Original Article

Journal of Wellness and Health Care Vol. 42 (1)
21～28 2018

# The sex-specific effect of dioxin exposure on the growth of children: A Vietnamese cohort study

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**Abstract**

The effects of dioxins on children's growth have been investigated extensively. This follow-up study was conducted in 89 mother–child pairs in Vietnam (43 pairs from a dioxin hotspot and 46 pairs from an unsprayed area) to assess the effects of lactational dioxin exposure on postnatal growth. Maternal breast milk was collected in 2008 from women who had given birth 4 – 16 weeks previously. The children's growth parameters were measured at 3, 5, and 7 years of age. Dioxin levels in breast milk were determined by gas chromatography/high-resolution mass spectrometry. Toxic equivalency values of polychlorinated dibenzodioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and PCDDs + PCDFs in maternal breast milk were 2 – 4 times higher in women residing in the hotspot. Among the children from the dioxin hotspot, lower weight was observed for girls at 3 years of age, reduced body mass index (BMI) and head and chest circumference were observed in girls at 5 years of age, and reduced height and head and chest circumference were observed in girls at 7 years of age. There were no significant differences in body parameters in boys between the dioxin hotspot area and those from the unsprayed area. In girls, maternal breast milk dioxin levels were negatively correlated with BMI and head and chest circumference at 5 years of age, and with height and head circumference at 7 years of age. Multiple regression analysis indicated that BMI at 5 years of age and chest circumference at 5 and 7 years of age showed stronger inverse associations with maternal age than with dioxin exposure. In summary, we found sex-specific effects on postnatal growth in Vietnamese children exposed to dioxin.

**KEY WORDS**

Dioxin, breast milk, mother-child pairs, growth retardation, sex -specific

## Introduction

Dioxin levels are still elevated in the environment, food, and body fluids of humans residing in contaminated areas in Southern Vietnam, nearly five decades after dioxin-contaminated herbicides were sprayed during the Vietnam War[1-4)]. The contaminated areas, such as Bien Hoa, Phu Cat, and Da Nang, are termed dioxin hotspots, and long-term exposure may cause adverse health effects in residents of these areas[5)]. Various epidemiological studies have found that dioxin levels in breast milk were related to steroid hormone disruptions in mothers and children in these hotspots, and may decrease expressive communication scores and increase autistic traits and developmental coordination disorders in infants[6-10)]. High serum dioxin levels have also been related to increases in prostate cancer rates and hormone disruption in men[3, 11)].

Because it is highly lipophilic, dioxin can cross the placental barrier to fetus during pregnancy and be transmitted to infant through breastmilk[12)]. The cumulative dioxin dose of exclusively breastfed infants has been reported to be 3.6 and 4.6 times higher than the dose in formula-fed infants at 6 months and 1 year, respectively, and 10–18 times higher than levels at birth[13)]. Breastfeeding for 6 months can contribute

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12% and 14% to the body burdens of dioxin in men and women, respectively, measured at the age of 25[14]. Thus, breast milk is a high-risk source of dioxin exposure in infants. Moreover, dioxin levels in breast milk are related to their levels in the placenta, maternal serum, and umbilical cord blood, suggesting that dioxin levels in breast milk could be used as a perinatal exposure marker in breastfed infants[15].

Perinatal exposure to dioxin can cause growth retardation in infants and children[16]. Most published epidemiological studies have focused on perinatal exposure and its effects on infancy growth. High dioxin levels in maternal serum, breast milk, or umbilical cord blood have been correlated with reduced birth weight, head circumference, and weight for gestational age, shorter gestational age, and lower growth rate, weight, and body mass index (BMI) in infants[17-21]. Few studies, however, have evaluated the effect of dioxin exposure on older children.

Our previous studies of mother-infant pairs, conducted in a dioxin hotspot (Phu Cat) and a control (non-sprayed) area, found significant differences in the levels of dioxin congeners and hormones in mothers residing in the two areas[9, 22]. Furthermore, a high percentage of low birth weight was observed in the hotspot; birth weight was negatively correlated with toxic equivalency (TEQ) values for 2,3,7,8-tetrachlorodibenzo-p-dioxin and 2,3,4,7,8-pentachlorodibenzofuran[22]. To investigate whether early-life exposure to dioxin continues to affect childhood growth beyond infancy, we followed up with participants from that study and measured children's body parameters at 3, 5, and 7 years.

## Materials and methods

### Study areas

The hotspot area was the Phu Cat district of Binh Dinh province, the site of a US Army airbase in which dioxin-contaminated herbicides were stored and used during the Vietnam War (1965–1971) [5]. The non-sprayed area was the Kim Bang district of Ha Nam province, which was not exposed to dioxin during the war. Both areas are agricultural and have not been contaminated by industrial pollution.

### Study participants and measurements

Women (60 from Phu Cat and 63 from Kim Bang) who were breastfeeding their infants (from 4 to 16 weeks) and had resided in the study areas for more than 5 years were invited to participate in 2008. Each woman donated 10–20 mL of breast milk and was measured for anthropometric indicators (height, weight) and interviewed regarding age, family income, length of residence, occupation, educational level, disease status, smoking habit, or alcohol consumption.

Body parameters in the children (height, weight, and head and chest circumference) were measured by medical staff at the ages of 3, 5, and 7 in 2011, 2013, and 2015, respectively. BMI was calculated from height and weight. The final number of participating mother-child pairs was 89 (43 from Phu Cat and 46 from Kim Bang).

The Medical Ethics Committee of Kanazawa University approved this study (No. 455). The mothers or fathers gave consent for medical examination of the children.

### Analysis of dioxin in breast milk

Polychlorinated dibenzodioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) levels in breast milk were determined by gas chromatography/high-resolution mass spectrometry (JMS-700 MS station mass spectrometer, JEOL Ltd., Tokyo, Japan) in accordance with a previously reported method[23]. Dioxin detection limits were determined at a signal-to-noise ratio of 3 on a lipid. Congener levels below the limit of detection were assigned a value equal to half the limit of detection. The determined values are shown as picograms per gram of lipid and were converted to TEQs using the World Health Organization toxic equivalency factor[24].

### Statistical analysis

Data were analyzed using the JMP 12 software package (SAS Institute, Cary, NC, USA) and Microsoft Excel 2010 (Microsoft Corp., Redmond, WA, USA). The significance level was set at $p \leq 0.05$.

Dioxin levels were $\log_{10}$ transformed to improve normality. Data are shown as mean and standard deviation or median (interquartile range) for original data and as geometric mean with geometric standard deviation for $\log_{10}$-transformed data. The mean difference in each indicator was calculated using Student's *t*-test or the Wilcoxon signed rank test for normal or non-normal distribution, as determined by the Shapiro-Wilk test. Pearson's correlation coefficient and Spearmen's correlation coefficient were also calculated depending on distribution. To determine the influence of confounding

factors, we used multiple regression analysis with body parameters at 3, 5, and 7 years as dependent variables. Maternal age, BMI, and educational level, as well as the length of the breastfeeding period and TEQ-dioxin congener levels in breast milk were selected as independent variables.

## Results

### Demographic characteristics

Table 1 displays the demographic characteristics of the mothers and children, stratified by sex. In girls, TEQ of PCDDs, PCDFs, and PCDDs + PCDFs in the hotspot were more than twice the values in girls residing in the non-sprayed area. In boys, TEQ of PCDDs, PCDFs, and PCDDs + PCDFs in the hotspot were nearly four times higher than the values in boys residing in the non-sprayed area. There was no significant difference in the lengths of breastfeeding periods or maternal age, BMI, educational level, smoking status, or alcohol consumption between the two groups.

### Comparison of growth parameters in children

Table 2 displays the growth parameters measured in children and stratified by sex. Weight at 3 years was significantly lower in girls from the hotspot area. BMI and head and chest circumference differed significantly in girls from the two areas at 5 years, and height and head and chest circumference differed in girls at 7 years. Growth parameters in boys did not differ significantly between the two areas.

Table 1. Demographic characteristic of mothers and children

| Parameters | Girls | | | Boys | | |
|---|---|---|---|---|---|---|
| | Hotspot | Non-sprayed | p-value | Hotspot | Non-sprayed | p-value |
| **Children** | | | | | | |
| Subjects | n = 18 (41.9%) | n = 27 (58.7%) | | n = 25 (58.1%) | n = 19 (41.3%) | |
| Full breastfeeding (months) | 5.5 (4.0-6.0) | 4.0 (3.0-6.0) | 0.417[b] | 6.0 (4.0-6.0) | 6.0 (3.0-6.0) | 0.832[b] |
| **Mothers** | | | | | | |
| Age (years) | 26.6 (4.1) | 25.0 ( 2.8) | 0.160[a] | 27.0 (3.4) | 26.6 ( 2.3) | 0.667[a] |
| BMI | 21.1 (1.9) | 20.9 (2.0) | 0.771[a] | 20.2 (19.0 -21.7) | 20.2 (19.3-22.0) | 0.868[b] |
| Education (%) | | | | | | |
| Elementary (%) | n = 6 (33.3%) | n = 6 (22.2%) | 0.702[c] | n = 6 (24.0%) | n = 3 (15.8%) | 0.660[c] |
| Junior | n = 9 (50.0%) | n = 14 (51.9%) | | n = 9 (36.0%) | n = 10 (52.6%) | |
| High school | n = 3 (16.7 %) | n = 6 (22.2%) | | n = 7 (28.0%) | n = 5 (26.3%) | |
| University | n = 0 (0%) | n = 1 (3.7%) | | n = 3 (12.0%) | n = 1 (5.3%) | |
| Alcohol habit (% no) | n = 16 (88.9%) | n = 27 (100%) | 0.154[d] | n = 24 (96.0%) | n = 19 (100%) | 1.000[d] |
| Smoking habit (% no) | n = 18 (100%) | n = 25 (92.6%) | 1.000[d] | n = 25 (100%) | n = 19 (100%) | |
| TEQ PCDDs (pg/g lipid) | 5.1 (1.3) | 2.0 (1.6) | < 0.001[b] | 7.3 (1.4) | 1.8 (1.4) | < 0.001[a] |
| TEQ PCDFs (pg/g lipid) | 3.2 (1.4) | 1.4 (1.5) | < 0.001[a] | 5.1 (1.4) | 1.3 (1.3) | < 0.001[a] |
| TEQ PCDDs+PCDFs (pg/g lipid) | 8.4 (1.3) | 3.5 (1.5) | < 0.001[a] | 12.5 (1.4) | 3.2 (1.5) | < 0.001[a] |

Data are shown as geometric mean ± geometric standard deviation for TEQ of dioxin levels and mean ± standard deviation or median (interquartile range) for other variables.

[a] t-test, [b]Wilcoxon signed rank's test, [c] Chi-square test, [d] Fisher exact test

Table 2. Comparison of growth parameters in children

| Parameters | Girls | | | Boys | | |
|---|---|---|---|---|---|---|
| | Hotspot (n = 18) | Non-sprayed (n = 27) | p-value | Hotspot (n = 25) | Non-sprayed (n = 19) | p-value |
| **3 years** | | | | | | |
| Height (cm) | 90.0 (3.1) | 90.0 (2.2) | 0.296* | 93.3 (3.4) | 92.1 (2.5) | 0.203* |
| Weight (kg) | 11.9 (1.2) | 12.7 (1.0) | 0.042* | 13.1 (12.0-14.6) | 13.0 (11.5-14.0) | 0.403 |
| BMI | 14.8 (1.5) | 15.4 (1.0) | 0.158* | 15.0 (14.2-15.8) | 14.7 (14.2-15.8) | 0.981 |
| Head Cir. (cm) | 48.0 (1.4) | 48.5 (1.1) | 0.226* | 49.4 (1.6) | 48.8 (1.0) | 0.131* |
| Chest Cir.(cm) | 48.0 (2.0) | 48.8 (1.6) | 0.156* | 50.5 (2.6) | 50.0 (2.0) | 0.445* |
| **5 years** | | | | | | |
| Height (cm) | 104.9 (4.5) | 105.9 (2.4) | 0.379* | 107.3 (4.4) | 107.7 (3.2) | 0.709* |
| Weight (kg) | 15.7 (14.1-16.8) | 16.2 (15.4-17.9) | 0.056 | 16.9 (15.9-21.2) | 17.4 (15.5-18.9) | 0.619 |
| BMI | 14.1 (13.6-14.7) | 14.8 (14.0-15.4) | 0.046 | 15.4 (13.8-18.2) | 14.6 (14.0-16.1) | 0.441 |
| Head Cir. (cm) | 48.7 (48.5-49.7) | 50.0 (40.9-50.9) | 0.002 | 50.6 (1.8) | 50.3 (1.6) | 0.524* |
| Chest Cir.(cm) | 50.3 (49.5 -52.3) | 53.9 (52.0-55.2) | <0.001 | 53.0 (51.0-58.3) | 53.2 (50.2-54.4) | 0.394 |
| **7 years** | | | | | | |
| Height (cm) | 115.3 (4.2) | 118.4 (3.2) | 0.013* | 120.5 (4.9) | 120.6 (4.3) | 0.940* |
| Weight (kg) | 19.2 (17.2-21.5) | 20.2 (19.3-23.7) | 0.082 | 21.5 (19.7-27.6) | 22.2 (19.9-23.7) | 0.943 |
| BMI | 14.1 (13.2-16.5) | 14.8 (14.0-16.0) | 0.336 | 15.3 (13.8-17.7) | 14.6 (13.7-16.6) | 0.896 |
| Head Cir. (cm) | 50.5 (1.4) | 51.4 (1.2) | 0.037* | 51.9 (1.9) | 51.5 (1.5) | 0.345* |
| Chest Cir.(cm) | 55.0 (2.7) | 57.3 (3.8) | 0.002* | 57.3 (54.9-64.3) | 59.3 (56.3-60.8) | 0.320 |

Data are shown as mean (standard deviation) or median (interquartile range). Cir. Circumference

* t-test, others: Wilcoxon sign rank's test

**Correlations of dioxin levels in breast milk and body parameters in children**

Table 3 displays correlation data between TEQ values of dioxin in maternal breast milk and body parameters in children. In girls at 5 years, inverse correlations were found between BMI and head circumference and TEQ of PCDDs (r = − 0.32, $p$ = 0.031 and r = − 0.29, $p$ = 0.050, respectively), and chest circumference and TEQ of PCDDs, PCDFs, and PCDDs + PCDFs (r = − 0.38, $p$ = 0.011; r = − 0.31, $p$ = 0.039; r = − 0.35, $p$ = 0.017, respectively). Similarly, negative correlations were observed between height and TEQ of PCDDs + PCDFs (r = − 0.33, p = 0.027) as well as between chest circumference and TEQ of PCDFs (r = − 0.30, p = 0.042) in girls at 7 years. There was no significant correlation between body parameters and dioxin levels in girls aged 3 years.

In boys, no significant correlations were found between body parameters and dioxin levels, with the exception of height and TEQ of PCDF values at 3 years, chest circumference and TEQ of PCDD at 5 years, and head circumference and TEQ of PCDD at 7 years.

**Multiple regression analysis of dioxin congener levels in breast milk and body parameters in girls**

Table 4 displays data from multiple regression analysis of body parameters in girls as dependent variables and

Table 3. Correlations of dioxin levels in breastmilk and body parameters in children

| Parameters | Girls | | | | | | Boys | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | TEQ PCDDs | | TEQ PCDFs | | TEQ PCDDs+PCDFs | | TEQ PCDDs | | TEQ PCDFs | | TEQ PCDDs+PCDFs | |
| | r | p | r | p | r | p | r | p | r | p | r | p |
| **3 years** | | | | | | | | | | | | |
| Height | -0.06 | 0.714 | -0.17 | 0.278* | -0.12 | 0.450* | 0.30 | 0.051 | 0.30 | 0.046 | 0.280 | 0.069 |
| Weight | -0.27 | 0.077 | -0.12 | 0.449* | -0.20 | 0.196* | 0.23 | 0.131 | 0.19 | 0.220 | 0.210 | 0.181 |
| BMI | -0.29 | 0.053 | -0.01 | 0.964* | -0.13 | 0.391* | 0.13 | 0.412 | 0.05 | 0.759 | 0.100 | 0.504 |
| Head Cir. | -0.06 | 0.682 | 0.05 | 0.721* | -0.01 | 0.959* | 0.29 | 0.057 | 0.20 | 0.201 | 0.240 | 0.113 |
| Chest Cir. | -0.17 | 0.278 | -0.01 | 0.961* | -0.10 | 0.521* | 0.17 | 0.262 | 0.10 | 0.537 | 0.140 | 0.353 |
| **5 years** | | | | | | | | | | | | |
| Height | -0.08 | 0.592 | -0.01 | 0.925* | -0.03 | 0.824* | 0.15 | 0.334 | 0.22 | 0.156 | 0.180 | 0.245 |
| Weight | -0.24 | 0.118 | -0.21 | 0.176 | -0.22 | 0.146 | 0.23 | 0.125 | 0.16 | 0.296 | 0.200 | 0.192 |
| BMI | -0.32 | 0.031 | -0.27 | 0.072 | -0.29 | 0.057 | 0.24 | 0.112 | 0.12 | 0.449 | 0.180 | 0.236 |
| Head Cir. | -0.29 | 0.050 | -0.24 | 0.106 | -0.29 | 0.053 | 0.28 | 0.061 | 0.15 | 0.342 | 0.230 | 0.127 |
| Chest Cir. | -0.38 | 0.011 | -0.31 | 0.039* | -0.35 | 0.017* | 0.30 | 0.046 | 0.22 | 0.151 | 0.260 | 0.086 |
| **7 years** | | | | | | | | | | | | |
| Height | -0.27 | 0.070 | -0.29 | 0.058* | -0.33 | 0.027* | 0.15 | 0.316 | 0.20 | 0.193 | 0.180 | 0.250 |
| Weight | -0.25 | 0.099 | -0.19 | 0.209 | -0.20 | 0.181 | 0.18 | 0.252 | 0.15 | 0.328 | 0.170 | 0.276 |
| BMI | -0.18 | 0.249 | -0.17 | 0.277 | -0.14 | 0.362 | 0.18 | 0.235 | 0.10 | 0.502 | 0.150 | 0.341 |
| Head Cir. | -0.23 | 0.125 | -0.12 | 0.448* | -0.20 | 0.197* | 0.34 | 0.024 | 0.23 | 0.140 | 0.290 | 0.053 |
| Chest Cir. | -0.24 | 0.120 | -0.30 | 0.042 | -0.27 | 0.070 | 0.05 | 0.767 | 0.00 | 0.990 | 0.030 | 0.835 |

p, p-value, r, correlation coefficient, Cir. Circumference

*, Pearson correlation coefficient; others, Spearman correlation coefficient

Table 4. Multiple regression analysis of dioxin congener levels in breastmilk and body parameters in girls

| Parameters | Height | | | Weight | | | BMI | | | Head Cir. | | | Chest Cir. | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | β | p | $R^2$ | β | p | $R^2$ | β | p | $R^2$ | β | p | $R^2$ | β | p | $R^2$ |
| **3 years** | | | | | | | | | | | | | | | |
| Mother Age | -0.03 | 0.869 | 0.06 | -0.36 | 0.027 | 0.22 | -0.39 | 0.020 | 0.19 | -0.44 | 0.006 | 0.26 | -0.48 | 0.003 | 0.20 |
| TEQ PCDDs | -0.08 | 0.619 | | -0.24 | 0.122 | | -0.20 | 0.197 | | -0.03 | 0.831 | | -0.11 | 0.442 | |
| Mother Age | -0.03 | 0.856 | 0.08 | -0.38 | 0.024 | 0.18 | -0.40 | 0.018 | 0.16 | -0.45 | 0.006 | 0.27 | -0.49 | 0.003 | 0.25 |
| TEQ PCDFs | -0.16 | 0.316 | | -0.12 | 0.446 | | -0.01 | 0.953 | | 0.07 | 0.626 | | 0.00 | 0.978 | |
| Mother Age | -0.03 | 0.874 | 0.07 | -0.37 | 0.026 | 0.20 | -0.39 | 0.020 | 0.17 | -0.45 | 0.006 | 0.26 | -0.48 | 0.003 | 0.26 |
| TEQ PCDDs+PCDFs | -0.12 | 0.480 | | -0.19 | 0.218 | | -0.12 | 0.432 | | 0.01 | 0.956 | | -0.06 | 0.681 | |
| **5 years** | | | | | | | | | | | | | | | |
| Mother Age | -0.11 | 0.516 | 0.09 | -0.32 | 0.050 | 0.21 | -0.35 | 0.025 | 0.30 | -0.51 | 0.001 | 0.31 | -0.09 | 0.588 | 0.23 |
| TEQ PCDDs | -0.02 | 0.904 | | -0.27 | 0.084 | | -0.35 | 0.019 | | -0.18 | 0.223 | | -0.33 | 0.036 | |
| Mother Age | -0.11 | 0.509 | 0.09 | -0.34 | 0.044 | 0.16 | -0.37 | 0.023 | 0.23 | -0.52 | 0.001 | 0.30 | -0.10 | 0.514 | 0.20 |
| TEQ PCDFs | 0.01 | 0.968 | | -0.16 | 0.317 | | -0.21 | 0.157 | | -0.14 | 0.333 | | -0.28 | 0.076 | |
| Mother Age | -0.11 | 0.513 | 0.09 | -0.33 | 0.048 | 0.19 | -0.36 | 0.025 | 0.26 | -0.51 | 0.001 | 0.31 | -0.09 | 0.567 | 0.22 |
| TEQ PCDDs+PCDFs | -0.01 | 0.941 | | -0.23 | 0.148 | | -0.30 | 0.049 | | -0.17 | 0.247 | | -0.32 | 0.039 | |
| **7 years** | | | | | | | | | | | | | | | |
| Mother Age | -0.09 | 0.581 | 0.14 | -0.28 | 0.092 | 0.20 | -0.26 | 0.132 | 0.12 | -0.53 | 0.001 | 0.36 | -0.42 | 0.007 | 0.31 |
| TEQ PCDDs | -0.32 | 0.053 | | -0.31 | 0.049 | | -0.18 | 0.274 | | -0.23 | 0.101 | | -0.30 | 0.040 | |
| Mother Age | -0.11 | 0.513 | 0.12 | -0.30 | 0.082 | 0.12 | -0.27 | 0.116 | 0.10 | -0.55 | 0.001 | 0.32 | -0.44 | 0.006 | 0.30 |
| TEQ PCDFs | -0.27 | 0.092 | | -0.11 | 0.492 | | 0.03 | 0.829 | | -0.10 | 0.478 | | -0.27 | 0.064 | |
| Mother Age | -0.10 | 0.561 | 0.14 | -0.28 | 0.089 | 0.16 | -0.27 | 0.124 | 0.10 | -0.54 | 0.001 | 0.35 | -0.42 | 0.007 | 0.30 |
| TEQ PCDDs+PCDFs | -0.31 | 0.056 | | -0.23 | 0.156 | | -0.08 | 0.619 | | -0.18 | 0.190 | | -0.29 | 0.049 | |

β, standardized coefficient; p, p-value; $r^2$, coefficient of determination, Cir. Circumference

Dependent variables are height, weight, BMI, head and chest circumference at 3, 5 and 7 years old.

Independent variables are mother age, mother BMI, education, full breastfeeding period and TEQ of dioxin.

adjusted maternal dioxin levels as independent variables. Negative associations were observed between maternal age and children's weight and BMI at 3 and 5 years, as well as between head and chest circumference at all ages surveyed, except for chest circumference at 5 years. Furthermore, TEQ of PCDD and PCDDs + PCDFs in breast milk were inversely associated with BMI at 5 years ( $\beta = -0.35$, $p = 0.019$ and $\beta = -0.30$, $p = 0.049$, respectively) and chest circumference at 5 ( $\beta = -0.33$, $p = 0.036$ and $\beta = -0.32$, $p = 0.039$, respectively) and 7 years ( $\beta = -0.30$, $p = 0.040$ and $\beta = -0.29$, $p = 0.049$, respectively). No significant association was found between body parameters and other independent variables, such as maternal BMI, maternal educational level, or length of breastfeeding period (data not shown).

## Discussion

The findings of this study suggest that lactational exposure to PCDDs and PCDFs results in sex-specific postnatal growth effects. Differences in body parameters between children from the hotspot area and the non-sprayed area and correlations of these parameters with dioxin levels in maternal breast milk were found only in girls. In particular, a lower BMI at 5 years and chest circumference at 7 years were negatively correlated with breast milk levels of PCDDs and PCDDs + PCDFs, although no significant correlations between body parameters and breast milk dioxin levels were observed in children aged 3 years.

These results are partially consistent with those of epidemiological studies of the effects of perinatal exposure to dioxin or dioxin-like compounds on children's growth that found differences only in girls. Maternal polychlorinated biphenyl (PCB) levels have been correlated with reduced growth in Japanese girls whose mothers consumed contaminated oil and reduced weight in girls in an American cohort[25, 26]. One European study reported an association between maternal PCB levels and height and weight of children[27]. Lamb et al. reported that maternal levels of mono-ortho-substituted PCBs and ortho-substituted PCBs were associated with reduced weight in girls through 17 years of age[28]. In a cohort of German children, exposure to background levels of dichlorodiphenyldichloroethylene (DDE) was reported to correlate with an overall height reduction of 1.8 cm in girls, although the differences disappeared after the age of eight[29]. In contrast with our findings, other studies reported a statistically significant BMI increase in 7-year-old girls perinatally exposed to dioxin and dioxin-like compounds[27]. Caucasian girls with high transplacental PCB exposures in an American cohort were reported to be 5.4 kg heavier for their height than other girls included in the analysis[30]. Prenatal DDE exposure was positively associated with waist circumference and the waist/height ratio in Belgian girls aged 7–9 years[31].

Other studies have reported the effects of dioxin exposure on growth in 4-month-old Vietnamese boys (weight and BMI), in 8–12-year-old Russian boys (BMI and height), and in 4-year-old American children of both sexes (weight)[18, 32, 33]. Some animal studies reported that maternal PCB exposure resulted in growth retardation in offspring in guinea pigs and rats [34, 35].

In the present study, girls appeared to be more sensitive to the effects of PCCDs and PCDFs. One potential reason is a reduction in thyroid hormones, responsible for regulating growth. A number of studies in humans have found that exposure to dioxin and PCBs was negatively correlated with levels of triiodothyronine and thyroxine in infants or with thyroid-stimulating hormone in females[36-38]. In juvenile fish, one PCB congener was shown to inhibit levels of triiodothyronine and thyroxine, leading to reduced total body weight and length and retarded metamorphic progress[39]. As mentioned above, our results have been consistent with some animal experiment and human studies about the effect of dioxin on growth in female [25-29, 34, 35]. However, the main reason for the sex-specific differences in effects is still unclear and we need more evidence in the further researches in the future.

The limitations of the study should be noted. First, PCB congener levels in maternal breast milk were not estimated, precluding analysis of perinatal PCB exposure and developmental delays in the study cohort. Second, the sample was small, and a larger sample may assist in elucidating the effects of dioxin on children's growth. Third, the study lacks data on postnatal exposure after breastfeeding. Dioxin exposure from contaminated sources could be contributed to the growth retardation of children in this study.

To our knowledge, this is the first longitudinal/cohort study to investigate the effects of lactational dioxin exposure on postnatal growth in Vietnamese children

living in a dioxin hotspot area. We found a negative association between TEQ of PCDDs and PCDFs and BMI at 5 years and head circumference at 7 years in girls. No significant effects were found in boys. Periodic follow-up is necessary for assessing growth retardation in children exposed to persistent organic pollutants.

## Acknowledgment

We would like to thank the participants as well as the organizations that supported the performance of this study, including 10-80 Division, Hanoi Medical University, and Kim Bang and Phu Cat medical centers in Vietnam. The authors declare that they have no conflict of interest.

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# ダイオキシン暴露の子供の成長に関する性特異的な影響：ベトナムでのコホート研究

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## 要　　旨

ダイオキシン類は残留性有機汚染物質であり、子供の成長に影響することが報告されている。本追跡研究は授乳中のダイオキシン暴露が生後の子どもの発達に影響するかを明らかにするため、ベトナムの枯葉剤撒布地区（Phu Cat）と非撒布地区（Kim Bang）で実施された。母乳は 2008 年に生後 4-16 週の児を持つ母親より収集した。その子供の身体計測が 3 才、5 才、7 才の時に実施された。本研究では、すべての調査に参加した 89 組の母子（Phu Cat 43 組、Kim Bang 46 組）を対象とした。母乳中のダイオキシンの測定には GC-HRMS を用いた。母乳中の polychlorinated dibenzo-dioxins (PCDDs)、-furans (PCDFs) と PCDDs/Fs の毒性当量は男女とも枯葉剤撒布地区の方が非撒布地区より 2- 4 倍有意に高かった。3 才児の体重、5 才児の BMI、頭囲と胸囲、7 才児の身長、頭囲と胸囲は女児でのみ枯葉剤撒布地区の方が非撒布地区より有意に小さかった。男児では両地区間で身体計測値に有意差は無かった。ダイオキシンと 5 才児の BMI、頭囲と胸囲の間に、さらに 7 才児の頭囲と胸囲との間に有意な負の相関が女児にのみ見られた。重回帰分析では 5 才児の BMI と胸囲、7 才児の胸囲はダイオキシンよりも母親の年齢と強い負の相関を示した。結論として、ダイオキシンはベトナムの子供の生後の発達遅延に、性により異なる影響を与えていることが判明した。