist) on 203 east coast fishermen and 194 east coast fishermen's wives. A standardized interview was performed and blood and urine samples were drawn in the morning after 12 hs fasting, for analysis of serum biomarkers of bone metabolism, hormones, vitamins (for a subsample of 100 women), CB-153, p,p'-DDE, OH-PCBs (for a subsample of 100 subjects) and cadmium in urine.

The levels of CB-153 were determined as previously described.[10] In addition, p, p'-DDE was analyzed by the same method. Briefly, the CB-153 and p, p´-DDE were extracted from the serum by solid phase extraction (Isolute ENV+; IST, Hengoed, UK) using on-column degradation of the lipids and analysis by gas chromatography mass spectrometry. $^{13}C_{12}$-labeled CB-153 and $^{13}C_{12}$-labeled p, p´-DDE were used as internal standards.

Data from some of the analysed variables are not yet available and the current presentation is restricted to the BMD results in relation to CB-153 and p,p'-DDE, taking into account age, smoking, BMI and cadmium in urine as potential confounders. Among the men, 40 (20 %) were current smokers and 113 (56 %) were ex-smokers. The corresponding figures for the women were 33 (17 %) and 69 (36 %). The other descriptive data are given in Table 1.

Table 1. Distribution of potential confounders (age, BMI, U-Cd), POP biomarkers (CB-153 and p,p'-DDE) and bone mineral density (BMD) for 203 fishermen from the Swedish east coast at the Baltic Sea and from 194 fishermen's wives from the same area.

	Men		Women	
	Median	Range	Median	Range
Age (years)	59	48-82	61	48-82
BMI (kg/m^2)	28.3	21.5-44.0	27.6	19.8-43.1
U-Cd (µmol/mol creatinine)	0.23	0.04-2.92	0.36	0.08-1.40
S-CB-153 (ng/g lipid)	365	54-1892	240	5-950
S-p,p'-DDE (ng/g lipid)	583	10-5050	600	5-7444
BMD (g/cm^2)	0.57	0.36-0.83	0.43	0.20-0.70

The effect of the exposure variables CB-153 and p, p'-DDE, respectively, on BMD was evaluated by linear regression models. The exposure variables were treated as continuous variables as well as categorized into four equally sized groups. The categorized variables were entered as dummy

variables in the models. In men both age and BMI, but not smoking or cadmium in urine, showed univariate associations with BMD, and these potential confounders were therefore included in the multivariate linear regression models. In women, age and BMI, but also smoking showed univariate associations with BMD, which guided the choice of multivariate model.

Results and Discussion

Fracture incidence studies

In the register linkage study neither the incidence of all fractures nor of all osteoporotic fractures differed between the east and west coast cohorts, irrespectively of gender. However, there was a significantly increased incidence of vertebral fractures among the east coast women as compared with the west coast women (age-adjusted Incidence Rate Ratio 2.29, 95% CI 1.34-4.28). The effect went in the same direction for the men, but the difference was not significant.

In the postal questionnaire study no differences in fracture incidence were observed between the east and west coast cohorts. East coast wives with more than one meal of fatty fish from the Baltic Sea per month had, however, an increased fracture incidence as compared with east coast wives that ate at most one such meal per month (age-adjusted Incidence Rate Ratio 1.68, 95% CI 1.00-2.84). No such exposure-response association was seen among the fishermen.

The results from the two fracture incidence studies gave only a minor support for an association between POP exposure through contaminated fish and increased risk for osteoporotic fractures in women. The associations were even weaker for men. A problem with the interpretation is that the results from the two studies are not obviously in coherence with each other. The effect of cohort affiliation found in the register-linkage study was not supported by the questionnaire study, in which an exposure-response association was observed only within the east coast cohort. The strength of the studies is their considerable size, but a weak point is the lack of individual biomarkers of exposure. Thus, non-differential misclassification of exposure might have blurred moderate or weak associations.

POP exposure and bone mineral density

The univariate analysis showed in both men and women weak negative associations between CB-153 and BMD (Figures 1 and 2), but after adjustment for the potential confounders no significant associations remained ($p=0.13$ for men and $p=0.41$ for women). In women, but not in men, there was a weak negative univariate association between p.p'-DDE and BMD (Figures 1 and 2), but after confounder adjustment the association disappeared ($p>0.5$). The results were not changed when CB-153 and p,p'-DDE were categorized into quartiles instead of being used as continuous variables.

Figure 1. POPs in serum versus Bone Mineral Density among 203 Swedish fishermen.

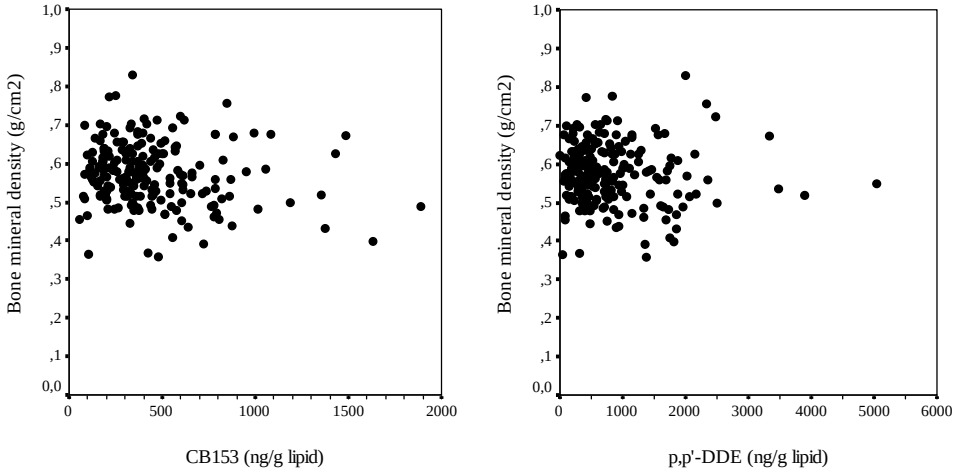
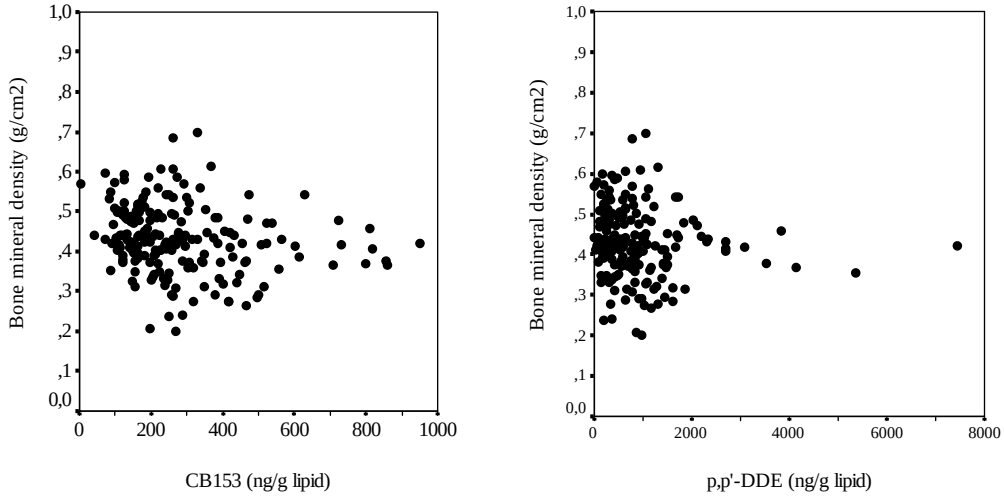


Figure 2. . POPs in serum versus Bone Mineral Density among 194 fishermen's wives from SwedenSweden.



The cross-sectional study did not support the hypothesis that the exposure levels for POP in the present study would be harmful for bone density. A more thorough and detailed analysis will be performed later when data on a number of additional variables (exposure and outcome variables as well as effect-modifiers) will be available. However, up to now our data from the COMPARE study do not support that the relatively high exposure levels for POPs found in the Swedish fishermen populations have had any clear effects on neither fracture incidence nor bone mineral density in middle-aged and elderly subjects.

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