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Predicting the risk of cardiovascular disease in people exposed to moderate to high levels of dioxin

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ABSTRACT

Cardiovascular disease (CVD) is a leading cause of morbidity and mortality worldwide. Dioxins can cause cardiovascular toxicity in experimental animals. The potential role of dioxin exposure as a preventable risk factor has attracted the attention of public health services, especially because dioxin exposure is a ubiquitous problem. We aimed to investigate and clarify the effect on CVD risk of moderate-to-high exposure to dioxins. This cross-sectional study investigated 914 residents without CVD near a deserted pentachlorophenol factory. CVD-related factors were measured to examine their associations with serum dioxin. We also investigated associations between serum dioxins and the Framingham risk score. Serum PCDD/F levels were significantly positively associated with CVD risk in both genders (Men: $b = 0.023$, $P < 0.001$; Women: $b = 0.005$, $P < 0.001$; All: $b = 0.013$, $P < 0.001$). After adjusting for confounding factors, participants with higher serum PCDD/F levels had a higher risk for CVD than did the reference group (serum PCDD/levels < 9.8 pg WHO_{98}-TEQ_{DF}/g lipid) (25th to <50th percentile, adjusted odds ratio (AOR) = 2.96 [95% confidence interval (CI) = 1.13–7.75]; 50th to < 75th percentile, AOR = 3.37 [1.32–8.59]; ≥75th percentile, AOR = 6.22 [2.47–15.63]). We hypothesize that accumulated dioxins heightens the cardiovascular risk.

1. Introduction

Polychlorinated dibenzo-*p*-dioxins and dibenzofurans (PCDD/Fs), a class of well-known environmental contaminants, have been shown to cause cardiovascular toxicity in animals [1–4]. However, epidemiologic evidence of an association between high-level dioxin exposure with cardiovascular disease (CVD) morbidity and mortality in humans is inconsistent. Weakly or modestly elevated rate ratios for mortality from ischemic heart disease and all CVDs have been found in several cohorts, in which there was occupational or accidental relatively brief exposure to high doses of several persistent organic pollutants (POPs) [5–8]. In the large, worldwide burden of CVDs, the potential role of dioxin exposure as a preventable risk factor has garnered the attention of public health and clinical research services, especially because exposure to dioxins is a ubiquitous problem [9].

In the 1999–2002 National Health and Nutrition Examination Survey (NHANES), the US general population showed only in women a positive association between background exposure to persistent organic pollutants such as dioxin-like PCBs, nondioxin-like PCBs, and OC pesticides and the prevalence of CVD [10]. Compared with those in the lowest quartile of serum concentration, the odds ratios (ORs) for CVD across increasing quartiles were 0.9, 2.0, and 5.0 for dioxin-like PCBs ($P_{trend} < 0.01$), 1.2, 1.2, and 3.8 for nondioxin-like PCBs ($P_{trend} < 0.01$), and 1.9, 1.7, and 4.0 for OC pesticides ($P_{trend} = 0.03$). In both genders, there was a positive association between PCDDs and the prevalence of CVD; adjusted odds ratios (AORs) were 1.4, 1.7, and 1.9 ($P_{trend} = 0.07$, men and women combined) [10]. In a follow-up study of workers highly exposed to industrial dioxins, the standardized mortality ratio (SMR) for heart disease showed a weak increasing trend with higher dioxin exposure (SMR: 0.93, 1.00, 1.05, 0.97, 1.10, 1.20, and 1.28, $P = 0.14$) [5].

CVD remains a leading cause of morbidity and mortality worldwide [11], including in the United States [12]. The lifetime risk

Abbreviations: CVD, Cardiovascular disease; CHD, Coronary heart disease; MetS, Metabolic syndrome; PCP, Pentachlorophenol; PCDD/Fs, Polychlorinated dibenzo-*p*-dioxins and dibenzofurans; TCDD, 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin; POPs, Persistent organic pollutants; FRS, Framingham Risk Score; TG, Triglycerides; HDL-C, High-density lipoprotein cholesterol; NO, Nitric oxide; AhR, Aryl hydrocarbon receptor.

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of CVD is substantial [13], and the condition is often silent or may strike without warning, which underscores the importance of prevention. Several CVD risk-assessment instruments have been sequentially developed, each seeking to address the limitations of prior tools. The National Cholesterol Education Program (NCEP) guidelines recommend using the Framingham risk score (FRS) to identify patients with an increased 10-year risk for CVD events. For instance, the Framingham formulation for predicting coronary heart disease (CHD) was incorporated into the Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) [14]. Unrestricted to predicting a specific atherosclerotic disease, the Framingham general CVD risk profile [15] has progressed to predicting, in order to prevent, all CVD events, such as atherosclerotic CVD (coronary heart disease, stroke, transient ischemic attack, intermittent claudication, and heart failure). In addition, the performance of this general CVD risk profile also was good for predicting its individual CVD events, allowing, with simple adjustments, an estimation of the risks of each CVD component. The Framingham general CVD risk profile increases risk communication, which translates the estimated CVD risk into a notion of "vascular age," comparing a given individual with one who has an optimal CVD risk profile [15].

In our previous studies and environmental survey [16–18], PCDD/F-contaminated marine biota in the nearby sea reservoir of a now-deserted pentachlorophenol (PCP) factory in the northwest portion of Tainan City in southwestern Taiwan generated a great deal of attention. Because the deserted factory was only 1–2 km from major residential area, the residents have a high risk of being exposed to PCDD/Fs from eating contaminated seafood from that reservoir. The association between insulin resistance, metabolic syndrome, and exposure to PCDD/Fs has also recently been reported [19,20].

Although several studies [1–5] have suggested that exposure to dioxins is associated with mortality from CVD, it is necessary to identify high-risk candidates for CVD, the levels of dioxins to which they have been exposed, and the duration of their exposure. This type of analysis will facilitate the most efficient use of healthcare resources and, perhaps, reduce CVD risk. Our non-CVD study population, which was exposed to moderate-to-high levels of PCDD/Fs, provided a rare opportunity to examine the hypothesis that exposure to PCDD/Fs is associated with an increased risk of CVD (Framingham risk score) and to determine whether this effect differs by gender.

2. Experimental

2.1. Study participants

This cross-sectional study was done from July 2005 to December 2009 in a district health center near the deserted PCP factory. The only recruitment criterion was that the participant had to reside near the factory. Details of the study's protocol and all testing procedures are available elsewhere [19,20]. The study protocol was reviewed and approved by the Human Ethics Committee of National Cheng Kung University Hospital; additionally, informed written consent was obtained from all participants before they took part in the study. The modified classic Framingham equation [15] was used to calculate the Framingham risk score, which has been used for more than 50 years to predict the 10-year risk of developing general cardiovascular disease in 30–74-year-old without CVD. The equation requires the input of weighted risk factors: age, sex, systolic blood pressure, total and high density lipoprotein cholesterol concentrations, smoking, and diabetes mellitus. The estimated absolute CVD event rates can be used to quantify risk and to guide preventive care [14]. Older age most likely implies the accumulation of persistent chemicals and modifies the effect between serum PCDD/F levels and CVD risk. We first excluded all participants with a history of CVD, including myocardial infarction, stroke, peripheral arterial disease (intermittent claudication or surgery for non-cardiac arterial disease) and then recruited 30–45-year-old adults to further reduce the potential confounding effect of age. Participants were asked to fast overnight before 80 mL of venous blood samples were drawn. Information obtained from the questionnaire included personal characteristics (age, gender, medical history of diabetes and cardiovascular disease, etc.), and current lifestyle habits (alcohol intake, tobacco use, eating habits, etc.). Information about the participants' history of diabetes or CVD included questions about prior diagnoses of CVD by a physician, and their current use of related drugs. Participants were also considered to have diabetes if their fasting plasma glucose was $\geq$126 mg/dL or they reported a history of physician-diagnosed type 1 or type 2 diabetes.

2.2. Laboratory procedures

Blood samples were drawn into Vacutainer tubes (BD Vacutainer, Franklin Lakes, NJ) without anticoagulants, and serum samples obtained after centrifugation were immediately transferred to Eppendorf tubes (Eppendorf, Hamburg, Germany) and stored at −70 °C until they were analyzed (within 3 days). Controls (blanks) were created to verify that dioxin contamination had not occurred while preparing or storing the serum samples. Each analytic run consisted of a method blank, a quality control sample, and 10 unknown samples, according to the protocols defined in USEPA Method 1613. The quality control sample in each run had to have a recovery percentage rate between 77 and 122%. Quality assurance/quality control protocols were followed to ensure positive identification and the quality of the measurements. We used isotope dilution high-resolution gas chromatography/high-resolution mass spectrometry (HRGC/HRMS), as previously described [19,20], to measure seventeen 2,3,7,8-substituted PCDD/Fs in serum samples. All PCDD/Fs were adjusted to the lipid content analyzed from the corresponding samples. Quality assurance/quality control (QA/QC) protocols followed USEPA Method 1613 to ensure positive identification and the quality of the measurements.

Blood biochemistry tests for fasting glucose (FG), high-density lipoprotein (HDL) cholesterol, and triglycerides (TG) were analyzed in the pathology laboratory of National Cheng Kung University Hospital by technicians blinded to the participants' characteristics and their serum PCDD/F levels. Serum insulin was measured using a radioimmunoassay (Coat-A-Count; Siemens Medical Solutions Diagnostic, Los Angeles, CA, USA). Coefficients of variation for inter-assay and intra-assay variability for insulin were all below 10%. Fasting glucose was determined with a modular system (Modular DP system; Roche Diagnostics GmbH, Mannheim, Germany), which used a glucose oxidase method with hexokinase and glucose 6-phosphate dehydrogenase. In addition, serum TG, total cholesterol (TC), and HDL-cholesterol (HDL-C) were measured using enzymatic colorimetric test kits (Roche Diagnostic GmbH, Mannheim, Germany). The intra-assay precisions were 0.8, 1.5, and 0.95%, respectively.

2.3. Data management and statistical analysis

PCDD/F concentration is expressed in picograms (pg = 10^{-12} g) WHO_{98}-TEQ_{DF}/g lipid. JMP 5.0 (SAS Institute, Cary, NC) was used for statistical analysis, and the Kruskal–Wallis and Wilcoxon rank-sum tests to evaluate serum PCDD/Fs among different demographic characteristics.

To assess the association between CVD risk and serum PCDD/F levels by gender, a multiple linear regression was

first used. The explanatory variables included gender (categorical); obesity (BMI > 30 kg/m^2) (categorical); drinking (categorical); higher seafood consumption (quantity of seafood consumption >10 kg/month); physical activity (categorical); and a family history of hypertension (categorical), stroke (categorical), and diabetes (categorical). Multiple logistic regressions were used to assess the association between serum PCDD/F levels and the Framingham CVD risk. The response variable of interest, measured as a dichotomous variable, was high and low CVD risk (≤ and >10%) based on the calculated Framingham risk scores. The main exposure variables of interest, serum PCDD/Fs, were divided into quartiles (cut off levels of quartiles of PCDD/Fs were 9.8, 13.8, and 21.2 pg WHO_{98}-TEQ_{DF}/g lipid), and adjusted odd ratios were calculated using the lowest quartile as the referent group.

3. Results

3.1. Demographic characteristics and quantitative aspects of the CVD of study participants

Of the initial 2714 study participants enrolled, we excluded 63 CVD patients, and 1737 who were out of the 30–45-year-old age range, which finally left us with 914 participants (491 men, 423 women; 58 with diabetes; mean age: 37.5 years) (Table 1). The mean serum PCDD/F level was 18.3 pg WHO_{98}-TEQ_{DF}/g lipid (range: 3.5–281.0 pg WHO_{98}-TEQ_{DF}/g lipid). In general, men had higher Framingham risk scores than women did (Men: 5.8 ± 4.0; Women: 1.5 ± 3.7, $P < 0.001$). People who were obese (BMI ≥ 30 kg/m^2) had higher cholesterol and blood pressure and lower HDL levels than normal-weight participants. The percentage of participants with diabetes was significantly higher in the fourth quartile of serum PCDD/F levels than in the other three groups ($P < 0.001$). In addition, the percentage of smokers was significantly lower in the ≥75th quartile (30.4%) than in the <25th quartile (49.6%) of serum PCDD/F levels ($P < 0.001$). Participants with higher serum PCDD/F levels had significantly higher Framingham risk scores by quartile (<25th = 3.2, 25th to <50th = 3.4, 50th to <75th = 4.4, and ≥75th = 4.4; $P = 0.016$).

3.2. Multiple regression model

CVD risk was significantly higher with higher serum PCDD/F levels in both genders (Men: $b = 0.023$, $P < 0.001$; Women: $b = 0.005$, $P < 0.001$; All: $b = 0.013$, $P < 0.001$) (Table 2). We found that participants with higher serum PCDD/F levels had a higher risk for CVD than did the reference group (serum PCDD/F levels < 9.8 pg WHO_{98}-TEQ_{DF}/g lipid) after adjusting for confounding factors (25th to < 50th quartile: adjusted odds ratio (AOR) = 2.96, 95% CI = 1.13–7.75; 50th to <75th: AOR = 3.37, 95% CI = 1.32–8.59; and ≥75th: AOR = 6.22, 95% CI = 2.47–15.63) (Table 3). These data show that serum PCDD/Fs affected the association with cardiovascular risk in participants without CVD.

4. Discussion

We found that participants without CVD but with higher serum PCDD/F levels were at a significant risk of having a higher CVD risk in both genders, which supports the hypothesis that serum PCDD/Fs are involved in the etiology before full-blown CVD.

We also found that men were significantly more often at a higher risk for CVD than women were. Another epidemiologic study [21] showed a greater prevalence and earlier development of CVDs (hypertension, atherosclerosis, and heart failure) in men than in premenopausal women. Findings in several studies [22–24] also indicate that estrogen induces the regulation of cardiovascular

Table 1
Demographic characteristics of all study participants ($N = 914$).

Characteristics	Number (%)	Diabetes (Yes/No)	Drinking (Yes/No)	Smoking (Yes/No)	Age (years)	HDL (mg/dL)	CHOL (mg/dL)	Systolic BP (mmHg)	Diastolic BP (mmHg)	Framingham Risk Score	
										CVD	CHD
Total	914	58 (6.3%)	167 (18.3%)	337 (36.9%)	37.5 ± 4.4	50.9 ± 14.8	192.4 ± 38.5	115.4 ± 15.8	73.9 ± 11.3	3.8 ± 4.4	−1.3 ± 5.6
Gender											
Male	491 (53.7%)	35 (7.1%)	153 (31.2%)	309 (62.9%)	37.2 ± 4.4	45.3 ± 12.4	193.3 ± 39.2	118.6 ± 15.3	76.7 ± 10.9	5.8 ± 4.0	2.3 ± 2.7
Female	423 (46.3%)	23 (5.4%)	14 (3.3%)	28 (6.6%)	37.8 ± 4.4	57.5 ± 14.8	191.3 ± 37.6	111.8 ± 15.5	70.6 ± 10.9	1.5 ± 3.7	−5.5 ± 5.0
$p^{\dagger}$		0.296	<0.001	<0.001	0.047	<0.001	0.208	<0.001	<0.001	<0.001	<0.001
Obesity[a]											
No	814 (89.6%)	45 (5.5%)	144 (17.7%)	296 (36.3%)	37.5 ± 4.4	51.8 ± 15.1	191.5 ± 38.4	114.1 ± 15.3	73.0 ± 11.0	3.5 ± 4.3	−1.7 ± 5.6
Yes	94 (10.4%)	13 (13.5%)	23 (24.0%)	39 (40.6%)	37.3 ± 4.6	43.6 ± 10.2	199.9 ± 38.9	126.4 ± 16.0	81.5 ± 11.4	6.6 ± 4.2	1.5 ± 4.7
$p^{\dagger}$		0.002	0.130	0.403	0.769	<0.001	0.042	<0.001	<0.001	<0.001	<0.001
PCDD/F quartiles[b]											
<25th	227 (24.9%)	12 (5.3%)	41 (18.0%)	113 (49.6%)	34.9 ± 3.8	48.5 ± 15.0	188.4 ± 37.7	113.0 ± 13.4	72.3 ± 10.6	3.2 ± 3.9	−1.5 ± 5.7
25th to <50th	226 (24.8%)	10 (4.4%)	33 (14.5%)	79 (34.8%)	36.7 ± 4.1	50.7 ± 14.1	193.2 ± 37.6	115.0 ± 15.1	73.6 ± 11.1	3.4 ± 4.5	−1.8 ± 5.9
50th to <75th	230 (25.3%)	13 (5.7%)	44 (19.2%)	75 (32.8%)	38.4 ± 4.0	51.7 ± 15.3	196.6 ± 40.9	117.2 ± 17.2	75.4 ± 11.7	4.4 ± 3.9	−0.5 ± 4.7
≥75th	227 (24.9%)	23 (10.0%)	49 (21.3%)	70 (30.4%)	39.9 ± 4.0	52.7 ± 14.7	191.4 ± 37.3	116.4 ± 16.9	74.1 ± 11.6	4.4 ± 5.1	−1.4 ± 5.8
$p^{\dagger}$		0.065	0.298	<0.001	<0.001	0.002	0.115	0.079	0.024	0.016	0.252

Abbreviations: CVD, cardiovascular disease; CHD, coronary heart disease; CHOL, cholesterol; BP, blood pressure.

[a] Body mass index ≥ 30 kg/m^2.

[b] Quartiles of serum PCDD/F levels: (1) <25th, <9.86; (2) 25th to <50th, 9.86–13.8; (3) 50th to <75th, 13.8 to <21.2; (4) ≥75th, ≥21.2 pg WHO_{98}-TEQ_{DF}/g lipid.

[†] p: indicates whether Framingham risk factors differed between different demographic characteristics, calculated using the Wilcoxon Rank-Sum test for dichotomous variables and the Kruskal–Wallis test for categorical variables with 3 or more classifications; all tests were 2-sided.

Table 2
Multiple regression models using serum PCDD/F levels as independent variables to assess their association to cardiovascular disease (CVD) risk as dependent variables in non-CVD participants.

Dependent variable	CVD risk					
	Men (n = 491)		Women (n = 423)		All (N = 914)	
Independent variable	b (SE)	P	b (SE)	P	b (SE)	P
Gender (Men/Women)	–	–	–	–	−0.033 (0.002)	<0.001
Physical activity[a] (Yes)	−0.002 (0.004)	0.651	0.001 (0.002)	0.790	−0.001 (0.002)	0.570
Drinking (Yes)	0.024 (0.004)	<0.001	0.001 (0.004)	0.871	0.022 (0.003)	<0.001
Higher seafood consumption[b] (Yes)	−0.005 (0.004)	0.250	0.001 (0.002)	0.862	−0.003 (0.002)	0.202
Family history of hypertension (Yes)	0.004 (0.005)	0.452	0.003 (0.002)	0.093	0.003 (0.003)	0.213
Family history of stroke (Yes)	0.008 (0.010)	0.395	−0.005 (0.003)	0.155	0.003 (0.005)	0.597
Family history of diabetes (Yes)	0.002 (0.005)	0.618	0.001 (0.002)	0.875	0.001 (0.003)	0.714
BMI (kg/m^2)	0.001 (0.001)	0.005	0.002 (0.001)	<0.001	0.002 (0.001)	<0.001
PCDD/Fs[c] (pg WHO_{98}-TEQ_{DF}/g lipid)	0.023 (0.003)	<0.001	0.005 (0.001)	<0.001	0.013 (0.002)	<0.001

Abbreviation: SE, standard error.
[a] Self-report of a brisk daily 30-min walk or even a 15-min run.
[b] Self-report of quantities of seafood consumption was higher than 10 kg per month.
[c] PCDD/F levels were log-transformed. All tests were 2-sided.

function via genomic and nongenomic mechanisms, and that its effects are triggered by estrogen receptor (ER)-dependent and ER-independent mechanisms. It is well known that there are gender differences in many aspects of vulnerability to environmental xenobiotics.

PCDDs (but not PCDFs) and self-reported CVD have been associated in a nationwide American study [10]. The adjusted odd ratios (AORs), by PCDD exposure quartile, in both genders combined were 1.0 (reference category), 1.4, 1.7, and 1.9 (P_{trend} = 0.07) after adjustment for age, race, BMI, smoking, alcohol consumption, exercise, cholesterol, hypertension, and C-reactive protein. Sergeev and Carpenter [25,26] conducted a population-based semi-ecological study of hospitalizations in relation to presumed environmental exposure to POPs and found that residential proximity to sources of POPs is associated with an increase in either the RR of ischemic stroke with comorbid diabetes mellitus (IS-DM) or metabolic syndrome (MetS)-related hospitalization, which supports the growing body of evidence that POPs are an important risk factor for atherosclerosis-related diseases. In our large-scale study with a moderate-to-high level of exposure to PCDD/Fs, we found that PCDD/Fs monotonically and positively affected the risk of CVD. When we compared the differences in CVD risk with the same serum PCDD/F levels in the 30–45- and 45–74-year-old age groups and evaluated the association between serum PCDD/F levels and CVD risk in these two age groups with the same adjustments in the present study, we found a consistent positive relationship in the 30–45-year-old age group (b = 0.031, P < 0.001) (Fig. 1). The individual contributions from these two risk factors, long-term accumulation of PCDD/Fs and advancing age, could not be easily clarified in the current study design. Although cardiovascular changes are very common among the elderly, they are not part of the normal aging process [27]. Indeed, the aging process does not necessarily imply CVD [28], and it has been shown [27] that healthy elderly people have normal cardiovascular function, although their cardiovascular system does experience important age-related changes that may determine how they respond to exercise and other types of stress.

In our previous studies [19,20], we found associations between insulin resistance, MetS-related factors, especially for blood pressure, and exposure to PCDD/Fs in the same population. Although the mechanisms responsible for the relationship between PCDD/Fs and CVD in this cross-sectional study have not been clearly elucidated, we have summarized several possibilities from our recent studies and those of others. Reaven [29] has proposed that the majority of insulin-resistant individuals continue to secrete enough insulin to maintain normal or near-normal glucose tolerance and were more likely to have some degree of glucose intolerance, a high plasma triglyceride and low HDL cholesterol concentration, and elevated blood pressure. In addition, several studies [30–33] showed that these changes will increase the risk of cardiovascular disease (CVD). Wilson et al. [34] also provides clear evidence that insulin resistance and its cluster of associated abnormalities (MetS) increases the risk of type 2 diabetes and CVD. In addition, MetS increases the risk of myocardial infarction (heart attack) and stroke; it is also associated with increased CVD mortality and all-cause mortality [35,36].

One study [1] found that an acute high dose of TCDD resulted in the modest increase in blood pressure, triglycerides, and low-density lipoproteins in a mouse model, while another [2] reported that chronically exposing rats to TCDD induced a dose-dependent

Table 3
Multiple logistic regression models, including serum PCDD/F level as an independent variable, to assess its association with the risk of general cardiovascular disease as a dependent variable in participants.

Independent variables	CVD risk >10% n (%)	OR (95% CI)
Gender		
Male	59 (12.0)	1.0
Female	4 (1.0)	0.08 (0.03–0.23)
Obesity[a]		
No	45 (5.5)	1.0
Yes	17 (17.7)	3.39 (1.71–6.69)
Family history of following disease		
Hypertension[b]		
No	48 (6.6)	1.0
Yes	15 (7.9)	1.1 (0.54–2.19)
Stroke[c]		
No	62 (7.1)	1.0
Yes	1 (2.6)	0.32 (0.04–2.91)
Diabetes[d]		
No	50 (6.6)	1.0
Yes	13 (8.6)	1.50 (0.73–3.07)
Drinking		
No	31 (4.2)	1.0
Yes	32 (19.2)	2.52 (1.40–4.51)
PCDD/F quartiles[e]		
<25th	7 (3.1)	1.0
25th to <50th	14 (6.2)	2.96 (1.13–7.75)
50th to <75th	17 (7.4)	3.37 (1.32–8.59)
≥75th	25 (10.9)	6.22 (2.47–15.63)

Abbreviations: CVD, cardiovascular disease; OR, odds ratio; CI, confidence interval.
[a] Body mass index ≥30 kg/m^2.
[b] Self-reports of living or deceased parents, siblings, or both, with hypertension.
[c] Self-reports of living or deceased parents, siblings, or both, with stroke.
[d] Self-reports of living or deceased parents, siblings, or both, with diabetes.
[e] Quartiles of serum PCDD/F levels: (1)<25th,<9.8; (2) 25th to <50th, 9.8–13.8; (3) 50th to <75th, 13.8 to <21.2; (4) ≥75th, ≥21.2 pg WHO_{98}-TEQ_{DF}/g lipid.

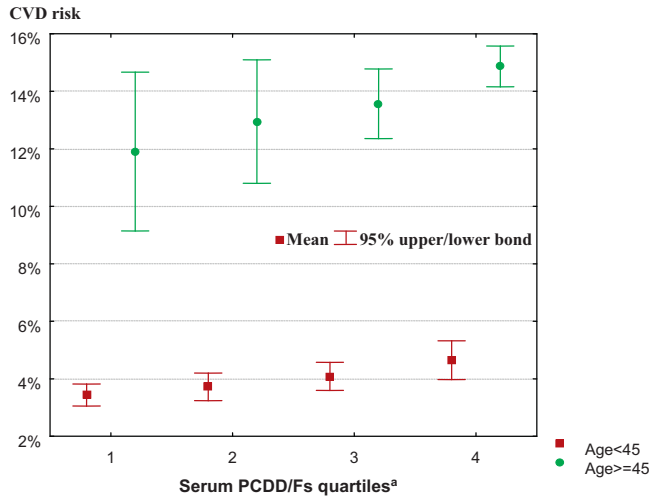

Fig. 1. Differences in CVD risk with the same serum PCDD/F levels in the 30–45- and 45–74-year-old groups. [a]Quartiles of serum PCDD/F levels: (1) < 25th, < 9.86; (2) 25th to < 50th, 9.86–13.8; (3) 50th to < 75th, 13.8 to < 21.2; (4) ≥ 75th, ≥ 21.2. pg WHO_{98}-TEQ_{DF}/g lipid.

increase in cardiomyopathy and chronic active arteritis. In a third study [37] of mice with constitutively active aryl hydrocarbon receptor (CA-AhR), heart weights and the cellular expression of CYP1A1 in CA-AhR mice corresponded well with observations in TCDD-exposed mice older than 58 days. These data suggest that continuous AhR activation causes CVD. Subchronic TCDD exposure increases systemic arterial blood pressure, left ventricle weight and wall thickness, and cardiovascular superoxide, and induces endothelial dysfunction, which is characterized by a reduction in nitric oxide (NO)-dependent vasorelaxation [3]. One study [38] found that serum concentrations of PCBs, especially those congeners with multiple ortho chlorines, were strongly associated with both systolic and diastolic blood pressure. Moreover, reactive oxygen species (ROS) are commonly elevated in CVD, including hypertension [39], and TCDD-induced AhR activation has been linked to oxidative stress in mice [40]. However, ROS production and its elimination by antioxidant systems are balanced under normal conditions [41]. Mitochondrial dysfunction will increase ROS generation and then cause cardiovascular disease, particularly atherosclerosis and hypertension [42], and AhR-dependent mitochondrial production of ROS has been shown to rise in mice whose livers had been exposed to TCDD [43]. Additionally, pesticide production workers exposed to TCDD showed impaired microvascular reactivity, which was negatively correlated with superoxide dismutase activity [44], an indicator of vascular superoxide and endothelial dysfunction. Thus, the activation of AhR appears to increase ROS in multiple organ systems. In an apolipoprotein E (ApoE)/mouse model [45], the results suggest that CXCR2, which is a G protein-coupled receptor mediating chemotaxis in immune responses, mediates the atherogenic activity of dioxins, and contributes to the development of atherosclerosis by inducing a vascular inflammatory response caused by activating the AhR-signaling pathway. All these similar findings in different models provide biological evidence for the association observed in epidemiologic studies between exposure to dioxins and CVD toxicity.

The present study has several limitations. It is critical to note that the absolute CVD risk is likely influenced by several factors that are not part of the Framingham general CVD risk profile. Other risk factors are not included in the general risk profile must be taken into account in evaluating risk and selecting the most efficacious treatment. Several factors have been highlighted in the contemporary literature [46]. They include socioeconomic position and newer risk factors (genetic, circulating, and imaging biomarkers). Moreover, people with insulin resistance or diabetes are more likely to develop CVD. We previously [19] found that non-diabetic persons with higher serum PCDD/F levels were at a significant risk of having insulin resistance, which supports the hypothesis that PCDD/Fs are involved in the etiology before full-blown CVD. Therefore, if PCDD/Fs are correlated with diabetes, which seems likely based on our data and the literature, an adjustment for diabetes would be mechanistic rather than confounding.

To prevent first coronary event, it is necessary to identify high-risk individuals who are candidates for intensive medical intervention. Framingham CVD risk estimates are influenced strongly by chronological age; however, the atherosclerotic burdens of individuals with the same chronological age and similar risk profiles can differ substantially [47].

Although we were unable to verify at what age our participants began to be exposed to PCDD/Fs, and the duration of their exposure, or to establish a cause-effect association between PCDD/Fs and CVD, we did identify the non-negligible role of exposure to PCDD/Fs and cardiovascular risk. Our findings have important ramifications for public policy.

5. Conclusion

We found a significant association between serum PCDD/Fs and cardiovascular risk even in persons without CVD. An accumulated body burden of dioxins, rather than individual exposures, may heighten the risk of developing CVD. Additional study is needed to confirm these findings in other persons exposed to high levels of PCDD/Fs. In addition, properly reducing the CVD risk factors through, for example, blood pressure control, diabetes management, and measuring and managing serum lipids, can also help prevent the development of clinical CVD. Information about the long-term health implications of CVD should be promptly delivered to those with high Framingham risk levels, and to those with a history of exposure to PCDD/Fs because of the extra risk they may incur.

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