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The impact of iron status and smoking on blood divalent metal concentrations in Norwegian women in the HUNT2 Study☆

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ABSTRACT

Low iron (Fe) stores may result in increased absorption of divalent metals, in particular cadmium (Cd). We have previously shown that in non-smoking women participating in the Norwegian HUNT2 cohort study this also included other divalent metals, e.g. manganese (Mn) and cobalt (Co). The diet is the main source of metals in non-smoking individuals, whereas in smoking individuals tobacco smoke contributes significant amounts of Cd and lead (Pb). The aim of the present study was to investigate the impact of smoking on the relationship between low iron status and divalent metals.

Blood concentrations of the divalent metals Cd, Mn, Co, Pb, copper (Cu) and zinc (Zn), determined using an Element 2 sector field mass spectrometer (ICP-MS), were investigated in smoking women of fertile age (range 21–55 years) (n = 267) from the HUNT2 cohort. Among these, 82 were iron-deplete (serum ferritin < 12 μg/L) and 28 had iron deficiency anaemia (serum ferritin < 12 μg/L & Hb < 120 g/L). 150 (56%) women smoked 10 or more cigarettes daily, 101 (38%) had smoked for more than 20 years, and 107 (40%) had smoked for 11–20 years. Results from the smoking population were compared with results from our previous study in non-smoking women (n = 448) of which 132 were previous smokers, all from the same cohort.

Increasing concentrations of Cd in blood were observed for previous smokers, low-to-moderate smokers and high intensity smokers in all subgroups compared to never smokers, and according to age groups, education level, BMI and serum ferritin. Smokers had higher Pb concentrations than non-smokers in all subgroups, but less pronounced than for Cd. Smoking was not associated with Mn and Co concentrations in blood.

In multiple regression models, low ferritin was associated with increased blood concentrations of Cd, Pb, Mn and Co. Ferritin was strongly associated with Cd at low smoking intensity, but was not a significant factor in heavy smokers, where intensity and duration of smoking emerged as main determinants. Ferritin associations with Co and Pb varied with tertiles of blood Cd. Ferritin emerged as the main determinant of blood Co and Mn, while for blood Pb, age and smoking intensity had higher impact. Cu and Zn remained within reference values and no significant associations with ferritin were found. Strong positive associations between blood concentrations of Pb, Mn, Cd and Co were observed, also when controlled for their common association with ferritin. Apart from these associations, the models showed no significant interactions between the divalent metals studied. Mild anaemia (110 < Hb < 120 g/L) did not seem to have any effect independent of low ferritin.

Abbreviations: DMT, divalent metal transporter; HUNT, The North Trøndelag Health Study.

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The results indicate that low serum ferritin facilitates absorption of certain divalent metal ions in female smokers as well as the previously shown effect in non-smokers. Even if smoking provides Pb and Cd, the mutual associations between Cd and other divalent metals in blood persisted in medium and heavy smokers. This indicates that the interrelationship between Cd and divalent metals not only reflect effects on the absorption, but possibly also on kinetic processes such as transportation in blood and other compartments, including excretion.

1. Introduction

Humans are exposed to metal compounds from several sources and they often come in mixtures. For non-occupationally exposed individuals the diet is a main source whereas in smokers tobacco smoke in addition contributes significantly. Metal compounds may interact both on a toxicokinetic and a dynamic level and joint action may take place both between non-essential metals as well as with the essential ones. The kinetics of the latter group is usually tightly regulated [1]. This includes in particular the kinetics of the essential element iron such that when there is lack of iron, the uptake from food is up-regulated [2]. However, it is well known that several divalent metals, both toxic and essential ones, use similar transporters as ferrous iron, e.g. the divalent metal transporter 1 (DMT 1) [3]. We [4] and others [5–7] have shown that low iron stores appear to impact the kinetics of particular cadmium (Cd), but also other divalent metals like manganese (Mn) and cobalt (Co), but not copper (Cu), zinc (Zn) and lead (Pb) [1]. Most previous studies used non-smokers or mixed populations. Tobacco smoke contributes considerably to the Cd and Pb exposure [8–12].

The aim of the present study was to expand our previous investigations in women and examine whether the associations between low iron status and increased concentrations of the blood divalent metals Cd, Mn and Co also would be found in smokers, where element balance and uptake mechanisms, e.g. for Cd, are different. In addition, Pb exposure is larger in smokers, and this might result in Pb being included in the mutual associations. We included only smoking women of fertile age and used results on non-smoking women from the same cohort from our previous study for comparison.

2. Materials and methods

2.1. Participants

The HUNT2 Study is a collaboration between the HUNT Research Centre, Faculty of Medicine, Norwegian University of Science and Technology (NTNU, Levanger), The Norwegian Institute of Public Health, and Nord-Trøndelag County Council. Between 1995 and 1997, all inhabitants aged 20 years or more in Nord-Trøndelag County in Norway were invited to enter this health survey program. The participants were invited by post and blood samples were drawn at different stationary field stations or mobile health units in the county.

In addition to blood samples and other types of tests, the screening included a questionnaire especially designed for women. A sub-group of the participating women (n = 3557, age 20–55), was invited to donate two extra blood samples for evaluation of iron status.

To investigate the impact of low iron stores on divalent metals specifically, a randomly drawn sub-set of women in the iron status study (n = 3005) was included in the present study, stratified on the basis of their serum ferritin concentrations being < or ≥ 12 μg/L and < 150 μg/L. Details of the procedures in the iron status study are described in [13]. Blood analyses of iron status and Hb were available for a total of 884 women. Only the 329 confirmed smokers were included in the main analyses of the present study, excluding n = 518 non-smokers and 37 women who did not answer the smoking questions. Furthermore, since menopause might influence the metabolism of some elements, i.e. iron, only participants who confirmed having menstruation (n = 215) or did not answer this question (n = 52, 14 above 40 years) and were 46 years of age or below, were included, excluding n = 62. This left us with 267 women for the final analyses. Of these, 120 women had serum ferritin < 12 μg/L and 34 had Hb < 120 g/L. Smoking intensity was defined as number of cigarettes smoked per day. Smoking load (pack-years) was defined as product of cigarettes/d and years.

For reference purposes, some results were compared with non-smoking women in the same sub-set of the HUNT study as mentioned above. The results from the non-smoking group (n = 448) were published in Ref. [4].

The study was approved by the Regional Committee for Medical and Health Research Ethics, Regions II and IV, and the Data Inspectorate of Norway. Oral and written information about the projects were given and the participants signed a written consent for the iron status project.

2.2. Analysis of blood parameters

For the measurements of elements in whole blood, the digested blood was analysed using an Element 2 sector field mass spectrometer (Thermo Electron, Bremen, Germany) calibrated with whole blood matched standard solutions. Seronorm™ Trace Elements human whole blood quality control materials were used for quality assurance of all element measurements. Further details are described in Meltzer et al. [4].

Whole blood was analysed for haemoglobin with Coulter JS (Coulter, USA). Serum iron was measured on a Hitachi 911 analyser using a ferrozin-method with reagents from Boehringer Mannheim, Germany. Serum ferritin was measured with Abbott AxSym and reagents from Abbott Laboratories, USA. Also here, further details are given in Meltzer et al. [4].

Blood sampling was done at different times of the day and sampling hour of day was recorded. Sampling time could be a possible confounding factor in this study. However, this variable did not have any significant influence when entered into the multivariate models for Cd, Mn, Pb and Co.

2.3. Statistical analysis

The distributions of trace element concentrations were somewhat skewed towards high concentrations, with the exception of Co and Fe, but log-transforming variables produced essentially the same results as those reported here. For multivariate modeling, variables were transformed as necessary to obtain good fit, in most cases either the basic or the log-transformed form (ln(x)) was used.

Differences between groups were checked for significance by pairwise *t*-tests, using Holm's correction for multiple comparisons when appropriate.

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