Environmental Health

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Association of polychlorinated biphenyls with vitamin D among rural Chinese adults with normal glycaemia and type 2 diabetes mellitus

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Abstract

Background Endocrine function in patients with type 2 diabetes (T2DM) typically differs from those with normal glucose tolerance (NGT). However, few epidemiologic studies have explored how these differences impact the association between exposure to polychlorinated biphenyls (PCBs) and vitamin D levels.

Methods This study included 1,705 subjects aged 18–79 years from the Henan Rural Cohort [887 NGT and 818 T2DM]. Linear regression was applied to evaluate the associations between PCB exposure and vitamin D levels. Quantile g-computation regression (QG) and Bayesian kernel machine regression (BKMR) were applied to evaluate the impact of PCB mixtures on vitamin D levels. Interaction effects of ΣPCBs with HOMA2-%β and HOMA2-IR on vitamin D levels were assessed.

Results Plasma ΣPCBs was positively associated with 25(OH)D2 in the NGT group (β = 0.060, 95% CI: 0.028, 0.092). Conversely, in T2DM group, ΣPCBs was negatively associated with 25(OH)D3 and 25(OH)D (β = -0.049, 95% CI: -0.072, -0.026; β = -0.043, 95% CI: -0.063, -0.023). Similarly, both QG and BKMR analysis revealed a negative association between PCB mixture exposure and vitamin D levels in the T2DM group, contrary to the results observed in the NGT groups. Furthermore, the negative association of ΣPCBs with 25(OH)D2 and 25(OH)D disappeared or changed to a positive association with the increase of HOMA2-%β levels.

Conclusions These findings suggest that decreased β cell function may exacerbate the negative effects of PCB exposure on vitamin D levels. Recognizing T2DM patients' sensitivity to PCBs is vital for protecting chronic disease health.

Keywords Polychlorinated biphenyls, Vitamin D, Type 2 diabetes mellitus, Interactive effects

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Introduction

Polychlorinated biphenyls (PCBs), known for their low electrical conductivity and excellent flame-retardant properties, are an organochlorine pollutant of global concern. In industrial production, PCBs are often utilized as insulating compound [1], cement gypsum [2], and plasticizers [3], etc. PCBs are difficult to completely degrade and are slowly and continuously released to the environment from various PCB-containing products [4], present in soil, sediments, air, and water [5, 6], and accumulate in biological and human tissues due to their high lipophilicity [7]. Exposure to PCBs induces drug-metabolizing enzyme activity, exacerbates oxidative stress and inflammatory responses, thereby contributing to the development of chronic inflammatory diseases [8, 9]. In addition, PCBs, as disruptors of environmental endocrine functions, interfere with the endocrine mechanism of humans [10, 11], leading to disruptions in vitamin D metabolism [12].

As we all know, vitamin D, existing as ergocalciferol (25(OH)D2) and cholecalciferol (25(OH)D3) [13], is primarily assessed through 25-hydroxyvitamin D (25(OH)D) levels in clinical assessment. Research indicates its crucial role in preventing various health issues, including specific forms of cancer [14], cardiovascular disease [15], several autoimmune diseases [16], and diabetes [17]. However, hypovitaminosis D is emerging as prevalent in China [18], especially in the adult population, with a deficiency rate of 63.2% [19].

Previous research indicates that PCB exposure can affect levels of vitamin D, although the findings have been inconsistent. For instance, an animal experiment observed a decrease in vitamin D levels in rats exposed to PCB mixtures, with the reduction being dependent on the dosage [20]. Similarly, a Spanish study of pregnant women indicated that exposure to PCBs could potentially lead to a decline in 25(OH)D3 levels [21]. Conversely, another study found positive associations between ΣPCBs, PCB153, PCB180, and 25(OH)D3 in non-obese women; however, these associations lost statistical significance after adjusting for body mass index (BMI) [22]. Of note, endocrine dysfunctions can influence the metabolism, absorption, and excretion of vitamin D [23, 24]. In patients with type 2 diabetes (T2DM), the endocrine system's function often significantly differs due to the disease's impact [25], making it crucial to investigate the association between PCB exposure and vitamin D levels among normal glucose tolerance (NGT) and T2DM populations, as well as the interaction of relevant potential factors. Moreover, studies have also shown that PCB exposure is associated with chronic inflammatory diseases (such as T2DM), where impaired function of pancreatic beta cells triggers an inflammatory response in the body, which in turn affects vitamin D levels [26]. Therefore, this study further explores the interaction of plasma PCBs with HOMA2-%β and HOMA2-IR on vitamin D levels.

Methods

Study design and participants

For this case-control study, 925 T2DM patients aged 18–79 were chosen via simple random sampling from the Henan Rural Cohort study between 2015 and 2017. Matching for gender and age (±3 years) was done for the NGT groups. Finally, 1,705 participants were included (145 participants were excluded owing to missing data). The details are depicted in Supplementary Fig. 1. All of the subjects were signed the informed consent before recruitment.

Date collection and determinations

The face-to-face questionnaire-based approach collected demographic data (e.g., age, gender, marital status, education, average monthly income) and lifestyle data (e.g., smoking and drinking status, and physical activity) from participants. Smoking status was classified into two groups: those who have never smoked or have quit, and those who currently smoke. Drinking status was classified into two groups: those who have never drank or have quit, and those who currently drink. The definition of physical activity and BMI have been described elsewhere [27]. Moreover, biochemical indices such as total cholesterol (TC) and triglyceride (TG) levels were determined either through direct measurement or enzymatic methods (ROCHE Cobas C501). The total lipids were the sum by the equation: total lipids=2.27*TC+TG+0.623 [28]. The HOMA2-%β and HOMA2-IR were computed via an online homeostatic model assessment (HOMA) computing website [29].

Definition of T2DM

According to American Diabetes Association (2002) and the WHO (1999). Diagnosis of T2DM was established if participants met any of these conditions: (1) fasting plasma glucose (FPG) levels≥7.0 mmol/L; (2) glycated hemoglobin (HbA1c) levels≥6.5%; (3) self-reported history of T2DM with current use of glucose-lowering medications.

PCB exposure and vitamin D assessment

The pretreatment method has been reported in previous published articles [30]. Briefly, for each 300 μL plasma sample, 0.5 ng of internal standard is added successively, followed by ultra-pure water and acetonitrile. After 10 min of ultrasound, 3 mL n-hexane was added, the supernatant was extracted after shock centrifugation. Next, 3 mL n-hexane/dichloromethane was added, and the supernatant was extracted again after shock

centrifugation. The extracted supernatant was evaporated under pure nitrogen, reconstituted with 200 μL n-hexane, and then eluted on Florisil column. Reconstruction with 100 μL n-hexane before gas chromatography-mass spectrometry (GC-MS/MS) analysis. Values below the limit of detection (LOD) were specified by 1/2 LOD. In this study, we detected 7 types of PCBs. The non-dioxin-like PCBs (NDL-PCBs) are comprised of PCB28, PCB52, PCB101, PCB138, PCB153, and PCB180, while PCB118 is categorized as a dioxin-like polychlorinated biphenyl (DL-PCBs).

The liquid chromatography-tandem mass spectrometry (LC-MS/MS) was employed to determine 25(OH)D2 and 25(OH)D3 levels, detailed methods have been reported in previous published articles [31]. The concentrations below the LODs were assigned by 1/2 LOD. The 25(OH)D levels was the sum by the equation: 25(OH)D = 25(OH)D2 + 25(OH)D3.

Statistical analysis

For the comparison of continuous variables, the Student's t-test or Mann-Whitney U test was selected according to the results of the normality test, and the chi-square test was used for the comparison of categorical variables. Given that the distributions of PCBs and vitamin D levels were skewed, a natural logarithm transformation was applied to these values.

First, a linear regression model was employed to estimate the association of individual and multiple PCB exposure on vitamin D levels in the NGT and T2DM groups, respectively. Based on previous literature [30, 31], we incorporated meaningful covariates in our study. In model 1, we adjusted for total lipids; in model 2, we adjusted for age, gender, smoking status, drinking status, marriage status, educational levels, average monthly income, physical activity, BMI, and total lipids. When we explored the associations of individual PCB exposure on vitamin D levels, corrected using the Benjamini-Hochberg (B-H) method, and the false discovery rate (FDR) value below 0.05 was considered significant.

Second, quantile g-computation regression (QG) model was employed to assess the associations of PCB mixtures with vitamin D levels. When conducting mixed exposure assessment, it's crucial to consider the interactions among chemicals. The QG model allows for the adjustment of "weights" in any direction, highlighting the potential beneficial or harmful effects of different exposures [32]. Positive weight coefficients in the QG model indicate a positive correlation between these chemicals and health biomarkers, whereas negative weight coefficients suggest a negative correlation between the chemicals and health biomarkers [33].

Third, Bayesian kernel machine regression (BKMR) models were employed to assess the associations of PCB mixtures with vitamin D levels. Bayesian methods are a type of statistical approach, kernel methods are a technique for processing data, and regression models are used to estimate relationships between variables. The BKMR model integrates these three concepts, enabling it to handle nonlinear relationships and interactions between multiple exposures [34]. It is particularly suited for studying the combined impact of various environmental exposures on health outcomes [35]. For BKMR model, we standardized all PCBs through z-score transformation to estimate the multivariable exposure-response function on the same scale. The Markov chain Monte Carlo technique was applied to fixed parameters with 10,000 iterations. Furthermore, the assessment of the significance of each component in the mixture for choosing variables was conducted using posterior inclusion probabilities (PIPs).

Fourth, the interaction effects of ΣPCBs with HOMA2-%β and HOMA2-IR on vitamin D levels were estimated using generalized linear models in the total population. All analyses were conducted utilizing R 4.0.0.

Results

Participant characteristics

Among 1,705 participants included in the current study, participants with T2DM exhibited lower levels of 25(OH)D2 [median: 8.38 vs. 6.92 (ng/mL)], and 25(OH)D [median: 32.44 vs. 30.45 (ng/mL)] levels when compared to NGT group (all P value < 0.05) (Table 1). Furthermore, physical activity, BMI, TC, TG, total lipids, HOMA2-%β, and HOMA2-IR differed significantly between the NGT and T2DM groups (all P value < 0.05).

The correlation of plasma PCB concentrations

Table 2 showed the plasma PCBs levels of the study population, with a detection rate of PCBs in plasma samples was ranging from 99.0 to 100.0%. The experimental parameters of PCB detection are displayed in Supplementary Table 1. In NGT group, the average concentration was 0.082 to 0.227 ng/mL; and in T2DM group, the average concentration was 0.094 to 0.264 ng/mL, respectively. Moreover, the individual PCBs showed positive correlations with one another, ranging from 0.26 to 0.90 (Supplementary Fig. 2).

Associations of individual PCB exposure with vitamin D

The associations of individual PCB exposure with vitamin D levels are demonstrated in Fig. 1. In the NGT group, the levels of PCB118, and PCB180 were positively associated with 25(OH)D2, and the levels of PCB101 were positively associated with 25(OH)D2, 25(OH)D3, and 25(OH)D (all FDR adjusted P < 0.05). However, in T2DM group, the levels of PCB153 and PCB180 were negatively associated with 25(OH)D2, the β coefficient (95% CI) of these

Table 1 Basic characteristic of the study population

Variables	Total	NGT group	T2DM group	*P* value
	(*N* = 1705)	(*N* = 887)	(*N* = 818)	
Age (years), median (IQR)	61.00 (12.00)	59.73 (12.00)	59.81(12.00)	0.806
Gender (n, %)				0.776
Male	650 (38.12)	341 (38.44)	309 (37.78)	
Female	1055 (61.88)	546 (61.56)	509 (62.22)	
Smoking status (n, %)				0.248
Never/former	1394 (81.76)	716 (80.72)	678 (82.89)	
Current	311 (18.24)	171 (19.28)	140 (17.11)	
Drinking status (n, %)				0.515
Never/former	1481 (86.86)	775 (87.37)	706 (86.31)	
Current	224 (13.14)	112 (12.63)	112 (13.69)	
Marital status (n, %)				0.784
Married/living together	1520 (89.15)	789 (88.95)	731 (89.36)	
Divorced/widowed/separated/single	185 (10.85)	98 (11.05)	87 (10.64)	
Educational level (n, %)				0.101
Never attended school or primary school	945 (55.43)	503 (56.71)	442 (54.03)	
Junior high school	597 (35.01)	312 (35.17)	285 (34.84)	
Senior high school or above	163 (9.56)	72 (8.12)	91 (11.12)	
Average monthly income (n, %)				0.420
< 500 RMB	685 (40.18)	350 (39.46)	335 (40.95)	
500–1000 RMB	501 (29.38)	273 (30.78)	228 (27.87)	
> 1000 RMB	519 (30.44)	264 (29.76)	255 (31.17)	
Physical activity, (n, %)				**0.049**
Low	445 (26.10)	211 (23.79)	234 (28.61)	
Moderate	820 (48.09)	448 (50.51)	372 (45.48)	
High	440 (25.81)	228 (25.70)	212 (25.92)	
BMI, kg/m^2	24.56 ± 3.56	23.58 ± 3.32	25.63 ± 3.51	**< 0.001**
TC, mmol/L	4.73 ± 0.93	4.60 ± 0.81	4.87 ± 1.02	**< 0.001**
TG, mmol/L	2.02 ± 1.36	1.65 ± 1.00	2.40 ± 1.56	**< 0.001**
Total Lipid, mg/dL	606.38 ± 136.98	571.40 ± 108.90	644.30 ± 153.30	**< 0.001**
HOMA2-%β, median (IQR)	98.60 (75.20)	135.50 (51.90)	63.43 (49.75)	**< 0.001**
HOMA2-IR, median (IQR)	1.74 (0.92)	1.54 (0.74)	2.03 (1.15)	**< 0.001**
25(OH)D2 (ng/mL), median (IQR)	6.87 (3.34)	8.38 (3.79)	6.92 (2.58)	**< 0.001**
25(OH)D3 (ng/mL), median (IQR)	22.93 (9.30)	24.06 (8.85)	23.53 (9.76)	0.152
25(OH)D (ng/mL), median (IQR)	30.49 (11.02)	32.44 (11.16)	30.45 (10.53)	**< 0.001**

Abbreviations: Data are shown as means ± standard deviations or median (interquartile range) for continuous variables and numbers (percentages) for categorical variables. Student's t-tests or Mann-Whitney U tests were performed to examine the difference in continuous variables, and the significance of the difference in categorical variables was assessed by chi-squared tests

BMI, body mass index; TC, total cholesterol; TG, triglyceride; HOMA2-%β, β-cell function; HOMA2-IR, homeostasis model assessment 2 of insulin resistance; NGT, normal glucose tolerance; T2DM, type 2 diabetes mellitus. *P* values were calculated using the t-test or Mann–Whitney U test and chi-square test

P value < 0.05 were considered statistically significant

were −0.035 (-0.057, -0.012) and −0.035 (-0.057, -0.013); the levels of PCB52, PCB101, PCB118, PCB153, and PCB180 were negatively associated with 25(OH)D3 and 25(OH)D. (Supplementary Tables 2–4).

Associations of multiple PCB exposure with vitamin D

Figure 2 showed the associations of multiple PCB exposure with vitamin D levels in fully adjusted linear regression model. In the NGT group, the levels of ΣPCB were positively associated with 25(OH)D2 (β = 0.060, 95%CI: 0.028, 0.092); However, in T2DM group, the levels of ΣPCB were negatively associated with 25(OH)D3 (β = -0.049, 95%CI: -0.072, -0.026) and 25(OH)D (β = -0.043, 95%CI: -0.063, -0.023). When the analysis was stratified by gender, we observed positive associations between PCB exposure and 25(OH)D2 only among females (Supplementary Tables 5–7). When the analysis was stratified by age, the association between PCB exposure and vitamin D levels was found to be significant only among participants younger than 65 years old (all FDR adjusted $P < 0.05$) (Supplementary Tables 8–10).

The fully adjusted QG model indicated that PCB mixture was positively associated with 25(OH)D2 (β = 0.087, 95% CI: 0.054, 0.121), 25(OH)D3 (β = 0.027, 95% CI:

Table 2 The detection rates and plasma PCB concentrations among study participants

PCBs, ng/mL	PCB28	PCB52	PCB101	PCB118	PCB138	PCB153	PCB180	ΣPCBs
LOD	0.001	0.005	0.002	0.0004	0.002	0.002	0.003	-
Total (*N* = 1705)								
DR (%)	100.0	100.0	100.0	99.2	99.9	100.0	100.0	-
Median	0.066	0.101	0.040	0.139	0.069	0.054	0.052	0.545
GM	0.069	0.118	0.052	0.094	0.079	0.052	0.056	0.702
Mean	0.139	0.209	0.088	0.240	0.199	0.095	0.097	1.067
Min	0.003	0.012	0.004	< LOD	< LOD	0.003	0.005	0.180
Max	2.125	2.238	2.696	7.339	3.725	4.030	1.424	18.207
NGT group (*N* = 887)								
DR (%)	100.0	100.0	100.0	99.5	99.9	100.0	100.0	-
Median	0.070	0.100	0.041	0.246	0.067	0.055	0.043	0.550
GM	0.075	0.119	0.055	0.119	0.061	0.048	0.052	0.706
Mean	0.136	0.212	0.082	0.227	0.139	0.089	0.092	0.978
Min	0.003	0.013	0.004	< LOD	< LOD	0.003	0.005	0.180
Max	2.125	1.863	1.228	4.511	1.461	1.269	1.424	10.247
T2DM group (*N* = 818)								
DR (%)	100.0	100.0	100.0	98.8	100.0	100.0	100.0	-
Median	0.051	0.103	0.035	0.057	0.075	0.049	0.054	0.526
GM	0.064	0.117	0.048	0.073	0.104	0.057	0.060	0.696
Mean	0.142	0.206	0.094	0.254	0.264	0.101	0.102	1.164
Min	0.003	0.012	0.004	< LOD	0.003	0.003	0.010	0.180
Max	1.850	2.238	2.696	7.339	3.725	4.030	1.371	18.207

Abbreviation: PCBs, Polychlorinated biphenyls; NGT, normal glucose tolerance; T2DM, type 2 diabetes mellitus; DR, detection rates; GM, geometric mean; ΣPCBs was summed by the seven PCBs measured above

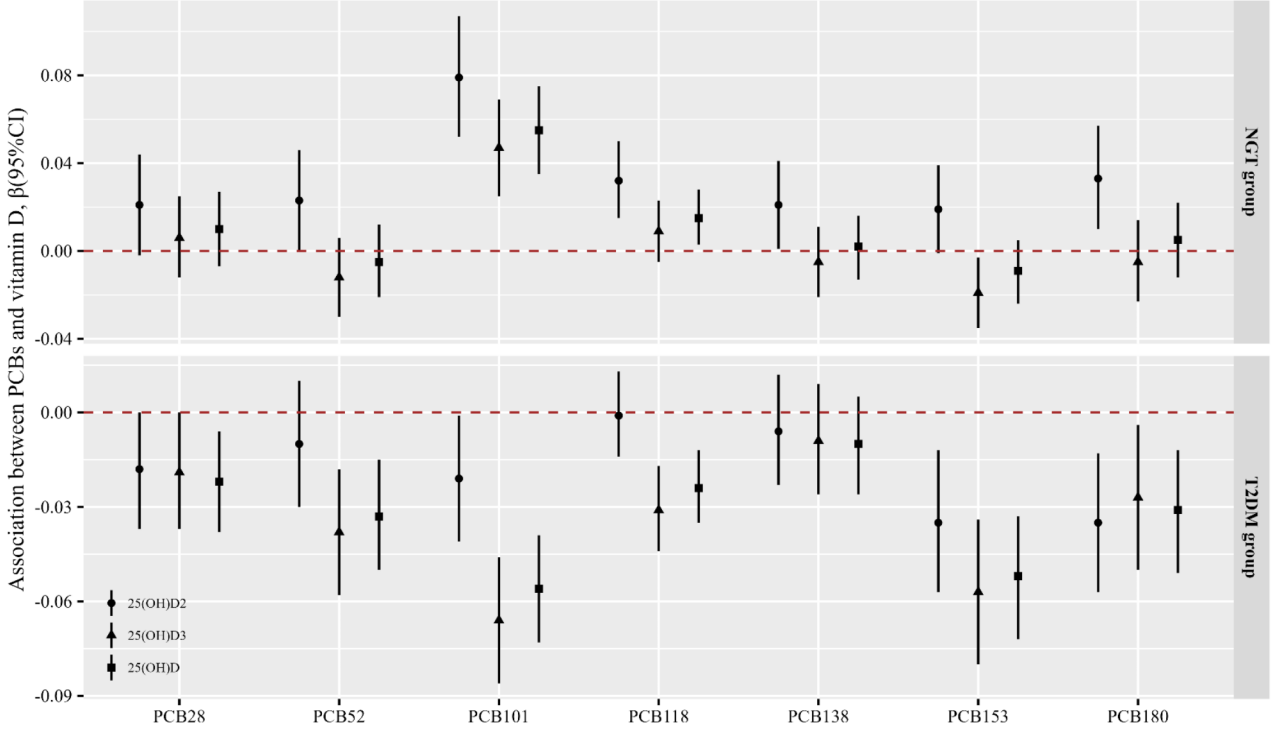

Fig. 1 Associations of individual PCB exposure with vitamin D from linear regression model among NGT and T2DM groups. Adjusted variables included age, gender, smoking status, drinking status, marriage status, educational levels, average monthly income, physical activity, BMI and total lipids. *FDR adjusted *P* values < 0.05

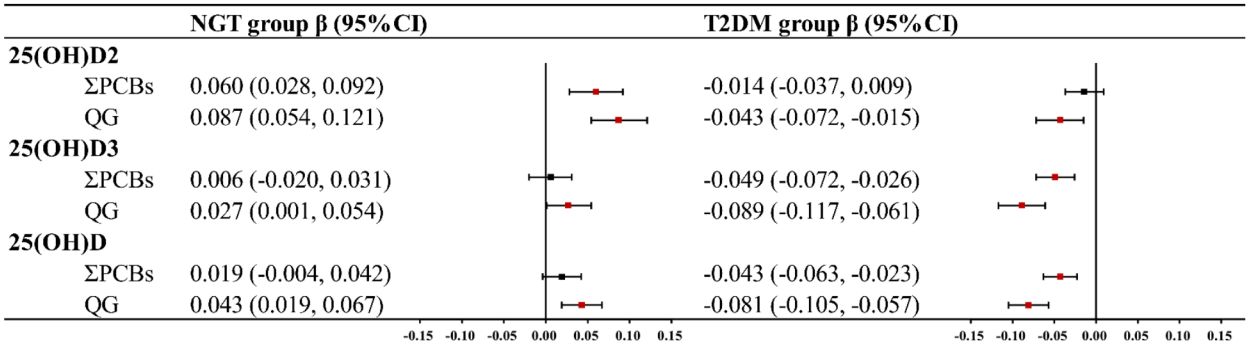

Fig. 2 Associations of multiple PCB exposure with vitamin D among NGT and T2DM groups. Adjusted variables included age, gender, smoking status, drinking status, marriage status, educational levels, average monthly income, physical activity, BMI and total lipids

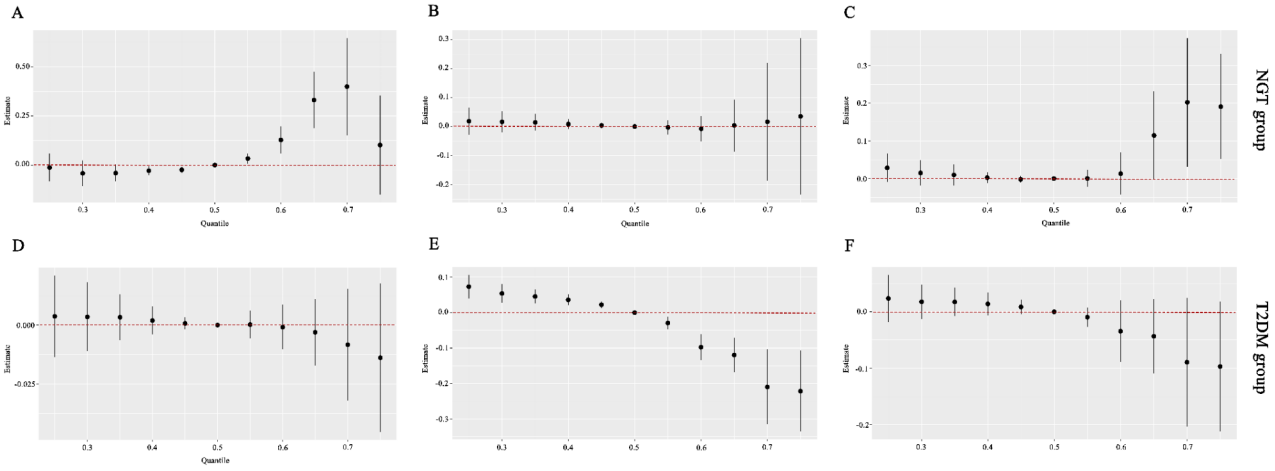

Fig. 3 The overall effects (estimates and 95%CI) of mixed-exposure to PCBs on vitamin D by Bayesian kernel machine regression analysis, defined as the difference in the response when all the exposures are fixed at a specific quantile (ranging from 0.25 to 0.75), as compared to when all the exposures are fixed at their median value. (**A**) The overall effects (estimates and 95%CI) of mixed-exposure to PCBs on 25(OH)D2 in NGT group; (**B**) The overall effects (estimates and 95%CI) of mixed-exposure to PCBs on 25(OH)D3 in NGT group; (**C**) The overall effects (estimates and 95%CI) of mixed-exposure to PCBs on 25(OH)D in NGT group; (**D**) The overall effects (estimates and 95%CI) of mixed-exposure to PCBs on 25(OH)D2 in T2DM group; (**E**) The overall effects (estimates and 95%CI) of mixed-exposure to PCBs on 25(OH)D3 in T2DM group; (**F**) The overall effects (estimates and 95%CI) of mixed-exposure to PCBs on 25(OH)D in T2DM group. Adjusted variables included age, gender, smoking status, drinking status, marriage status, educational levels, average monthly income, physical activity, BMI and total lipids

0.001, 0.054), and 25(OH)D (β=0.043, 95% CI: 0.019, 0.067) in NGT group, respectively. However, in T2DM group, the PCB mixture was inversely associated with 25(OH)D2 (β = -0.043, 95% CI: -0.072, -0.015), 25(OH)D3 (β = -0.089, 95% CI: -0.117, -0.061), and 25(OH)D (β = -0.081, 95% CI: -0.105, -0.057), respectively (Details presented in Supplementary Fig. 3).

Figure 3 presents the results of BKMR analysis, demonstrating the effects of varying PCB concentrations in comparison to their median (50th percentile) levels. In T2DM group, when the PCB mixture was at or above the 55th percentile compared with the 50th percentile, a higher level of the PCB mixture was significantly associated with a decrease in 25(OH)D3. Although no statistically significant difference was found in the 25(OH)D2 and 25(OH)D, there was a decreasing trend. The posterior inclusion probabilities (PIPs) were calculated to describe the relative importance of each PCBs (Details presented in Supplementary Table 11).

Interaction effect of PCB mixture exposure and HOMA index on vitamin D

After adjusting for confounding factors, we did not observe interaction between ΣPCBs and HOMA2-IR on vitamin D levels in Table 3 (all *P* value>0.05). However, we found significant interaction of ΣPCBs and

Table 3 Estimated effect of PCBs, HOMA index and their interaction on vitamin D

Outcome	ΣPCBs (β,95%CI)	HOMA index (β,95%CI)	$P_{ΣPCBs×HOMA\ index}$
25(OH)D2			
ΣPCBs	0.017 (-0.003, 0.036)	-	-
HOMA2-%β	-	0.099 (0.072, 0.126) *	-
HOMA2-IR	-	-0.105 (-0.146, -0.064) *	-
ΣPCBs + HOMA2-%β + ΣPCBs×HOMA2-%β	-0.187 (-0.317, -0.056) *	0.117 (0.087, 0.146) *	**0.002**
ΣPCBs + HOMA2-IR + ΣPCBs×HOMA2-IR	0.001 (-0.034, 0.036)	-0.097 (-0.140, -0.054) *	0.400
25(OH)D3			
ΣPCBs	-0.026 (-0.044, -0.009) *	-	-
HOMA2-%β	-	-0.011 (-0.035, 0.013)	-
HOMA2-IR	-	-0.003 (-0.039, 0.034)	-
ΣPCBs + HOMA2-%β + ΣPCBs×HOMA2-%β	-0.139 (-0.254, -0.024) *	-0.001 (-0.027, 0.024)	0.056
ΣPCBs + HOMA2-IR + ΣPCBs×HOMA2-IR	-0.012 (-0.043, 0.018)	-0.015 (-0.053, 0.022)	0.204
25(OH)D			
ΣPCBs	-0.018 (-0.033, -0.002) *	-	-
HOMA2-%β	-	0.016 (-0.005, 0.037)	-
HOMA2-IR	-	-0.030 (-0.062, 0.002)	-
ΣPCBs + HOMA2-%β + ΣPCBs×HOMA2-%β	-0.157 (-0.258, -0.055) *	0.028 (0.006, 0.051) *	**0.007**
ΣPCBs + HOMA2-IR + ΣPCBs×HOMA2-IR	-0.010 (-0.037, 0.017)	-0.038 (-0.072, -0.005) *	0.386

Abbreviations: PCBs, Polychlorinated biphenyls; HOMA: Homeostatic Model Assessment; HOMA2-IR: homeostasis model assessment 2 of insulin resistance; HOMA2-%β, β-cell function; ΣPCBs was summed by the seven PCBs measured above

Adjusted for age, gender, smoking status, alcohol consumption status, marriage status, educational levels, average monthly individual income, physical activity, BMI, and total lipids

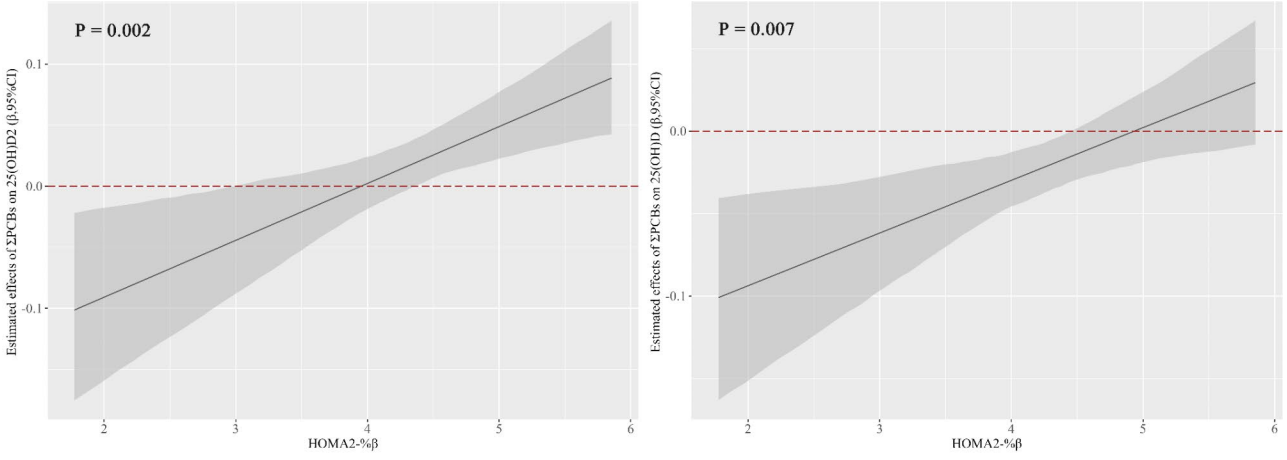

Fig. 4 The multiplication interactive effects of PCBs and HOMA2-%β on 25(OH)D2 and 25(OH)D. Adjusted variables included age, gender, smoking status, drinking status, marriage status, educational levels, average monthly income, physical activity, BMI and total lipids

HOMA2-%β on 25(OH)D2 and 25(OH)D. As Fig. 4 shown, the negative association of ΣPCBs with 25(OH)D2 and 25(OH)D disappeared or changed to a positive association with the increase of HOMA2-%β levels.

Discussions

In the current study, a variety of statistical methods were employed to investigate the associations between PCB exposure and vitamin D levels in populations with NGT and T2DM in rural China. First, linear regression models indicated that in the NGT group, PCB118, PCB180, and ΣPCBs were positively associated with 25(OH)D2, and PCB101 was positively associated with vitamin D levels. Conversely, in T2DM patients, PCB153 and PCB180 were inversely related with 25(OH)D2; PCB52, PCB101, PCB118, PCB153, PCB180, and ΣPCBs were negatively associated with 25(OH)D3 and 25(OH)D. Second, QG and BKMR analysis revealed PCB mixture exposure was inversely related to vitamin D levels in the T2DM group, contrary to the results observed in the NGT groups. Third, the negative association of ΣPCBs with 25(OH)D2 and 25(OH)D disappeared or changed to a positive association with the increase of HOMA2-%β levels.

This study, as far as we know, is the inaugural exploration of the associations between PCB exposure and vitamin D levels among NGT and T2DM groups. Thus, the findings of this study have limited comparability with existing studies. In the NGT groups, our study indicated a positive association between PCBs and vitamin D levels. Another study found that PCBs (such as PCB153 and PCB180) were positively associated with 25(OH)D3 levels, but these associations disappeared after adjusting for BMI [22]. In this study, PCBs remained positively associated with vitamin D levels after adjusted for BMI, and multiple exposure model results remained consistent, which may be related to dietary intake. Studies have shown that the main route of human exposure to PCBs is via eating foods laced with these chemicals [36–38]. Specifically, over 90% of PCB intake comes from eating meat, dairy, and fish [39, 40]. Thus, fish and seafood consumers may be at increased risk for taking compounds with potentially toxicological effects while supplementing vitamin D [41, 42].

However, PCBs were negatively associated with vitamin D levels among T2DM patients. A population-based cohort study is consistent with our results, suggesting that maternal PCB180 were inversely associated with circulating 25(OH)D3 concentrations [21]. Likewise, another study found that PCB treatment changed the chemical and mineral composition of the vertebrae of Sprague-Dawley rats, and the 25(OH)D level of Sprague-Dawley rats was also significantly reduced [43]. However, as none of these studies specifically focused on T2DM, the mechanisms linking PCB exposure to vitamin D levels remain unclear in T2DM group. On the one hand, research suggests that PCBs can negatively affect islet β-cell function [44] and prompt inflammation in living organisms [45]. This effect is linked to PCBs activating the aryl hydrocarbon receptor (AhR), which in turn stimulates cytochrome P450 1A1 (CYP1A1), resulting in accelerated metabolism of endogenous and exogenous substrates, a process that may produce excess reactive oxygen species (ROS) [46]. This increase in ROS can disturb the cellular redox balance, and promote inflammation by activating NFκB and increasing the expression of pro-inflammatory genes [47]. Based on the aforementioned evidence, it appears that PCB exposure may impair islet β cell function, which is often accompanied by chronic inflammation. On the other hand, epidemiological studies have found a correlation between inflammatory biomarkers and the development of T2DM [48]. For example, numerous studies suggested that β-cell dysfunction in T2DM is often associated with chronic inflammation [49, 50]. Inflammation markers, like IL-1α, C-reactive protein, and TNF-α, have been consistently related to β-cell failure [51–53]. Of note, some experts currently believe that low 25(OH)D levels may be caused by chronic inflammation [26]. Mangin M et al. propose that diseases may cause disrupted vitamin D metabolism, resulting in low 25(OH)D levels due to ongoing inflammation from persistent infections [26]. Garbossa SG et al. suggested that low vitamin D levels are linked to heightened expression of TLRs and a pro-inflammatory state [54]. Therefore, a plausible explanation was that PCB exposure causes chronic inflammation in the body, and the function of islet beta cells in T2DM population is weakened, aggravating chronic inflammation, thereby leading to lower vitamin D levels.

In addition, further interaction analysis discovered that the negative association of ΣPCBs with 25(OH)D2 and 25(OH)D disappeared or changed to a positive association with the increase of HOMA2-%β levels. The shift suggested that islet β cell function could influence the link between PCBs and vitamin D levels. However, it is crucial to note that these findings do not fully elucidate the direct mechanism linking PCBs with vitamin D metabolism in T2DM patients. More specific and detailed studies are needed to fully understand this relationship, which will inform strategies to prevent and manage vitamin D deficiencies in targeted groups.

This study identifies the association between PCB exposure and vitamin D levels among NGT and T2DM groups, and further explores the interaction of plasma PCBs with HOMA2-%β on vitamin D levels. Nonetheless, the study has some limitations. First, being a case-control study, it cannot prove causation. Second, since it was investigated in rural Henan province with a primary focus on farmers, the findings may not be applicable to urban populations. Third, this study only examined the association between PCB exposure and vitamin D levels, and did not address other potential pollutants, such as pesticides, bisphenol A, and air pollutants. Therefore, it is necessary to further comprehensively evaluate the mixed exposure of other pollutants and their association with vitamin D levels in NGT and T2DM groups. Fourth, our study only involved the determination of PCBs and vitamin D levels in a single plasma sample, and repeated measurements were not performed. However, previous studies have pointed out that PCBs and vitamin D concentrations are relatively stable in plasma [55, 56]. Lastly, despite the adjustment for many pertinent variables, the possibility of residual confounding factors still exists. Hence, caution is advised in interpreting these findings, and further research is necessary to confirm our conclusions.

Conclusions

In summary, we found negative associations of individual and mixtures PCB exposure with vitamin D levels in the T2DM group, contrary to the results observed in the NGT groups. Additionally, the negative association

of ΣPCBs with 25(OH)D2 and 25(OH)D disappeared or changed to a positive association with the increase of HOMA2-%β levels, indicating that the negative association between PCB exposure and vitamin D levels in T2DM patients may be related to the decline of islet β cell function. These findings indicate that the effect of PCB exposure on vitamin D levels should be taken seriously, especially in T2DM patients.

Abbreviations

PCB	Polychlorinated biphenyls
T2DM	Type 2 diabetes mellitus
NGT	Normal glucose tolerance
TC	Total cholesterol
TG	Triglyceride
BMI	Body mass index
FPG	Fasting plasma glucose
HbA1c	Glycated hemoglobin
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
HOMA	Homeostatic model assessment
NDL-PCBs	Non-dioxin-like PCBs
DL-PCBs	Dioxin-like polychlorinated biphenyl
GC-MS/MS	Gas chromatography-mass spectrometry
FDR	False discovery rate
rpm	Revolutions per minute
MW	Molecular weight
RT	Retention time
LODs	Limits of detection
QG	Quantile g-computation regression
BKMR	Bayesian kernel machine regression
PIPs	Posterior inclusion probabilities

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12940-024-01130-x.

Supplementary Material 1

Acknowledgements

The authors thank the participants, coordinators, and administrators for their supports, and laboratory for the facility support at the school of Public Health, Zhengzhou University, during the study.

Author contributions

All authors contributed to the study conduct/data collection. Material preparation and data analysis were performed by Rui Zhang, Qingqing Xu and Huadong Ni. The first draft of the manuscript was written by Rui Zhang and Qingqing Xu, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding

This study was supported by National Key Research and Development Program of China (Grant No.: 2023YFC2506505), National Natural Science Foundation of China (Grant No.: 42177415, 21806146), Postdoctoral Science Foundation of China (Grant No.: 2020T130604, 2021M702934), Scientific and Technological Innovation of Colleges and Universities in Henan Province Talent Support Program (Grant No.: 22HASTIT044), Young Backbone Teachers Program of Colleges and Universities in Henan Province (Grant No.: 2021GGJS015),Science and Technique Foundation of Henan Province (Grant No.: 212102310074), and Excellent Youth Development Foundation of Zhengzhou University (Grant No.: 2021ZDGGJS057).

Data availability

No datasets were generated or analysed during the current study.

Declarations

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

Ethics approval was obtained from the "Zhengzhou University Life Science Ethics Committee" (Ethic approval code: [2015] MEC (S128) and written informed consent was obtained from all participants before this study.

Received: 15 April 2024 / Accepted: 8 October 2024
Published online: 17 October 2024

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