Blood pressure and hypertension in relation to levels of serum polychlorinated biphenyls in residents of Anniston, Alabama

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Objective **To determine risk factors for elevated blood pressure and hypertension in residents of Anniston, Alabama who live near a plant that manufactured polychlorinated biphenyls (PCBs).**

Methods **A total of 758 Anniston residents had multiple measurements of blood pressure, provided information on demographic factors, medications, smoking, and exercise, and provided blood samples for determination of PCBs and total serum lipid.**

Results **Rates of hypertension increased significantly ($P<0.05$) with age and concentration of serum PCBs and were higher in African–Americans ($n=351$) than in whites ($n=407$). Hypertension also increased with BMI, but was not related to total serum lipid, sex, smoking, or exercise. Among 394 persons not on antihypertensive medication, linear regression analysis demonstrated a significant positive relation between serum PCB level and both systolic and diastolic blood pressure. After adjustment for potentially confounding variables, logistic regression gave odds ratios for the highest to lowest tertiles of total serum PCBs that exceeded 3.5 for both systolic and diastolic hypertension. When analyzed by quintiles of PCBs, the highest odds ratio was in the third quintile, suggesting a low dose effect.**

Conclusion **In individuals not on antihypertensive medication, serum PCB levels were significantly associated with prevalence of hypertension. Significant positive associations were also observed between PCB concentrations and systolic and diastolic blood pressure even in normotensive ranges. The strength of the relationships between PCB exposure and both hypertension and blood pressure suggests that PCB exposure may be an important contributing factor in regulation of blood pressure.** ***J Hypertens*** **28:2053–2060 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

Journal of Hypertension 2010, **28**:2053–2060

Keywords: age, BMI, diastole, hypertension, lipids, polychlorinated biphenyls, race, systole

Abbreviations: ATSDR, Agency for Toxic Substances and Disease Registry; BMI, body mass index; CI, confidence interval; LOD, level of detection; NHANES, National Health and Nutrition Examination Survey; OR, odds ratio; PCBs, polychlorinated biphenyls; POPs, persistent organic pollutants; VIF, variance inflation factor

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Received 9 February 2010 **Revised** 17 May 2010
Accepted 21 May 2010

Introduction

In 2000, it was estimated that 26.4% of the world's adult population had hypertension, and this number was predicted to increase by 60% by 2025 [1]. Results from the Framingham Heart study show that nine out of 10 adults are likely to develop some degree of hypertension during their lifetime [2]. Hypertension is the most important, easily recognized risk factor for stroke, myocardial infarction, peripheral vascular disease, and heart failure [3]. Because hypertension is asymptomatic, it is often not diagnosed and treated.

Multiple factors contribute to the pathogenesis of hypertension, including genetics, increased sympathetic tone, decreased parasympathetic tone, overproduction of sodium-retaining hormones, inappropriate renin secretion, deficiencies of vasodilator substances, and abnormalities of blood vessel resistance [4,5]. There are a number of reported risk factors, including age, sex, obesity [6], smoking, elevated serum lipid [7], coexisting diabetes, [8] high salt intake, a sedentary life style, and stress [9]. In the United States, African–Americans have a higher incidence of hypertension than do whites [10].

Other than a possible relation with smoking, little attention has been paid to environmental exposures as risk factors for hypertension. However, we previously demonstrated that residence near a hazardous waste site containing persistent organic pollutants (POPs) in New York was associated with an increased risk of hospitalization for hypertension, after adjustment for age, race, and sex [11]. There was a significant rate ratio of 1.14 [95% confidence interval (CI) 1.05–1.23] for people living along the polychlorinated biphenyl (PCB)-contaminated portion of the Hudson river as compared to residence more distant from waste sites, even though average income was higher,

0263-6352 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI:10.1097/HJH.0b013e32833c5f3e

there was less smoking, and more regular physical exercise and consumption of fruits and vegetables in this population than in the rest of New York. Although exposure assessment in this study was crude, the results suggested an association between exposure to POPs and hypertension. Kreiss *et al.* [12] first reported an elevated incidence of hypertension in a population exposed to PCBs after adjustment for age, sex, BMI, and social class.

Two recent studies of the general US population, using data from the 1999–2002 National Health and Nutrition Examination Surveys (NHANES), examined rates of hypertension in relation to levels of POPs. Everett *et al.* [13] reported that concentrations of seven of 10 PCB congeners examined were significantly correlated with hypertension, and that those congeners with dioxin-like activity had the highest odds ratios (ORs). Ha *et al.* [14] examined 21 POPs (three dioxins, three furans, five dioxin-like PCBs, six nondioxin-like PCBs, and four organochlorine pesticides). They reported a statistically significant positive relationship between levels of dioxins or furans and hypertension in women, and weaker but still significant relations with both dioxin-like and non-dioxin-like PCBs in men. There was no association with levels of organochlorine pesticides.

Anniston, Alabama is the site of a plant that produced PCBs from 1929 until 1971 and was owned and operated by Monsanto since 1935. Residents of Anniston have been found to have elevated levels of PCBs [15–18], but these elevations have not been found tightly correlated with either employment at Monsanto or consumption of local fish or produce [17,18]. Significant release and spread of PCBs in Anniston has occurred via air transport [19,20] and movement of contaminated soils and water [21–23]. However, to date there has been little systematic study of the health of PCB-exposed residents of Anniston.

In 2003, the Agency for Toxic Substances and Disease Registry (ATSDR) funded a study of the health of Anniston residents through a consortium of universities. This report provides information on the relationship between serum PCB level and the prevalence of hypertension in 758 Anniston residents over 18 years of age, with a focus on 394 residents who were not taking antihypertensive medication.

Participants and methods

Anniston is a city of about 24 000 people, with about 8000 residents in west Anniston, an area close to the Monsanto plant. Participants were recruited into the study by a stratified random sample of housing units from all parts of the city, based on proximity to the Monsanto plant and race. A total of 1110 persons over 18 years of age agreed to be interviewed and provided information on demographics, medications taken, and activity patterns. Of these, 772 had blood drawn for biochemical and PCB analyses and blood pressure measurements taken in the years 2005–2007. Eight participants were excluded from the analysis because PCB measurements were missing. One was excluded because there was no medication information. An additional four participants were excluded from the analysis because they had less than three blood pressure measurements, and one participant was excluded because the race listed was neither white nor African–American. This left a sample of 758 persons who completed a questionnaire, had blood pressure, height, and weight measurements taken using a standard protocol, and provided blood samples for clinical chemistry parameters and contaminant levels. The questionnaire contained queries regarding health status and medications used, as well as sociodemographic information. Of the 758 persons, 364 (48.1%) reported that they were taking physician-prescribed antihypertensive medication. The descriptive characteristics of study participants are shown in Table 1.

We defined clinical hypertension as either being on antihypertensive medication or having a systolic blood pressure of greater than 140 mmHg and/or a diastolic pressure of greater than 90 mmHg. Three sequential blood pressure measurements were obtained by a nurse at 2-min intervals, beginning after the patient had been sitting for 5 min. Blood pressures were taken manually with a standard sphygmomanometer, arm cuff, and stethoscope; no automatic device was used. Different cuff sizes were available to accommodate for various sizes of participants. Using nested analysis of variance, we did not find any differences among the means of systolic and diastolic pressures on the first, second, and third measurements. Therefore, we used the mean value of the three different measurements for each study participant.

PCB analyses were done by the Centers for Disease Control and Prevention's National Center for Environmental Health laboratory using high-resolution gas chromatography/isotope-dilution high-resolution mass spectrometry, as previously reported [24]. Serum specimens (2 ml) were fortified with $^{13}C_{12}$-labeled internal standards and diluted with concentrated formic acid and water using a 215 liquid handler (Gilson Inc., Middleton, Wisconsin, USA) for automation. Automated solid phase extraction (SPE) and silica:silica/sulfuric acid lipid degradation were performed on the Rapid Trace SPE work station (Caliper Life Sciences Inc., Hopkinton, Massachusetts, USA). Samples were injected into a Hewlett-Packard 6890 gas chromatograph equipped with a DB-5 capillary column (30 m × 0.25 μm film thickness) coupled to a Thermo Finnigan MAT95 XP mass spectrometer operated in EI mode using selected ion monitoring at 10 000 resolving power. The concentration of each analyte was calculated from its calibration curve. Study specimens were analyzed in batches of 24 specimens intermixed with quality control ($n = 3$) and method blank ($n = 3$) samples. All data were reviewed using

Table 1 Descriptive statistics of the study variables and serum polychlorinated biphenyl levels in normotensive ($n = 322$) and hypertensive ($n = 72$) participants not on medication, those individuals on antihypertensive medication ($n = 364$), and the total study population ($n = 758$)[a]

		Not on medication			
Covariate	Parameter	Normotensive	Hypertensive[b]	On medication	Total
Total PCBs (ng/g or ppb wet weight)	Mean	3.8	8.5	8.7	6.6
	Median	1.7	3.4	4.8	3.2
	STD	7.2	20.5	12.6	12.0
	Range	0.1–82.9	0.2–170.4	0.2–146.0	0.1–170.4
	Referent	0.1–0.9	0.2–2.4	0.2–3.1	0.1–0.9
	2nd tertile	0.9–3.2	2.4–4.8	3.1–7.8	1.9–5.4
	3rd tertile	3.2–82.9	4.8–170.4	8.1–146.0	5.4–70.4
Age	Mean	46.3	52.9	62.8	54.9
	STD	15.7	13.2	11.8	15.8
	Range	18.0–87.0	21.0–92.0	23.0–93.0	18.0–93.0
BMI	Mean	29.7	29.9	32.8	31.2
	STD	7.1	7.7	7.9	7.7
	Range	18.0–65.0	19.0–50.0	16.0–61.0	16.0–65.0
Total lipids[c]	Mean	627.1	634.1	635.4	632.1
	STD	156.2	146.4	148.6	151.5
	Range	344.3–1436.2	335.8–1040.4	350.5–1264.6	335.8–1436.2
		Number (%)	Number (%)	Number (%)	Number (%)
Sex	Male	96 (29.8)	30 (41.6)	104 (28.5)	230 (30.3)
	Female	226 (71.2)	42 (58.4)	261(71.5)	529 (69.7)
Race	Whites	191(59.3)	32 (44.4)	184 (50.6)	407 (53.7)
	African–Americans	131(40.7)	40 (55.6)	180 (49.4)	351 (46.3)
Smoking[d]	Yes	173 (53.9)	47(65.3)	193 (53.0)	413 (54.5)
	No	148 (46.1)	25(34.7)	171 (47.0)	344 (45.5)
Physical activity[e]	Yes	180 (55.9)	41(58.6)	199 (54.9)	420 (55.7)
	No	142 (44.1)	29 (41.4)	163 (45.1)	334 (44.3)
Diabetes[f]	Yes	37 (11.5)	11(15.3)	139 (38.2)	187 (24.7)
	No	285 (88.5)	61 (84.7)	225 (61.8)	571 (75.3)

PCB, polychlorinated biphenyl. [a] Sample size may be less than shown for some characteristics due to missing data. [b] Hypertensive: systolic pressure $\geq$140 mmHg or diastolic pressure $\geq$ 90 mmHg. [c] Estimated total lipids based on direct measurement of serum total cholesterol and triglycerides. [d] Smoked more than 100 cigarettes during lifetime. [e] Daily moderate physical activity of at least 10 min of duration. [f] Yes=those with blood sugar more than 120 mg/dl or on glycemic control medication, no=those with blood sugar less than 120 mg/dl and not on glycemic control medication.

comprehensive quality assurance and quality control procedures. Values below the limit of detection (LOD) were set to the LOD divided by the square root of 2. The LOD for individual congeners ranged between 2.2 and 63.3 pg/g serum. Total PCBs were recorded as the sums of the concentrations of congeners 28, 44, 49, 52, 66, 74, 87, 99, 101, 105, 110, 118, 128, 138 + 158, 146, 149, 151, 153, 156, 157, 167, 170, 172, 177, 178, 180, 183, 187, 189, 194, 195, 196 + 203, 199, 206, and 209 and are presented as ng/g wet weight (ppb) unless otherwise specified. We elected to use wet weight values and included total lipid in statistical models as a separate variable, as recent statistical modeling has suggested that lipid-standardized PCB values may be more prone to bias [25]. To examine whether that may be the case in this study and for comparison with other studies that used lipid-standardized PCB levels, we have also included results with lipid standardization in Table 2. Results of the analysis of the relationship between blood pressure and single PCB congeners and congeners groups will be presented in a subsequent publication.

Serum cholesterol and triglycerides were determined by the clinical chemistry laboratory at the Jacksonville Medical Center. Total serum lipid was calculated using the formula proposed by Phillips *et al.* [26] and recently updated by Bernert *et al.* [27].

Information on other variables of importance came from the questionnaire administered to participants, which provided data on age, sex, race, medications, cigarette smoking, and physical activity.

Table 2 Odds ratios and 95% confidence intervals for clinical hypertension, diastolic hypertension, systolic hypertension, and systolic and diastolic hypertension in relation to total polychlorinated biphenyl concentrations by tertile after adjustment for age, BMI, total serum lipid, sex, race, smoking status, and physical activity in the participants who were not on medication

PCBs tertiles (ppb)	Hypertensive/ normotensive	OR (95%CI)[a]	OR (95%CI)[b]
Clinical hypertension			
1st 0.1–1.2	7/124	1.0	1.0
2nd 1.3–3.6	32/100	3.90 (1.4–10.5)	3.58 (1.4–10.3)
3rd 3.7–170.4	33/98	4.09 (1.3–12.7)	3.86 (1.1–10.9)
Diastolic			
1st 0.1–1.2	7/124	1.0	1.0
2nd 1.3–3.6	24/108	4.27 (1.5–12.1)	3.66 (1.1–11.9)
3rd 3.7–170.4	25/106	4.49 (1.3–14.9)	4.15 (1.4–11.6)
Systolic			
1st 0.1–1.2	4/127	1.0	1.0
2nd 1.3–3.6	25/107	3.05 (0.7–12.0)	2.95 (0.7–11.4)
3rd 3.7–170.4	24/107	3.87 (1.1–13.1)	3.82 (1.1–12.8)
Systolic and diastolic			
1st 0.1–1.0	3/116	1.0	1.0
2nd 1.1–3.4	17/103	5.21 (1.2–21.5)	4.64 (1.0–21.9)
3rd 3.4–82.9	17/103	5.26 (1.0–25.8)	4.95 (1.2–20.1)

[a] ORs for total PCBs with total lipids as a model covariate. [b] ORs for lipid-standardized total PCBs.

Statistical analysis

Statistical analysis was conducted using SAS 9.1.3 software (SAS Institute Inc., Cary, North Carolina, USA). The distributions of PCBs and other covariates were characterized by measures of centrality and variability. Normality of covariate distributions was assessed graphically and checked using the Kolmogorov–Smirnov test. Continuous variables were logarithmically transformed to normalize their distribution and stabilize their variances.

Logistic regression (without adjustment for any other variable except age) was initially employed to assess potential risk factors for hypertension, including total PCB concentration (in tertiles), age (in tertiles), BMI [weight (kg) divided by squared height (meters) and categorized as 'normal', $<25\,kg/m^2$; 'overweight', 25–29.9 kg/m^2; or 'obese', 30+ kg/m^2], total lipid (in tertiles), sex, race (white or African–American), smoking status (smoked less than or more than 100 lifetime cigarettes), and exercise (less than or more than 10 min of daily physical activity). In all other analyses, age, BMI, and total serum lipids were included as continuous variables. We used logistic regression models to contrast hypertensive participants with those without hypertension. For those persons not on antihypertensive medication, we conducted separate analyses for individuals with clinical hypertension (defined as elevation of either systolic or diastolic pressure beyond 140 and 90 mmHg, respectively), individuals with systolic hypertension (systolic pressure beyond 140 mmHg), individuals with diastolic hypertension (diastolic pressure beyond 90 mmHg), and for those who had both systolic and diastolic hypertension.

No interaction with PCB levels was found for any covariate (age, total lipid, sex, race, smoking, and exercise) except for BMI. After checking for an interaction effect, subsequent analysis was done with adjustment for sex, race, smoking status, and physical activity as potential confounders, and they were included as dichotomous variables. Serum PCB levels were recoded as tertiles with the lowest tertile serving as the reference (comparison) group. In another analysis, PCB levels were coded as quintiles, with the lowest quintile serving as the comparison. Age, BMI, and total serum lipid were included as continuous variables. To more expressly evaluate the effect of serum lipid on associations between PCBs and hypertension, total cholesterol, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol were entered into logistic regression models as individual continuous covariates in lieu of a single covariate describing total serum lipid. ORs and 95%CIs for all logistic regression models were estimated by exponentiation of model coefficients. Results were considered statistically significant when P value was less than 0.05 for a two-tailed test.

Multiple linear regression analysis was performed on log-transformed mean systolic and diastolic blood pressures among study participants not taking antihypertensive medication in order to evaluate linear associations between PCB concentration and systolic and diastolic blood pressure. All other covariates were treated as in the multiple logistic regression analysis. To determine whether multicollinearity was a problem among the covariates, we ran the variance inflation factor (VIF) analysis on all linear regression analyses. VIF did not exceed 3 in any of the analyses.

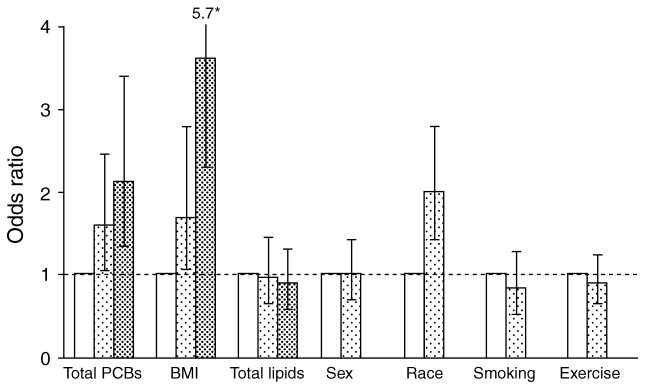
Results

Table 1 shows the characteristics of the study population for whom all serum PCBs, lipids, and blood pressure measurements were available and medication status known. This table presents concentrations of total PCBs, age, BMI, total serum lipid, sex, race, smoking status, and exercise. Normotensive individuals were on average 17 years younger (46 years) than those on antihypertensive medication (63 years) and their total mean PCBs was 3.8 vs. 8.7 ng/g wet weight, respectively. Hypertensive participants not on antihypertensive medication were 10 years younger (mean age = 53 years) than those on medication, but their total PCBs were similar (mean = 8.5 vs. 8.7 ng/g wet weight).

Because hypertension is strongly associated with older age (OR = 6.28 in the second tertile and 10.96 in the third), Fig. 1 shows ORs, adjusted only for age, for hypertension in relation to tertiles of increasing serum total PCB concentration, BMI based on categories of normal, overweight, and obese, tertiles of total serum lipid, sex (male, female), race (white, African–American), smoking (no, yes), and exercise (no, yes) in the whole study population ($n = 758$). Rates of hypertension were significantly elevated in relation to both the second (OR = 1.60) and third (OR = 2.13) tertiles of serum PCB concentrations after adjustment for age. Hypertension was significantly more frequent in persons with elevated BMI (OR = 1.70 in the second tertile and 3.62 in the third tertile) and in African–Americans as compared to whites (OR = 2.00). There was no statistically significant relationship with total serum lipid, sex, smoking, or exercise.

In our population, the serum PCB level in obese (BMI $\geq$ 30) persons was somewhat less than in those with a BMI less than 30 (median concentration 3.20 vs. 3.38 ng/g). Those with a BMI of at least 30 were also somewhat older (median age = 57 years) than those with a BMI less than 30 (median age = 54 years). There was no difference in the relationship between systolic blood pressure and PCB level in those persons with BMI less than 30 as compared to those with BMI at least 30. However, there was a difference in the relationship between diastolic blood pressure and PCB level within BMI categories, adjusted for age. Those with a BMI less than 30 showed β equal to 0.026 ($P = 0.0123$), whereas for those with a BMI at least 30 had β equal to 0.012 ($P = 0.28$; data not shown in any table).

Fig. 1



Odds ratios (±95% confidence intervals) for clinical hypertension in whole study population ($n = 758$) in relation to increasing tertiles of total polychlorinated biphenyls (PCBs), total lipid, BMI (normal, overweight, obese) as well as sex (male vs. female), race (white vs. African–American), smoking (more than 100 lifetime cigarettes), and exercise (10 min or more daily) adjusted for age. The open left hand bar represents the reference level, as indicated by the dashed line.

Table 3 Multiple regression analysis of $\log_{10}$-transformed systolic and diastolic blood pressures on tertiles of serum total polychlorinated biphenyl concentrations

Group	Blood pressure	Regression coefficient ± (SE) β_1	β_2
Full population ($n = 758$)	Systolic	$0.012 \pm 0.006^*$	$0.02 \pm 0.007^*$
	Diastolic	$0.016 \pm 0.006^*$	0.012 ± 0.007
On medication ($n = 364$)	Systolic	-0.004 ± 0.008	0.016 ± 0.01
	Diastolic	-0.005 ± 0.008	0.005 ± 0.01
Not on medication ($n = 394$)	Systolic	$0.023 \pm 0.01^*$	$0.027 \pm 0.01^*$
	Diastolic	$0.033 \pm 0.01^*$	$0.035 \pm 0.01^*$
Normotensive ($n = 341$)	Systolic	0.01 ± 0.006	$0.024 \pm 0.007^*$
	Diastolic	$0.015 \pm 0.007^*$	$0.022 \pm 0.008^*$

Multiple regression analysis of $\log_{10}$-transformed systolic and diastolic blood pressures on tertiles of serum total polychlorinated biphenyl concentrations for the full population, for those participants on antihypertensive medication, for those participants not on antihypertensive medication, and for those with normotensive systolic and diastolic blood pressures; all after adjustment for age, BMI, total lipid, sex, race, smoking, and physical exercise. $^*P < 0.05$.

Table 2 presents results of multiple logistic regression analysis of hypertension among those participants not on antihypertensive medication in relation to tertiles of serum PCBs, and also similar information on the basis of only systolic hypertension, only diastolic hypertension, and both systolic and diastolic hypertension. These models were adjusted for age, BMI, total lipid, sex, race, smoking, and exercise. In all cases, there were statistically significant relations even in the second tertile of PCBs, and the ORs were highest in the 37 persons with both systolic and diastolic hypertension (OR = 5.21, 95%CI 1.2–21.5 for the second tertile and OR = 5.26, 95%CI 1.0–25.8 for the third tertile). In this table, we also present ORs for PCB concentrations reported as lipid standardized. All relationships that were significant when lipids were treated as a covariate are also significant with traditional lipid standardization. Incorporation of individual serum lipid components as covariates, rather than total serum lipid as a covariate, resulted in an increase for all effect estimates, with substantial increases (i.e., >15%) for systolic hypertension as the outcome (i.e., 3.05 vs. 3.64 for the 2nd PCB tertile; 3.87 vs. 4.96 for the 3rd PCB tertile) and joint systolic and diastolic hypertension (5.21 vs. 7.25 for the 2nd PCB tertile; 5.26 vs. 7.42 for the 3rd PCB tertile; data not shown in Table 2).

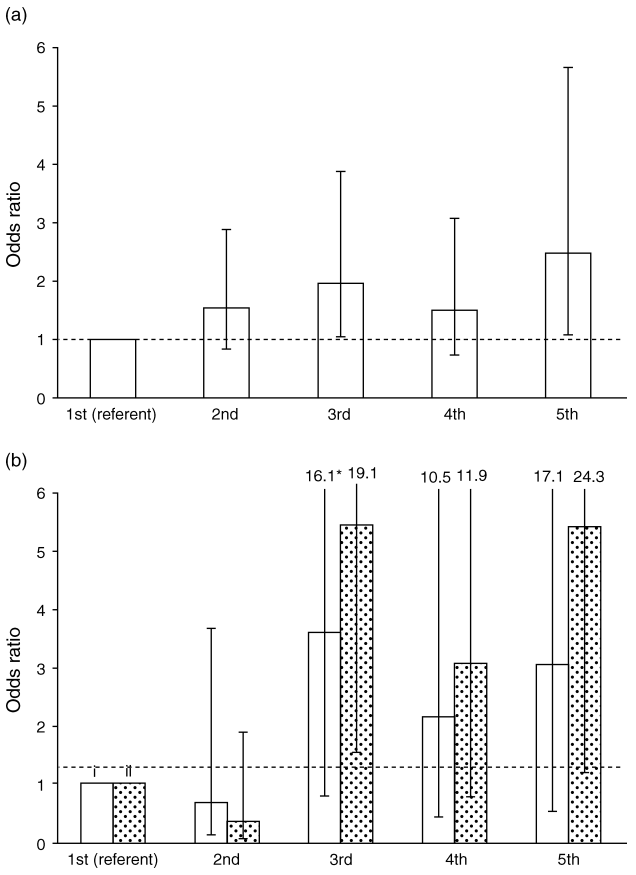
Table 3 shows multiple linear regression analysis for the associations between systolic and diastolic blood pressure and serum PCB concentration for the full population of 758 persons, for the 364 persons on antihypertensive medication, the 394 participants not on antihypertensive medication, and the 341 persons not on medication with blood pressure in the normotensive range after adjustment for age, BMI, total lipid, sex, race, smoking, and physical exercise. The strongest positive relationship was for all persons not on medication, but there were also statistically significant relations when considering both the full population and those persons not on medication with blood pressure in the normotensive range. There was no significant relationship for the 364 persons on antihypertensive medication, which indicates that the medication was effective in control of blood pressure.

Figure 2 shows results of logistic regression analysis by quintiles of serum PCBs for (a) clinical hypertension in the full population (including those on antihypertensive medication), and (b) systolic (i) and diastolic (ii) hypertension in those not on antihypertensive medication after adjustment for all covariates. When those on antihypertensive medication are included in the logistic regression analysis (Fig. 2a), the ORs are much reduced as compared to participants not on medication, but there is a significant elevation in hypertension even in the third quintile (PCB range 1.6–2.9 ng/g wet weight). The associations are much more striking among those persons not on antihypertensive medication, with ORs for diastolic hypertension greater than 5 in both the third and fifth quintiles (Fig. 2b).

Discussion

There have been only a few studies that have evaluated the possibility that environmental exposures other than smoking may contribute to rates of hypertension. The reports of Everett *et al.* [13], Ha *et al.* [14], our previous study [11], and the present study provide evidence that exposure to POPs, particularly PCBs, may be important risk factors for development of hypertension. We observed elevated odds of clinical hypertension in the whole Anniston sample, which reached statistical significance in the third and fifth quintile of the PCB distribution. When we included only those not taking antihypertensive

Fig. 2



(a) Odds ratios and 95% confidence intervals for the quintiles of total polychlorinated biphenyls in relation to clinical hypertension for all 758 participants. The referent polychlorinated biphenyl (PCB) concentration range was 0.1–1.1 ppb, and the ranges for the second to fifth quintiles were 1.2–2.4, 2.5–4.3, 4.4–9.3, and 9.4–170.4 ng/g. (b) Odds ratios and 95% confidence intervals for the quintiles of total PCBs in relation to systolic (i) and diastolic (ii) hypertension in those participants ($n = 394$) not on antihypertensive medication. The referent PCB concentration range was 0.1–0.5 ppb, and the ranges for the second to fifth quintiles were 0.6–1.5, 1.6–2.9, 3.0–5.7, and 5.8–170.4 ng/g.

medication, the associations were substantially strengthened for all measures of hypertension whether modeled with quintiles of PCB exposure in logistic regression or in linear regression models.

These results are basically supportive of those reported by Everett *et al.* [13] and also by Ha *et al.* [14], but with some important differences. Elevated ORs of hypertension in the study by Ha *et al.* [14] were found only in those with 'newly diagnosed' hypertension, excluding participants on antihypertensive medication. Those associations were reported mostly for dioxin and furan congeners (not measured in this study) and were statistically significant only in women. Suggestive associations with PCBs, in contrast, were only reported in men. The ORs for the highest tertiles of the rank-sum of the five dioxin-like PCBs were 2.3 (95%CI 0.8–6.6) and for the six nondioxin-like PCBs were 2.8 (95%CI 0.9–8.5). In this study, we did not find sex differences for hypertension in relation to the sum of PCBs. Whereas all mono-ortho dioxin-like PCBs (measured in NHANES) were included in the panel of PCBs for Anniston, the non-ortho (coplanar) dioxin-like PCBs 126 and 169 were not measured. Examining associations with individual PCB congeners will be the subject of a subsequent report.

Although participants in our study clearly had higher potential for exposure to PCBs than the general population, most living within a 2 miles radius from the former production facility, cut points for the second (20th percentile), third (40th percentile), and fourth quintile (60th percentile) of those not on antihypertensive medication were 0.5, 1.5, and 2.9 ppb wet weight for the sum of PCBs, which corresponds to approximately the 50th, 75th, and 90th percentiles of the background total US general population from 2003–2004 NHANES [28]. Although that means that our age-specific and race-specific levels are about three to five times higher than NHANES [18], it also indicates that our results are applicable to the majority of the top half of the US population PCB distribution – mostly older individuals at increased risk of hypertension. Our results may also have more general applicability. Up to two thirds of over 1000 superfund sites in the United States currently on the National Priority List contain PCBs [29]. Livestock, fish, and produce raised or grown in the vicinity of those sites may be contaminated [30] and, like residents of Anniston, those living near these sites may have elevated PCB exposure.

Age is well known to be a major risk factor for development of hypertension, and serum PCB levels are also generally higher in older individuals. However, even after adjustment for age, there was a significant elevated risk of hypertension with increasing serum PCB levels. African–American race was associated with elevated risk of hypertension, and there was a statistically significant positive relationship with BMI, as expected. No statistically significant relationships were found with total serum lipid, sex, smoking, or exercise. These results were supported by findings of the multiple linear regression analysis that demonstrated a relationship between both systolic and diastolic blood pressure and levels of PCBs even among the individuals whose blood pressure was in the 'normal' range.

Data from NHANES and studies of a native American population have both provided evidence for associations between serum levels of POPs and diabetes [31,32] and cardiovascular disease [33,34]. Although mechanisms responsible for these associations are still unclear, exposure to PCBs and dioxin-like compounds results in the induction of a very large number of genes involved in many different pathways [35,36]. There is an urgent need for further study of the role of exposure to these

compounds and chronic diseases such as hypertension, cardiovascular disease, and diabetes.

It is unclear why inclusion of those individuals on antihypertensive medication in the logistic regression analysis resulted in substantially weaker associations between PCBs and hypertension than those seen among individuals not on such medication. One possible factor is changes in lifestyle upon diagnosis of hypertension, or also the possibility that the medicines alter some component of metabolism. Investigation into this finding will be the subject for further study. The strong association of hypertension with elevated levels of PCBs in those individuals not on antihypertensive medication suggests that the association between exposure and the development of hypertension may not be easily explained by residual confounding or bias.

Incorporation of total cholesterol, HDL cholesterol, and LDL cholesterol as individual covariates into logistic regression models, rather than a single total serum lipid variable, increased the magnitude of all effect estimates for PCBs and hypertension. Whereas this increase was negligible for clinical hypertension and diastolic hypertension (i.e., $<10\%$), the increases in the magnitudes for effect estimates were substantial for systolic hypertension ($\geq 18.5\%$) and joint systolic and diastolic hypertension ($\geq 39.1\%$). Despite the reduced precision for the latter effect estimates (i.e., wider CIs likely due to increased number of covariates and smaller number of cases, especially for combined systolic and diastolic hypertension), there were no changes in direction of the estimates or in statistical significance when using the lipid component covariates, as compared to use of a total lipid covariate. Traditionally, a total lipid estimate is employed to accommodate the lipophilic nature of PCBs when studying related human health effects [25]. It is, however, the component cholesterols that constitute risk factors for hypertension [7]. The increases in PCB effect estimates observed when incorporating lipid components, rather than total serum lipid, raise the possibility that use of a total lipid variable may introduce measurement error into the estimation of the 'underlying' or 'latent' lipid compartment with a subsequent bias toward the null hypothesis. Investigators may consider incorporation of lipid components, rather than total lipid, in studies of PCB exposure and cardiovascular disease in the future.

The cross-sectional design of this study precludes assessment of temporality and thus assumptions about the possible causality of PCB exposure and hypertension. In addition, POPs tend to comigrate through environmental compartments and to be highly intercorrelated. Thus, it is possible that the PCB concentrations measured in this study are only markers for some other POP(s) that was not measured. Caution must be exercised in the interpretation of the potential effects of PCBs, as ORs tend to overestimate the underlying relative risk when the prevalence of an outcome exceeds approximately 10% in the study population [37], as it does here. In spite of these considerations, the observation that there is a statistically significant relationship between blood pressure and PCB concentration using linear regression analysis provides additional support for the tenability of the associations observed between PCB concentrations and hypertension in logistic regression analysis.

Acknowledgements

We thank Wayman Turner, Andreas Sjödin, Larry Needham, and Don Patterson (formerly) at the National Center for Environmental Health's Division of Laboratory Sciences, Center for Disease Control and Prevention, Atlanta, GA, for their expert analytical work on this study.

Anniston Environmental Health Research Consortium Steering Committee Members include Shirley Baker, community representative; Scott Bartell, UC Irvine; James Olson, University at Buffalo; Russell Foushee, Alan Percy, University of Alabama at Birmingham; David O. Carpenter, University at Albany; Jane Cash; Martha Lavender, Christie Shelton, Jacksonville State University; Howard Frumkin, University of Washington, Marian Pavuk, ATSDR/CDC; Paula Rosenbaum, Allen Silverstone, Ruth Weinstock, Upstate Medical University, Kirsten Moysich, Roswell Park Cancer Institute.

The present study was supported by a grant from the Agency for Toxic Substances and Disease Registry to Jacksonville State University, # 5U50TS473215. The contents of this publication are solely the responsibility of the authors and do not necessarily represent ATSDR's official views.

D.O.C. has served as an expert witness in legal cases in Anniston, Alabama with all payments going into research accounts at the University at Albany.

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