HEART DISEASE, LIPID PROFILES, AND ORTHO-SUBSTITUTED PCB CONGENERS IN RESIDENTS OF ANNISTON, ALABAMA

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Introduction

Coronary (ischemic) heart disease (CHD) affects more than 13 million Americans and while the mortality from CHD has declined in last three decades, it is still the second leading cause of death in developed countries.[1] High levels of cholesterol and low density lipoprotein (LDL) are potent risk factors for CHD with low levels of high density lipoprotein (HDL) and high triglycerides are also associated with higher risk of CHD.[1] The use of lipid lowering medications (LLM) by both those diagnosed with CHD or taken preventatively to control dislipidemia in those not yet diagnosed with CHD may obscure the associations between lipid levels and CHD, especially in cross-sectional studies. Whether levels of lipophilic organochlorine compounds may be affected by LLM has not been fully elucidated. [2] Mechanistic studies suggested potential effects on levels of serum cholesterol, blood pressure and heart weight, and observed cardiomyopathy and chronic active arteritis following exposure to the dioxin-like PCB 126 in laboratory animals. [3-4] Review of human studies that examined all cardiovascular and ischemic heart disease mortality found and elevated risk associated with elevation in levels of dioxin in the majority of studies with limited adjustment for the other major risk factors for cardiovascular disease.[5]

Our earlier investigations revealed the strong influence of anti-hypertensive medications on associations between high blood pressure and hypertension.[6-7] In the present study, we examined inter-relations between coronary heart disease, lipids, LLM, and PCB levels as a part of the evaluation of heart disease risk in the participants of Anniston Community Health Survey (ACHS) - a sample of African American and White residents of Anniston, Alabama, who were environmentally exposed to PCBs.

Materials and Methods

Anniston, Alabama, is a city of about 24,000 people where PCBs were manufactured from 1929 until 1971. With stratification by race and residential proximity to the plant, 1,110 randomly selected adults were interviewed. Of these, 765 had lipids and PCBs measured. An interviewer administered questionnaires provided information on demographics and health status. Medications use was verified by a nurse during home or office visit. About a quarter of the study population were taking LLM (n=187) including statins, other lipid lowering drugs, or a combination of lipid lowering drugs. CHD was defined as self-reported (ischemic/atherosclerotic) heart disease, myocardial infarction or congestive heart failure on the study questionnaire.

Analyses of 35 ortho-substituted PCBs were performed 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 published in detail elsewhere.[8] Values below the limit of detection (LOD)

were set to the LOD divided by the square root of 2. For this study, we selected four individual congeners to represent different groups of ortho-substituted PCB congeners: mono-ortho substituted dioxin-like PCB 118 (5-chlorinated), di-ortho substituted PCB 153 (6-chlorinated), tri-ortho substituted PCBs 196-203 (8-chlorinated), and tetra-ortho substituted PCB 209 (10-chlorinated). Serum total cholesterol, triglycerides, HDL, and LDL cholesterol were determined using automated enzymatic methods by the clinical chemistry laboratory at the Jacksonville Medical Center, Jacksonville, Alabama. Total serum lipids used to adjust organochlorine levels were calculated using the formula proposed by Phillips and updated by Bernert et al.[9] Multiple linear regression models of analyses of covariance were used to contrast lipid and PCB levels among individuals with and without prevalent CHD and stratified by taking LLM.. Models were adjusted for age, race, and body mass index (BMI), as well as for other major CHD risk factors such as gender, current smoking, exercise (at least 10 min of vigorous or moderate physical activity a week), and family history of heart disease.

Results and Discussion

Table 1 shows selected characteristics of the study population for those with and without prevalent CHD. Median age was 10 years higher in those with CHD (62 years vs 52 years). Median BMI, in spite of 10 year average age difference, was the same for both groups at 30 kg/m^2; the 75th and 90th percentiles were also similar at 36 kg/m^2 and 42 kg/m^2. Smoking (58% vs 53%) and family history of heart disease was more prevalent in those with CHD compared to those without (77% vs 61%, $p<0.001$, χ^2-test) and they exercised less (61% vs 58%; data not shown). In addition to 43.1% of those with CHD taking lipid lowering medication, 78.9% took anti-hypertensive medication and 29.4% were also on glycemic control medications. Corresponding proportions for those not diagnosed with CHD were 17.7%, 36.7%, and 13.9%, respectively (not shown in Table 1).

Table 1. Selected demographic characteristics of the study participants stratified by the use of lipid lowering medication.

	Coronary Heart Disease (CHD)	
Covariate	No (n=561)	Yes (n=204)
Age, years: Median (SD)	52.2 (16.1)	62.2 (12.7)
BMI (SD)	30.0 (7.8)	30.0 (7.5)
Gender, n (%): Male	164 (29.2)	64 (31.4)
Female	397 (70.8)	140 (68.6)
Race, n (%) Caucasian	272 (48.5)	81 (39.7)
African-American	289 (51.5)	123 (60.3)
Taking lipid lowering medication, n (%)	99 (17.7)	88 (43.1)

Lipid levels are shown in Table 2 by coronary heart disease status and further stratified by taking any lipid lowering medications. Contrary to the expected direction of association, cholesterol, and LDL were lower in those with CHD than in those without CHD after adjusting for age, BMI, and race. Higher triglycerides and lower HDL were associated with CHD in the expected direction. It is likely that due to a higher proportion of subjects taking LLM and possibly a more intensive treatment regiment in those with diagnosed CHD have resulted in lower levels of total cholesterol and LDL – primary targets of lipid lowering therapy. It is also possible that poor control of diabetes, underlying structural heart disease or symptoms have not yet been recognized or apparent among some of those without diagnosed CHD. Results in Table 2 further show that lipid lowering drugs may work well in lowering cholesterol and LDL (and total lipids). Substantial and significant

differences are thus apparent in both those with and without heart disease; i.e. those taking LLM have much lower levels of total lipid, cholesterol, and LDL.

Table 2. Adjusted geometric means for lipid fractions among ACHS participants.

Lipids (mg/l)	CHD		LLM		CHD			
					No		Yes	
	No (n=561)	Yes (n=204)	No (n=78)	Yes (n=187)	No LLM (n=462)	Any LLM (n=99)	No LLM (n=116)	Any LLM (n=88)
Total lipid	617	612	627	585*	622	580*	639	599
Total cholesterol	189	178*	193	167*	192	170*	192	166*
Triglycerides	112	125*	112	125*	108	114	122	144
LDL	114	101*	117	92*	118	94*	114	90*
HDL	46	43*	46	43*	46	45	45	40*

*Statistically significant at alpha=0.05. LLM – taking lipid lowering medication. Adjusted for age, race, and BMI.

Table 3 presents levels of PCBs118, 153, 196-203, and 209 by CHD status and stratified by taking LLM. Levels of four ortho-substituted PCB congeners were similar by CHD status when adjusted for age, BMI, and race. In contrast to lipids, taking LLM was not associated with substantially lower PCBs levels. Additional adjustment for CHD risk factors did not explain materially more variation in PCB levels but indicated that family history of heart disease was statistically significantly associated with all four PCBs, smoking with all but 153, gender with PCBs 118 and 196, and LDL and taking glycemic medication with PCB 118. No clear pattern emerged that would differentiate among the mono-orhto, di-orhto, or higher ortho substituted PCB congeners in association with CDH. In the analysis stratified by CHD and the LLM status, levels of PCBs were higher in those with CHD due to higher median age and no age adjustment between the CHD strata.

Although this study includes extensive data on individual congener-specific PCB serum measures, medication use, lipid measurements, and CHD diagnosis, its interpretation is somewhat limited by the cross-sectional design. In particular, the causal sequence of events relating PCB exposure, lipid production, LLM use, and CHD is complex and uncertain. Future studies should consider longitudinal study designs and statistical methods that accommodate multiple variables on the causal pathway, such as structural equation models.

In summary, no difference in PCB congener levels was observed between those with or without coronary heart disease. Taking lipid lowering medications was strongly associated with lipid levels (total cholesterol and LDL) but it was not associated with the adjusted geometric means of the four ortho-substituted PCBs. Inter-relation between multiple medications taken by a high proportion of participants, lipids, and organochlorine levels illustrate that detailed information on coronary heart disease risk factors is needed in evaluations of complex associations between cardiovascular health effects and environmental exposures in ageing populations.

Table 3. Ortho-substituted PCB congeners and PCB levels in participants of ACHS stratified by CHD status and adjusted for risk factors of CHD.

					CHD			
	CHD[1]		LLM[1]		No[2]		Yes[2]	
Organochlorines (ng/g lipid)	No (n=561)	Yes (n=204)	No (n=578)	Yes (n=187)	No LLM (n=462)	Any LLM (n=99)	No LLM (n=116)	Any LLM (n=88)
PCB 118	24.0	22.8	23.4	24.5	21.7	20.2	32.8	32.2
PCB 153	97.0	98.7	97.8	96.2	89.0	76.4	137	135
PCB 196-203	16.2	16.7	16.3	16.5	14.3	13.3	25.7	25.4
PCB 209	13.1	13.7	13.1	13.6	11.1	10.7	22.8	22.6

[1] Adjusted for age, BMI, and race. [2]Adjuted for age, BMI, race, gender, smoking, physical activity, family history of heart disease, LDL, HDL, taking glycemic medication, and taking anti-hypertensive medication. None of the differences were significant at alpha=0.05.

Acknowledgements

Members of the Anniston Environmental Health Research Consortium Steering Committee include S. Baker, community representative; S. Bartell, University of California–Irvine; D.O. Carpenter, University at Albany; J. Cash; A. Percy, University of Alabama–Birmingham; H. Frumkin, University of Washington; M. Lavender, Center for Domestic Preparedness; K. Moysich, Roswell Park Cancer Institute; J. Olson, University at Buffalo; M. Pavuk, Agency for Toxic Substances and Disease Registry/Centers for Disease Control and Prevention; P. Rosenbaum, A. Silverstone, and R. Weinstock, State University of New York Upstate Medical University; and C. Shelton, Jacksonville State University. We thank W. Turner, L. Needham, and D. Patterson (formerly) of the Centers for Disease Control and Prevention's Division of Laboratory Sciences within the National Center for Environmental Health for their expert analyses of polychlorinated biphenyls and chlorinated pesticides. This work was supported by Agency for Toxic Substances and Disease Registry grant 5U50TS473215 to Jacksonville State University and by the Institute for Health and the Environment of the University at Albany. The contents of this publication are solely the responsibility of the authors and do not necessarily represent Agency for Toxic Substances and Disease Registry's official views.

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