The Association between Blood Concentrations of PCDD/DFs, DL-PCBs and Risk of Type 2 Diabetes Mellitus and Thyroid Cancer

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Research

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Abstract

Background and Objectives: Dioxin, classified as a human carcinogen by International Cancer Research Institute, shows inconsistent results on type 2 diabetes mellitus (T2DM) and cancer in epidemiological studies. International Cancer Research Institute classifies dioxin as a human carcinogen, but epidemiological studies of its effects on type 2 diabetes mellitus (T2DM) and cancer show inconsistent results. Therefore, we conducted a Korean population study to ascertain if the blood concentration of dioxin-like polychlorinated biphenyls (DL-PCBs) and polychlorinated dibenzo-p-dioxins and dibenzofurans (PCDD/DFs) is associated with T2DM and thyroid cancer.

Methods: Within a nested case-control study, we identified 15 people diagnosed with thyroid cancer, 30 people diagnosed with T2DM, and 55 for control. Due to the 4ml human blood requirement for PCDD/DF and DL-PCB concentrations tests, a total of 500 samples were used in 100 pooling samples. The continuous variable of a pooled sample was calculated as an average value taking into account the blood weight of each sample. The odds ratios (ORs) and 95% confidence interval (95% CI) for determining the association between total dioxins and risk of T2DM and thyroid cancer were estimated using the multivariable logistic regression.

Results: The study population included 100 participants from the KCPS-II (median [IQR] baseline age, 54.06 [21.04] years; 48 women). The toxic equivalents of PCDD/DFs showed a significant positive association with T2DM and thyroid cancer, after adjustments for potential confounders (T2DM ORs = 1.23; 95% CI = 1.05-1.43; Thyroid cancer ORs = 1.34; 95% CI = 1.12-1.61). These results showed a stronger association in women than in men.

Conclusion: In this study, both T2DM and thyroid cancer appear to be associated with the levels of PCDD/DFs serum. The association between T2DM and levels of PCDD/DFs serum is found in women and not in men. Our findings suggest that further biochemical in vivo research and epidemiologic studies are needed to clarify the nature of the association between dioxins concentrations and diseases.

Introduction

Dioxins are a chemical compound consisting of 75 polychlorinated dibenzo-p-dioxin (PCDD) and 135 polychlorinated dibenzofurans (PCDFs) that occur most frequently during waste incineration processes and automobile emissions and cigarette smoke [1–4]. Polychlorinated dibenzo-p-dioxins, dibenzofurans (PCDD/DFs), and dioxin-like polychlorinated biphenyls (DL-PCBs) are persistent environmental pollutants (POPs), which are the compounds that accumulate in the environment and human body [5, 6].

Dioxins are a new candidate for the risk factors of type 2 diabetes mellitus (T2DM). An epidemiological investigation of a group exposed to a relatively high concentration of dioxins due to an accident or occupation shows a significant relationship between the blood dioxins concentration and the onset of T2DM or death from T2DM [7–14]. However, the relationship between dioxins concentration in blood and T2DM identified in groups exposed to relatively high concentrations of dioxins due to accidents or occupations is not completely consistent [10, 13]. In addition, studies on the association between dioxins and diabetes use estimate made using half-life in the dioxins body, so there is a problem with the accuracy of the exposure assessment, calling for caution when interpreting the results. Thus, in recent years, there have been studies on the association between low dioxins concentration, PCBs exposure, and T2DM in general environments, but due to the ethic of the Asian group, this is very rare [15, 16].

In 1997, the International Agency for Research on Cancer classified TCDD as a human carcinogen (IARC, 1997). Among PCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) is the most toxic to Ah-R, and molecular studies have shown that TCDD is a strong carcinogen that can disrupt various endocrine pathways in animals and humans [6, 17]. However, the relationship between TCDD and cancer incidence or mortality tested by epidemiology studies was inconsistent [8–10, 12, 18–30]. Evidence of how it affects humans have long been controversial [31]. A meta-analysis of epidemiological studies on carcinogenicity was published in 2016, and both external exposure and blood level of TCDD were significantly associated with all cancer mortality, but no studies confirming the relationship with thyroid cancer were included in this study [32]. Most of the dioxins studies are animal-based experiments. The reason epidemiological studies that confirm the occurrence of human diseases are rare that about 4ml of whole blood is needed to measure dioxins in human blood [33]. In addition, it takes a long time to study cohort considering the context of dioxins exposure and disease development. Therefore, we pooled the amount of blood needed for dioxin analysis using the pooling method in large-scale cohort data and investigated whether the blood concentration of DL-PCB and PCDD/DF is associated with T2DM and thyroid cancer in the Korean population.

Methods

Study population

This study was designed as a nested case-control study of 500 Koreans (men: 263, women: 237) selected from the Korean cancer prevention study-II (KCPS-II) (Supplementary Fig. 1). KCPS-II included 156,704 adults aged 20 to 84 who visited 18 health promotion centers nationwide from April 2004 to December 2013. A detailed description of the KCPS-II study design was published elsewhere [34].

In this study, the baseline period for the collected blood samples of participants was determined from January 2004 to December 2004. Due to the 4ml human blood requirement for dioxins tests [35], a blood sample was produced by combining 0.3 ml to 1.0 ml of the individual serum sample of five to nine participants. The subjects with disease samples were pooled with considerations for sex and age, and the control group sample was pooled with consideration of the sex, age and body mass index (BMI) of the disease group. A total of 500 samples were used in 100 pooling samples consisting of 30 cases of T2DM, 15 cases of thyroid cancer, and 55 for the control group.

Measurements

Sample Collection

After 12 hours of fasting, serum and whole blood were collected from each participant and put into storage at -70ºC for future study. These samples were used for PCDD/DFs, DL-DCBs measurements, as well as other clinical chemistry parameters, such as fasting blood glucose, total cholesterol, triglyceride, HDL-C, and LDL-C.

In compliance with the protocols of the Korean Organization of Laboratory Quality Management, the quality control of the clinical chemistry laboratory was maintained.

Analysis of dioxins

The analysis and quality control of 2,3,7,8-substituted PCDD/DFs and DL-PCBs in the pooled serum samples were performed with a slight modification of the Center for Disease Control and Prevention [36]. Before solid phase extraction, pooled serum samples were spiked 13C-labeled 2,3,7,8-substituted PCDD/DFs and DL-PCBs and were

made to homogenization. Series of 20 samples were processed on manifolds. Formic acid and pure water were added to samples prior to extraction. SPE-C18 cartridges (octadecyl, 2g) were pre-conditioned using methanol and water. Each cartridge was dried and eluted with 15 mL of hexane, followed by the eluate was concentrated to 1mL. The eluate was applied to a multilayer silica gel column (44% sulfuric acid and 10% $AgNo_3$ silica gel) then eluted with 20mL of hexane. The final evaporation using a nitrogen concentrator (Eyela MGS 3100) was performed after addition of nonane as keeper. Quantification and identification of 2,3,7,8-substituted PCDD/DFs congeners and DL-PCBs were performed by high resolution gas chromatography (HRGC) (Thermo scientific Trace 1310)/high resolution mass spectrometry (HRMS) (Thermo Scientific DFS). The HRMS was operated in the electron impact mode and in the selected ion monitoring mode at a resolution R > 10,000 (10% valley). Separation was achieved using a HRGC instrument equipped with a DB-5MS (Agilent Technologies; 60 m length, 0.32 mm i.d., 0.25 μm film thickness) capillary column with a splitless and solvent-cut mode. The column ovens for DB5-MS was programmed from an initial temperature of 160°C to a final temperature of 310°C (total running time 60 min). Before quantitative analysis, 13C-labeled 1,2,3,4-TeCDD, 1,2,3,7,8,9-HxCDD, 3,3',4,5'-TetraCB, 2,3,3',5,5'-pentaCB and 2,3,3',4,5,5'-hexaCB as internal standards were added for the estimation of recovery. Mean recovery of the spiked 13C-labeled 2,3,7,8-substituted PCDD/DFs and DL-PCBs in the entire analytical procedures were 75 ± 11% and 80 ± 25%, respectively. The levels were expressed in 2,3,7,8-TeCDD toxic equivalents using calculations of World Health Organization Toxic Equivalent Factors (WHO-TEFs) for PCDD/DFs and DL-PCBs.

The definition of outcome (Diagnosis of thyroid cancer and T2DM)

The incidence of thyroid cancer was collected from the registry of the National Cancer Center (NCC). And thyroid cancer code C73 of the 10th Amendment to the International Classification of Diseases (ICD-10) (WHO 2010) was used. The incidence of T2DM was identified from the National Health Insurance System (NHIS).

Statistical analysis

As POPs are mainly carried in the lipid portion of the blood, epidemiological studies have used lipid-adjusted concentrations (ng/g lipid) [37]. Concentrations adjusted for lipids (ng/g lipids) were determined using the formula proposed by Bernert et al (2007) [38].

The continuous variable of a pooled sample of 500 samples was calculated as an average value taking into account the blood weight of the configured sample. The average value considering the blood mass of the sample calculated by the PROC SURVEYSMEANS statement in SAS 9.4 was measured using the equation below:

$$\mathrm{Averagevalueconsideringtheweightofbloodvolume} = \sum (bloodvolume \times value) \,/\, \sum (bloodvolume)$$

We reported continuous variables as medians (± interquartile range; IQR) and categorical variables as proportions. We conducted the Kruskal-Wallis test to analyze between-group differences, as appropriate. Multiple logistic regression analyses were conducted to display the association between PCDD/DFs, DL-PCBs concentrations and thyroid cancer and T2DM. Additional sensitivity analyses were performed with the use of multivariable logistic regression adjusted for predefined baseline covariates. P values < 0.05 in the two-tailed test were considered significant. Statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute) and R software, version 4.1.2 (R Foundation for Statistical Computing).

Results

Study population and PCDD/DFs, DL-PCBs, and total dioxins in blood

The characteristics of the study population are shown in Table 1. Regarding the number of subjects according to disease group, the numbers for the non-disease group, T2DM, and thyroid cancer were 55, 30, and 15, respectively. Due to the study design, the participants were distributed almost equally according to sex, age, and BMI. The proportion of men and women were 48% and 52%, respectively, and the median value of age was 54.06 years (IQR = 21.04), and a median value of BMI was 24.28 kg/m^2 (IQR = 2.15).

Table 1
Baseline characteristics of 500 who constructed 100 blood samples in the KCPS-II

Characteristic	Overall	Control (n = 55)	Type 2 Diabetes (n = 30)	Thyroid Cancer (n = 15)	P-value
Sex	**N (%)**				0.795
Male	48 (48.00)	27 (49.09)	15 (50.00)	6 (40.00)	
Female	52 (52.00)	28 (50.91)	15 (50.00)	9 (60.00)	
	Median (IQR)				
Age, years	54.06 (21.04)	54.25 (20.57)	54.04 (22.14)	52.60 (19.20)	0.813
BMI, kg/m^2	24.28 (2.15)	24.31 (1.94)	24.36 (2.21)	24.20 (1.83)	0.619
FBS, mg/dl	92.88 (14.23)	89.42 (6.73)	135.73 (40.13)	92.88 (7.59)	< 0.001
HDL-C, mg/dl	52.89 (9.57)	55.20 (12.23)	51.56 (6.70)	50.00 (5.23)	0.004
LDL-C, mg/dl	117.32 (26.32)	112.35 (27.29)	121.61 (22.17)	115.51 (18.99)	0.046
SBP, mmHg	123.71 (14.35)	121.81 (10.95)	129.50 (12.44)	116.25 (16.32)	0.005
TG, mg/dl	135.95 (66.38)	131.56 (61.10)	163.28 (67.74)	125.05 (45.32)	0.009
TSH, uIU/mL	1.66 (0.83)	1.66 (0.82)	1.64 (0.79)	1.69 (0.92)	0.659
IQR, interquartile range; BMI, body mass index; SBP, systolic blood pressure; FBS, fasting blood sugar; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; TG, triglyceride; TSH, thyroid stimulation hormone					
*p values from Kruskal-Wallis test and all variables are calculated by weighted blood volume					

Figure 1 presents the blood TEQ concentration of PCDD/DFs, DL-PCBs, and total dioxins. For the TEQ of DL_PCBs, the difference in exposure levels between groups was not statistically significant (P-value < 0.34). The median of the PCDD/DFs and total dioxins material was highest in the thyroid cancer group, and the difference in exposure levels between groups is statistically significant (both P-value < 0.01).

Association between dioxins in blood and T2DM

The multiple-adjusted associations between blood levels of dioxins and T2DM are presented in Fig. 2. The PCDD/DFs TEQ and total dioxins, but not of DL-PCBs, showed significant associations with T2DM. The age and

sex-adjusted ORs of T2DM and total dioxins were 1.14 (95% CI = 1.03–1.25). Stratifying analyses by sex showed positive orientation but were not statistically significant in men (men ORs = 1.20; 95% CI = 0.99–1.45, women ORs = 1.15; 95% CI = 1.01–1.31) However, since the results are not considered significant at the boundary of the 95% confidence interval, increasing the sample size can be statistically significant.

To assess the possibility of confounding by BMI or systolic blood pressure or high-density lipoprotein, an analysis for T2DM was performed by additionally adjusting for the effects of these variables. In the adjusted models that include these variables (Model 2), the odds ratio for total dioxins was 1.20 (95% CI = 1.06–1.36). The results of Model 2 also showed statistically significant results only in the women group (men ORs = 1.16; 95% CI = 0.93–1.43, women ORs = 1.21; 95% CI = 1.02–1.45). Specifically, a 1-SD increase in 2378-TCDF level, is associated with a 71% increased risk of T2DM (ORs = 1.71; 95% CI = 1.0-2.91) (Supplementary Table 2).

Association between dioxins in blood and thyroid cancer

The multiple-adjusted associations between blood levels of dioxins and thyroid cancer are presented in Fig. 3. TEQ of PCDD/DFs and total dioxins, but not of DL-PCBs, showed significant associations with thyroid cancer. The age, sex-adjusted ORs of thyroid cancer of total dioxins were 1.25 (95% CI = 1.10–1.42). Both men and women subgroup analyses showed positive orientation (men ORs = 1.31; 95% CI = 1.02–1.67), women ORs = 1.24; 95% CI = 1.04–1.48). To assess the possibility of confounding by TSH serum levels or body mass index, an analysis for thyroid cancer was performed by additionally adjusting for the effects of these variables. In the adjusted models, which include body mass index (Model 2) or TSH serum levels (Model 3), the odds ratio for total dioxins was 1.28 for both models (both models 95% CI = 1.10–1.48). The DL-PCB TEQ did not show a significant association with thyroid cancer. However, the 1-SD increase at 4CB-77 levels was associated with an increase in risk of thyroid cancer (OR = 1.92; 95% CI = 1.02–3.64) (Supplement Table 3).

Discussion

This study measured DL_PCB and PCDD/DF using pooled serum from general population. PCDD/DFs in blood showed a significant positive association with T2DM and thyroid cancer development, but no significant association with DL_PCB was observed.

In 2016, International Agency for Research on Cancer (IARC) upgraded the classification of the PCBs to Category 1 carcinogenic to humans from the previous Category 2A classification on the basis of sufficient evidence of carcinogenicity in humans and animals [39, 40]. However, no evidence of a relationship between PCB exposure and the risk of malignant melanoma has been identified in the latest meta-analysis [41], and reviews of epidemiological studies on PCB exposure and cancer risk were inconsistent for other cancers [42]. Our result that DL_PCBs are not associated with cancer is similar to that of recently reported studies [41, 42].

Although previous studies have found an association between PCB levels and T2DM in women, our results are inconsistent with reports from other studies suggesting that PCBs are positively associated with T2DM in women. [43, 44]. However, the PCBs used in previously reported studies are a combination of DL-PCBs and non-dioxin-PCBs. In this study, however, there was included only DL-PCBs.

To the best of our knowledge, no case-control studies have yet been conducted to establish an association between dioxins and thyroid cancer. However, recent in vitro studies using immortal mouse cells have shown that TCDD exposure regulates the script of an endothelial carcinogen network thought to affect thyroid carcinoma [45]. TCDD can interfere with the activity and metabolism of thyroid hormones through various processes, including binding to protein transport of thyroid hormone [46], direct damage to the thyroid gland, and activation of thyroid metabolizing enzymes [47]. Previous reported epidemiological studies have found significantly increasing trends in mean TSH with TCDD category [48]. Having a high TSH level within the normal range is an independent risk factor for DTC, and may contribute to the initiation of thyroid carcinogenesis [49, 50]. These mechanisms can support the association between blood PCDD/DFs and thyroid cancer risks identified in our study.

Dioxins have been identified as endocrine disruptors of the environment, but epidemiology studies of their effect on diabetes found inconsistent results [7, 11, 18, 51]. In particular, this association is found in women and not in men [12, 44], which is similar to the results confirmed in our study. Several assumptions can explain this gender difference. First, men have lower levels of exposure and a higher prevalence of smoking, which stimulates the aryl hydrocarbon receptor related to the increased excretion of PCBs [52]. Second, women have a higher proportion of fat, resulting in these lipophilic compounds being stored longer. Third, women have higher estrogen levels and PCDFs. Certain PCBs can cause gene expression of CYP1A1 and CYP1B1 [53, 54], which catalyze estradiol A-ring hydroxylation to from 4-hydroxyl estradiol of catechol estrogen that can produce free radicals. It is understood that free radicals induce elevated oxidative stress related to diabetes [54].

Despite the fact that the results are similar to those of previous studies, there are some limitations in our study. First, we were unable to control the confounding variables such as exercise habits, food consumption, alcohol status, smoking status, and socioeconomic status. In this study, several blood samples were used to make pooled samples. In the case of a continuous variable, the mean value of the characters constituting the sample was used. And categorical variables were not included in this study. However, we used BMI, which is strongly associated with physical activity patterns, waist circumference, and dietary consumption, and may thus be considered a proxy indicator for such variables. Second, as an exposure measure, we used a 1-time dioxins level measurement in the blood and did not have accumulated exposure dose information. However, we had the strength of measuring PCDD/DFs and DL-PCB concentrations directly within the Korean population to collect exposure data. Also, since the half-life of PCDD/Fs in the serum can last for seven years or longer [51, 55] and over that duration, the causes of environmental exposure remained constant, we could conclude that the dioxins level in a given participant has remained similar over the years. This study also has strengths. This analysis is the first study between blood concentration of dioxin and health outcomes in general populations with low dose exposure. Thus, it has been evaluated for the health impact of dioxin on the general population. And the analysis showed the possibility of studying dioxins that needs a large amount of blood for detection using a pooled sample. Furthermore, this research will serve as a base for future studies, which identifies dioxin's health impact mechanism.

Conclusion

To our knowledge, this is the first study that shows the association between PCDD/DFs, DL-PCBs serum levels, and T2DM and thyroid cancer risk in the Korean population. In this study, both T2DM and thyroid cancer appear to have an association with PCDD/DFs serum levels. Our findings suggest that further biochemical in vivo research and epidemiologic studies are needed to clarify the nature of the association between dioxins concentration and diseases.

Declarations

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Conflicts of interest/Competing interests: The authors have no conflicts of interest to declare that are relevant to the content of this article.

Availability of data and material: Due to the nature of this research, participants of this study did not agree for their data to be shared publicly, so supporting data is not available.

Code availability: Statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute) and R software, version 4.1.2 (R Foundation for Statistical Computing).

Authors' contributions: All authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by Su Hyun Lee, Joyce Mary Kim, Young Wook Lim, Youn Seok Kang, and Sun Ha Jee. The first draft of the manuscript was written by Keum Ji Jung and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval: The study was approved by the Severance Medical Ethics Committee of A (No. 4-2019-0351).

Consent to participate: Informed consent was obtained from all individual participants included in the study.

Consent for publication: The participant has consented to the submission of the case report to the journal.

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Figures

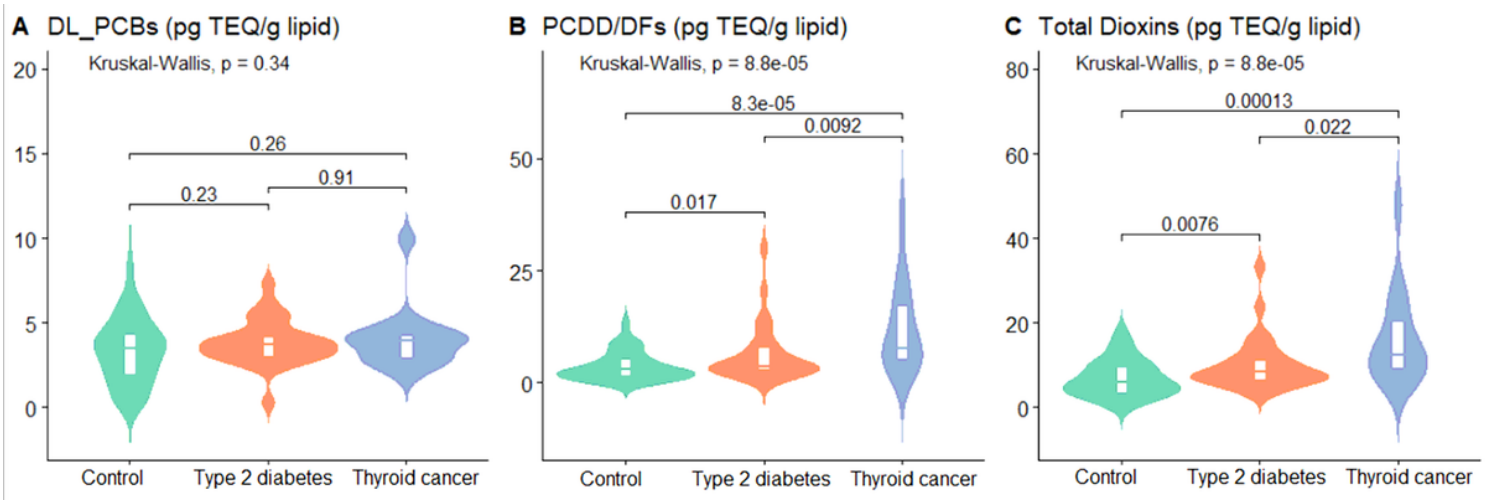

Figure 1

Serum concentrations for PCDD/DFs, DL-PCBs of the study group Violin plots show differences in blood of concentrations for DL_PCBs (A), PCDD/DFs (B), Total Dioxins (C) at the controls group (n=55), type 2 diabetes (n=30), or thyroid cancer (n=15). The line in the white box represents the median. The width of the shape represents blood concentration density, and the length illustrates the range of the blood concentration.

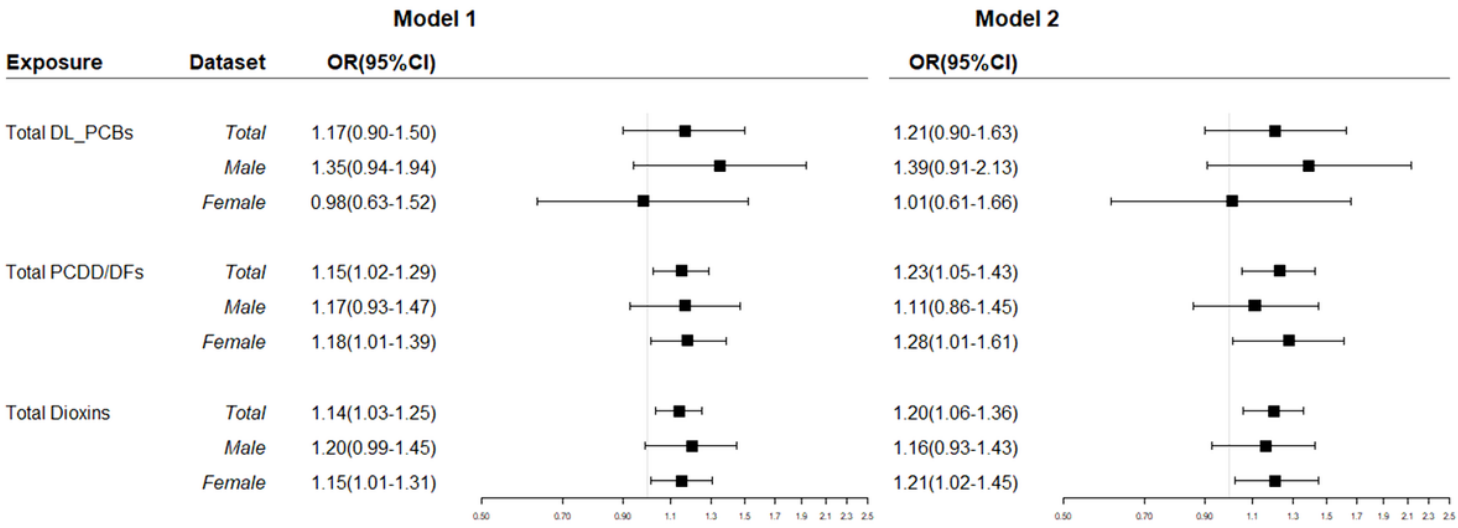

Figure 2

Odds Ratios of blood concentrations of PCDD/DFs, DL-PCBs (pgTEQ/g_lipid) and Type 2 Diabetes mellitus OR, Odds ratio; CI, confidence interval *Model 1: Adjusted for age and sex *Model 2: Adjusted for the model 1 variables, body mass index, systolic blood pressure and high-density lipoprotein

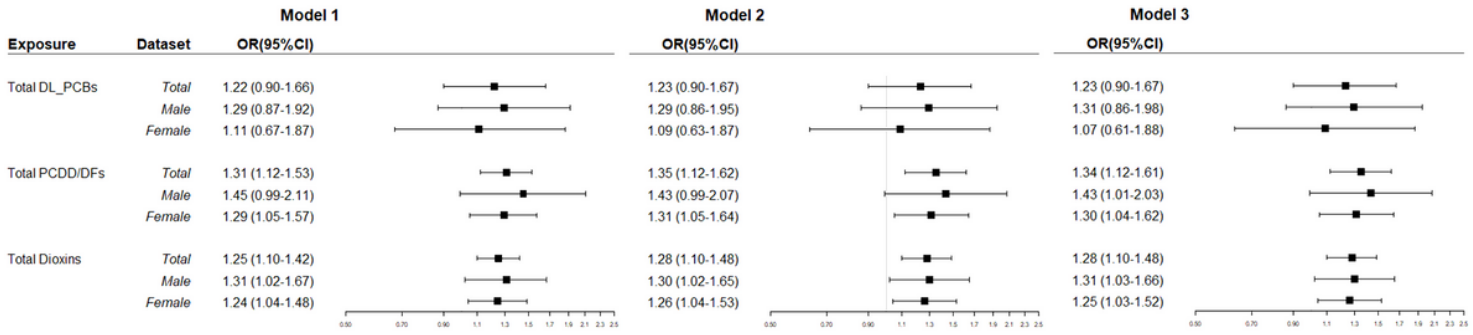

Figure 3

Odds Ratios of blood concentrations of PCDD/DFs, DL-PCBs (pgTEQ/g_lipid) and Thyroid Cancer OR, Odds ratio; CI, confidence interval *Model 1: Adjusted for age and sex *Model 2: Adjusted for the model 1 variables and body mass index *Model 3: Adjusted for the model 2 variables and thyroid stimulating hormone

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- 4SupplementaryMaterialDioxinandT2DMThyroidcancer.docx