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SERUM DIOXIN LEVELS AND NEUROPSYCHOLOGICAL FUNCTIONING IN THE SEVESO WOMEN'S HEALTH STUDY

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Introduction:

2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) is neurotoxic in animals¹⁻⁴ but few studies have investigated its effects on the human brain. Related dioxin-like compounds have been linked to poorer cognitive function in older adults⁵⁻⁸, with effects more pronounced in women⁹, perhaps due to the loss of neuro-protective estrogen in menopause.^{10,11}

Materials and methods:

We investigated the neurotoxic effects of dioxin in the Seveso Women's Health Study (SWHS), a historical cohort study of women residing around Seveso, Italy at the time of an industrial accident on July 10, 1976 that resulted in the highest levels of residential contamination known on record. Blood samples were collected from the participants shortly after the accident. For each woman, TCDD concentration was measured in archived serum by high-resolution mass spectrometry.

In 1996, women who were aged 31-40 at the time of the accident (n=229) completed a physical function assessment spanning grip strength, walking speed, balance, and manual dexterity. In a 2008 follow-up study, we measured working memory (n=459) via the Wechsler Memory Scale digit span and spatial span tests. The associations between 1976 serum TCDD and measures of physical and cognitive functioning were modeled with multivariate linear regression and semi-parametric targeted maximum likelihood estimation (tmle).

All women who completed the physical function assessment were menopausal in 1996. In contrast, about half the women in the 2008 subset that completed the digit span and spatial span tests were menopausal. Thus, we examined effect modification by menopause status in the 2008 sample.

Results and discussion:

In the 1996 study sample, the geometric mean of 1976 serum TCDD levels was 55.3 ppt, lipid-adjusted (range: 3.2-5730). The average age was 57 (± 3) years. In the 2008 study sample, the geometric mean of 1976 serum TCDD levels was 68.1ppt (range: 3.1-56,000) and the average age was 52.3(± 11.3) years.

Adjusting for age, education level of the head of household, BMI, smoking, and alcohol consumption, a 10-fold increase in TCDD was not associated with walking speed ($\beta=0.000624$ ft/sec, 95%CI: -0.12,0.12), grip strength ($\beta=0.1$ kg, 95%CI: -1.40,1.60), nor manual dexterity as measured by a timed coin flip test ($\beta=0.32$ s, 95%CI: -0.50, 1.15). Models using quartiles of TCDD exposure were consistently null across all levels of TCDD for the physical function endpoints as well.

On the working memory subtests in 2008, the proportion of women scoring below the age-scaled median on the digit span (7 points) and spatial span (8 points) tests was 44% and 41%, respectively. Adjusting for a priori confounders, a 10-fold increase in TCDD was not associated with performance on the digit span test [$\beta=0.10$ (95%CI -0.09, 0.30)], spatial span test ($\beta=0.01$ (95%CI -0.19, 0.21)), nor their forward and backward components. Further, we did not observe effect modification by menopause status in 2008.

This is the first study of the exclusive effects of TCDD on neuropsychological and physical functioning in women, particularly in the years surrounding menopause. Our findings do not indicate an adverse effect of dioxin exposure on motor function or working memory in adult women in Italy.

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