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# Metabolic syndrome is associated with exposure to organochlorine pesticides in Anniston, AL, United States☆

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## Abstract

The Anniston Community Health Survey, a cross-sectional study, was undertaken in 2005–2007 to study environmental exposure to polychlorinated biphenyl (PCB) and organochlorine (OC) pesticides and health outcomes among residents of Anniston, AL, United States. The examination of potential risks between these pollutants and metabolic syndrome, a cluster of cardiovascular risk factors (i.e., hypertension, central obesity, dyslipidemia and dysglycemia) was the focus of this analysis. Participants were 548 adults who completed the survey and a clinic visit, were free of diabetes, and had a serum sample for clinical laboratory parameters as well as PCB and OC pesticide concentrations. Associations between summed concentrations of 35 PCB congeners and 9 individual pesticides and metabolic syndrome were examined using generalized linear modeling and logistic regression; odds ratios (OR) and 95% confidence intervals (CI) are reported. Pollutants were evaluated as quintiles and as log transformations of continuous serum concentrations. Participants were mostly female (68%) with a mean age (SD) of 53.6 (16.2) years. The racial distribution was 56% white and 44% African American; 49% met the criteria for metabolic syndrome. In unadjusted logistic regression, statistically significant and positive associations across the majority of quintiles were noted for seven individually modeled pesticides

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(*p,p′*-DDT, *p,p′*-DDE, HCB, *β*-HCCH, oxychlor, tNONA, Mirex). Following adjustment for covariables (i.e., age, sex, race, education, marital status, current smoking, alcohol consumption, positive family history of diabetes or cardiovascular disease, liver disease, BMI), significant elevations in risk were noted for *p,p′*-DDT across multiple quintiles (range of ORs 1.61 to 2.36), for tNONA (range of ORs 1.62–2.80) and for *p,p′*-DDE [OR (95% CI)] of 2.73 (1.09–6.88) in the highest quintile relative to the first. Significant trends were observed in adjusted logistic models for $\log_{10}$ HCB [OR = 6.15 (1.66–22.88)], $\log_{10}$ oxychlor [OR = 2.09 (1.07–4.07)] and $\log_{10}$ tNONA [3.19 (1.45–7.00)]. Summed PCB concentrations were significantly and positively associated with metabolic syndrome only in unadjusted models; adjustment resulted in attenuation of the ORs in both the quintile and log-transformed models. In conclusion, several OC pesticides were found to have significant associations with metabolic syndrome in the Anniston study population while no association was observed for PCBs.

**Keywords**

Metabolic syndrome; Polychlorinated biphenyls; Organochlorine pesticides and herbicides; Insulin resistance; Obesity

## 1. Introduction

Metabolic Syndrome is a cluster of cardiovascular disease risk factors which include central obesity, hypertension, dyslipidemia and dysglycemia (Third Report of National Cholesterol Education Program (NCEP) Expert Panel, 2002; Grundy et al., 2006). Individuals with metabolic syndrome have a greater risk of development of cardiovascular diseases and type 2 diabetes, which in turn are associated with increased morbidity and mortality (Grundy, 2008). Other obesity-related conditions, such as fatty liver disease, chronic kidney disease, polycystic ovarian syndrome, sleep disorders and hyperuricemia/gout are also more common with metabolic syndrome. The age-adjusted prevalence of metabolic syndrome in the United States rose from 24.1% in the late 1980s – mid 1990s to 27.0% in the 1999–2000 NHANES data (Ford et al., 2004). Since 2005, the prevalence of metabolic syndrome declined somewhat in the United States, with an age-adjusted prevalence of 22.9% observed in the 2009–2010 NHANES survey (Beltran-Sanchez et al., 2013). The estimated prevalence of metabolic syndrome in Europe and Asia has also been in the range of 20% to 30% of the adult population (Grundy, 2008). The rates of metabolic syndrome among adolescents, particularly among those who are very obese [body mass index (BMI) ≥ 95th percentile] are high; it is estimated that 19–35% of youth in this BMI category have metabolic syndrome (Weiss et al., 2004; Laurson et al., 2014).

Known risk factors for metabolic syndrome include age, obesity, diet, dietary patterns across life stages, and lack of exercise with variation in the prevalence observed across gender and ethnic groups (Park et al., 2003; Josse et al., 2008; Otsuka et al., 2010; Li et al., 2011; Beltran-Sanchez et al., 2013). Current smoking has been associated with the presence of insulin resistance, diabetes and metabolic syndrome (Facchini et al., 1992; Will et al., 2001; Park et al., 2003; Weitzman et al., 2005) whereas alcohol consumption appears to be protective to some extent (Liu et al., 2008). Organochlorine pollutants such as PCBs and

pesticides have been associated with weight change (Lind et al., 2013), obesity, insulin resistance and diabetes (Lee et al., 2006; Lee et al., 2011; Dirinck et al., 2011). Of interest is whether these compounds also play a role in the development of metabolic syndrome. Analyses of NHANES data from 1999 to 2002 found positive associations with individual pesticides and dioxin-like PCBs and metabolic syndrome (Lee et al., 2007). Similar findings were observed in data from a cross-sectional study of the Japanese general population; in that study positive associations were noted between toxic equivalents (TEQ) of dioxin-like PCBs and metabolic syndrome (Uemura et al., 2009). Polychlorinated dibenzo-p-dioxins and polychlorinated dibenzo-furans also were linked to metabolic syndrome in a cross-sectional Taiwanese study (Chang et al., 2010). Associations between organochlorine compounds and metabolic syndrome were observed in a case-control study in Uljin County Korea (Park et al., 2010) and in a second case-control study (nested) from the same community-based cohort (Lee et al., 2014b). Increased organochlorine pesticide levels also have been observed in participants with metabolic syndrome in a small clinical study in India (Tomar et al., 2013).

Organochlorine (OC) pesticides/herbicides were used extensively in the United States to control agricultural pests, termites, ants and vector-borne diseases as well as for industrial uses. Alabama, a state with a long history of agriculture (e.g., cotton, soybeans, peanuts and corn) as well as the production of livestock and poultry, is no exception (http://www.nass.usda.gov/Statistics_by_State/Alabama/). While OC pesticides and herbicides are no longer manufactured or used in the United States, volatilization from previously contaminated soils is thought to be a continuing emission source especially from farming areas with heavy prior pesticide use (Bidleman and Leone, 2004). Moreover, new emission sources from countries still using DDT, primarily for vector control add to the “long-range transboundary transport” observed as air masses move across and within North America (Harner et al., 1999; Jantunen et al., 2000; Harner et al., 2001). Ingestion of food remains a large source of pesticide and herbicide exposure among residents of the United States (USDA Jan 2016, https://www.ams.usda.gov/sites/default/files/media/2014%20PDP%20Annual%20Summary.pdf).

In addition to pesticide/herbicide exposure from agricultural activities, Anniston, AL was the site of the largest PCB production facility in North America from 1929 to 1971, exposing many of the residents to PCB-containing waste through contamination of sediments, soil, water, food products and air (ATSDR, 2000; organochlorine pesticides have never been produced at the PCB production facility) (Schecter et al., 2001; Pavuk et al., 2014b). Previous analyses from the Anniston Community Health Survey demonstrated an association between PCB levels and diabetes, particularly in women and individuals < 55 years of age (Silverstone et al., 2012). Other analyses from Anniston residents also noted associations between PCB concentrations and blood pressure measurements, and lipid profiles (Goncharov et al., 2011; Aminov et al., 2013, respectively), two components of metabolic syndrome. In the current study we examine possible associations between PCB and OC pesticide levels with metabolic syndrome in adults *without* diabetes in the Anniston cohort to better understand the relationship between exposure to these pollutants and metabolic syndrome, a “precursor of cardiovascular disease and type 2 diabetes mellitus” (Wilson et al., 2005).

## 2. Methods

### 2.1. Study population and data collection

The Anniston Community Health Survey, a cross-sectional study conducted in 2005 through 2007, examined serum PCB and pesticide concentrations and health outcomes among residents of Anniston, Alabama. As described in previous analyses of data from this cohort (Silverstone et al., 2012; Pavuk et al., 2014a), contact was made with residents of 1823 of 3320 targeted households randomly selected from a commercial list of all residential sites within the city limits. An adult over 18 years of age was then randomly selected for completion of the 45 page survey in the 1110 of 1823 households (61%) who consented to participate in the study. The survey was administered in participants' homes and included demographic information, health behaviors, medical and family history data as well as occupational histories and duration of residence in Anniston. A majority (774/1110) of participants volunteered for an 8 h fasting blood draw for analysis of glucose, insulin, lipids as well as PCB and OC pesticide/herbicide levels as previously described (Silverstone et al., 2012). Measurements of height, weight, waist circumference and blood pressure were taken by a study nurse using a standard protocol at the time of the blood draw; participants' current medications also were reviewed with the nurse. Eligible participants totaled $n = 548$ in these analyses. All participants provided written informed consent, with overall study approval granted by the University of Alabama at Birmingham's Institutional Review Board.

### 2.2. PCBs, pesticide concentrations and total lipids

Measured persistent organic pollutants (POPs) included 33 individual PCB congeners, two pairs of co-eluting PCB congeners and 9 pesticides. All compounds were analyzed at the Division of Laboratory Sciences at the Centers for Disease Control and Prevention's (CDC) National Center for Environmental Health laboratory (Silverstone et al., 2012). The PCB congeners and pesticides were measured in serum using high-resolution gas chromatography/ isotope-dilution high-resolution mass spectrometry (HRGC/ID-HRMS) (Sjödin et al., 2004; Pavuk et al., 2014a). The 35 PCB congeners examined in the Anniston study included numbers 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. Total concentrations of the 35 PCB congeners in ng/g wet weight (ppb) were summed (Σ35PCBs); values below the detection limit were substituted with the congener-specific limits of detection (LOD) divided by the square root of 2 prior to summation (Hornung and Reed, 1990). The following individual PCB congeners also were evaluated: numbers 28, 66, 74, 99, 118, 156, 170, 187, 194, 206 and 209. These congeners were selected as they represent both historical and current toxicity groupings defined by structure and activity (Warner et al., 2012; Pavuk et al., 2014b). The OC pesticides under study included hexachlorobenzene (HCB), $\beta$-hexachlorocyclohexane ($\beta$-HCCH), $\gamma$-HCCH, oxychlordane (oxychlor), trans-nonachlor (tNONA), Mirex, and three dichlorodiphenyltrichloro ethanes ($p,p'$-DDE, $p,p'$-DDT, $o,p'$-DDT). Each pesticide was evaluated individually and is reported in pg/g wet weight (parts per trillion (ppt)). Values of OC pesticides below the detection limit were substituted with the pesticide-specific LOD divided by the square root of 2. Serum total lipids were calculated with the enzymatic

summation method using triglyceride and total cholesterol values obtained from the lipid panel (Bernert et al., 2007).

### 2.3. Insulin concentrations and homeostatic model assessment (HOMA)

Insulin concentrations were measured at the Northwest Lipid Metabolism and Diabetes Research Labs at the University of Washington using a two site immune-enzymometric assay run on a TOSOH 2000 autoanalyzer (http://www.diagnostics.us.tosohbioscience.com/analyzers/aia-2000); calibration specifics were based on the World Health Organization's international reference preparation (IRP) 66/304 maintained by National Institute for Biological Standards and Control in the United Kingdom (http://www.who.int/bloodproducts/catalogue/EndoMay2011.pdf). The sensitivity level of the assay is 0.5 uU/mL with an upper range on the standard curve of 330 uU/mL. The reference limit for fasting insulin levels among healthy individuals at this laboratory is < 17.0 uU/mL (Personal communication, S Marcovina, August 2015). Insulin resistance was calculated using fasting plasma glucose and insulin concentrations (HOMA method) as described by Matthews et al., 1985 and Wallace et al., 2004. Higher HOMA levels are consistent with greater insulin resistance, with a value of 2.6 corresponding to the 75th percentile, the cutoff point in defining insulin resistance (Ascaso et al., 2003).

### 2.4. Metabolic syndrome definition

The National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) criteria were used to define metabolic syndrome (Third Report of National Cholesterol Education Program (NCEP) Expert Panel, 2002; Grundy et al., 2004, 2006). Individuals with three or more of the following factors were categorized as having metabolic syndrome: 1. Waist circumference of > 102 cm in men or > 88 cm in women; 2. Triglyceride levels of ≥150 mg/dL or lipid-lowering medication; 3. High density lipoprotein (HDL) cholesterol < 40 mg/dL in men or < 50 mg/dL in women; 4. Systolic blood pressure ≥ 130 or diastolic blood pressure ≥ 85 mm Hg or medication for hypertension; 5. Fasting glucose ≥100 mg/dL. Individuals with self-reported physician diagnosed diabetes, glycemic control medication or a fasting glucose value > 125 mg/dL secondary to diabetes were excluded from the current analysis; consequently participants meeting the 5th criterion were considered to have prediabetes with fasting glucose values between 100 and 125 mg/dL (Grundy et al., 2006).

### 2.5. Covariable descriptions

Potential covariables and confounders were selected based on the literature and preliminary analyses, and included demographics, medical histories, clinical and behavioral factors with known or possible associations with PCBs, OC pesticides and/or metabolic syndrome. Demographic factors of interest were age (in years), race/ethnicity (white/nonwhite), sex (female/male), marital status (not married/ spouse-partner) and education (interval variable, ranging from elementary school to college graduate). With the exception of four Native Americans, all nonwhites were African American in the Anniston study population. Income was not included as a covariate due to the high prevalence of missing data among study participants (28%).

A family history (first and second degree blood relatives) of diabetes (no/yes) or of heart disease (no/yes), and participant liver disease (no/ yes) also were included in the analyses. Targeted behavioral factors were current smoking (no/yes) and alcohol consumption (non-drinker/ light-moderate/heavy or binge). The alcohol variable was based on a combination of amount and frequency of consumption by gender as defined the National Institute on Alcohol Abuse and Alcoholism and included 3 categories, non-drinker/moderate drinker/ heavy or binge drinker (http://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/moderate-binge-drinking). Body mass index (BMI) in $kg/m^2$ and total lipids (mg/dL) also were potential variables, the latter as a covariable in models with wet weight OC pollutants. The referent for no/yes categorical covariates was no; for other categorical variables, the referent is listed first in the descriptions above. Missing data for covariables ranged from none to 3%, reducing the sample size to $n = 498$ in the fully adjusted logistic regression models outlined below.

### 2.6. Statistical analyses

Descriptive analyses included the calculations of means, standard deviations, medians and ranges for continuous variables and frequencies for categorical variables. Demographics, behavioral factors, clinical characteristics and pesticide/PCB levels of participants with and without metabolic syndrome were compared using Pearson's chisquare test or independent *t*-tests as were potential associations among the independent variables. Correlations between pesticide/PCB levels and total lipids and continuous BMI values were evaluated using Pearson's correlation coefficient. Age-adjusted geometric means (GM) and 95% confidence intervals (CI) were calculated for the Σ35PCBs variable and for each of the pesticides. These analyses were undertaken for the total group ($n = 548$) and also across categories of metabolic syndrome status; age-adjusted race and gender comparisons were assessed using generalized linear modeling.

Possible associations of organochlorine pollutants and metabolic syndrome were assessed using unconditional logistic regression modeling. Odds ratios (OR) and 95% CI were reported for both unadjusted and adjusted parameter estimates. The Σ35PCBs variable was divided into quintiles, with the first quintile serving as the referent category. Quintile category limits were based on values from the entire participant group with PCB measurements ($n = 765$). A $\log_{10}$ transformed version of the summed PCB variable also was employed to assess linear trends and to evaluate possible effect modification by gender or race on a Σ35PCBs - metabolic syndrome association. Analyses with the individual PCB congeners (i.e., 28, 66, 74, 99, 118, 156, 170, 187, 194, 206 and 209) were undertaken using $\log_{10}$ transformed versions of the wet weight substituted congeners as was an analysis looking at the sum of dioxin-like PCBs (congeners 105, 118, 156, 157, 167 and 189).

To examine possible associations between OC pesticides and metabolic syndrome, wet weight concentrations (in ppt) of the nine pesticides were modeled individually. As with the summed PCB variable, HCB, β-HCCH, oxychlor, tNONA, *p,p′*-DDE, *p,p′*-DDT, and Mirex were divided into quintiles based on values for the entire subset of participants with pesticide-specific measurements ($n = 765$); the first quintile served as the referent category. Two pesticides, γ-HCCH and *o,p′*-DDT, were treated as dichotomous variables (non-detects

versus detectable) as > 50% of values were below the detection limit. To assess trend and evaluate possible effect modification by gender or race, $\log_{10}$ transformations of each pesticide were computed and models fitted employing the covariables outlined above.

The first step in modeling possible associations between wet weight PCBs, OC pesticides and metabolic syndrome was to fit bivariable models of each pollutant with the dichotomous metabolic syndrome outcome. Age was then forced into each model followed by other demographic factors of interest. Variables representing personal behaviors, clinical characteristics and family history variables also were forced into the models in subsequent steps. BMI and total lipids were added in separate steps, in that order, to individual POP models to gain a better understanding of potential confounding/over-adjustment of the pollutant effect estimate. Models also were fitted using backward stepwise elimination and the likelihood ratio statistic, with a $p$ for removal of 0.15. Final models were constructed using forced entry of all covariables and confounders based on both preliminary analyses and the literature. Covariables included in the final models were age, sex, race, current smoker, marital status, education, alcohol consumption pattern/frequency, family history of diabetes, family history of heart disease, personal history of liver disease and BMI. Identical final adjusted models also were run using wet weight OC serum levels of PCBs and pesticides, all listed covariables plus total lipids. To allow for further comparison to the wet weight results, models using lipid-standardized POPs rather than wet weight serum levels also were fitted using the covariables listed above, but with and without BMI. Extensive modeling using both wet weight and lipid standardized POP measurements was undertaken since triglycerides, a component of the lipid compartment are part of the definition of metabolic syndrome; lipids are likely on the causal pathway between POPS and metabolic syndrome and statistical control would bias effect estimates. BMI was retained in all final models since it is a proxy for fat mass, a major storage compartment for lipophilic pollutants. Loss of weight often results in higher serum levels of organochlorine compounds (Kim et al., 2011; Lim et al., 2010; Lind et al., 2013); consequently, BMI was treated as a confounder of possible POP and metabolic syndrome associations. The same set of covariables was used in each of the individual pesticide and PCB congener models as well as in the Σ35PCBs model.

Analyses stratified by gender and by race were undertaken as geometric mean values of PCBs and some pesticides differed across these demographic factors in previous analyses of this cohort (Silverstone et al., 2012). Moreover, women have a different body fat distribution than men as well as hormonal regulation of body weight which is further influenced by estrogen decline with menopause (Pradhan, 2014). Effect modification by gender or race was evaluated using a backward stepwise procedure in which the interaction term was assessed in the full model using the likelihood ratio statistic and a $p$ value of $\leq 0.05$. Statistical Package for the Social Sciences (SPSS) version 22 was used for all analyses (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY).

## 3. Results

Demographic and clinical characteristics of study participants are summarized in Tables 1 and 2. The majority were female (68%), white (56%) and not married (52%), with a mean

BMI of 30.2 kg/m$^2$ (range of 16–64). The mean age (standard deviation) of participants was 53.6 (16.2) years; individuals with metabolic syndrome were observed to be significantly older than those without, 58.2 years versus 49.1 years and more likely to have a BMI ≥ 30 kg/m$^2$. While the majority of participants were non-smokers (67%) and non-drinkers (69%), these behaviors were reported more frequently among participants *without* metabolic syndrome than among those with the constellation of clinical factors ($p < 0.05$).

Overall, metabolic syndrome was found in 452/753 (60%) of the Anniston study cohort including 176/205 (86%) individuals with diabetes. These analyses focus on those without diabetes ($n = 548$) of whom 271 (49%) were found to have metabolic syndrome. Table 2 shows the prevalence of the components of metabolic syndrome (hypertension, increased waist circumference, low HDL levels, high triglycerides or glucose levels in the prediabetes range) in participants with and without metabolic syndrome; all components were more frequent in those who met the definition of metabolic syndrome. Mean total lipid levels also were significantly higher in those with metabolic syndrome. HOMA, a measure of insulin resistance, significantly differed between those with and without metabolic syndrome, and was consistent with greater insulin resistance among those *with* the syndrome (Table 2).

Correlations between total lipids (mg/dL) and the seven OC pesticides (pg/g wet weight) with > 50% of values above the limits of detection ranged from 0.09 for Mirex to 0.246 for oxychlor; the correlation between total lipids and the summed PCB variable (ng/g wet weight) was 0.078. All were significant at the $p < 0.05$ level. Significant correlations were noted between BMI (kg/m$^2$) and three OC pesticides only; coefficient values were 0.137 for *p,p′*-DDT, −0.134 for oxychlor and −0.129 for tNONA. The Pearson's correlation coefficient between total lipids and BMI was 0.063 ($p = 0.08$).

Significantly higher age-adjusted geometric mean levels of HCB, β-HCCH, tNONA and *p,p′*-DDT were observed in participants with metabolic syndrome while Mirex geometric means were significantly lower in those with metabolic syndrome (see Tables 3a & 3b). Age-adjusted geometric means for oxychlor, *p,p′*-DDE, γ-HCCH (not shown) or *o,p′*-DDT (not shown) did not differ by metabolic syndrome category, nor were significant differences in geometric means observed across metabolic syndrome categories for the Σ35PCBs. Significant age-adjusted sex differences were observed for several of these compounds; females had higher levels of HCB, β-HCCH, oxychlor, and *p,p′*-DDE than males, whereas males had higher levels of Mirex. Age-adjusted racial and ethnic differences also were observed; nonwhites had significantly higher levels of Σ35PCBs, HCB, *p,p′*-DDE, *p,p′*-DDT, Mirex and γ-HCCH than whites. The geometric mean pesticide levels in the Anniston population were higher than those observed in the general U.S. adult population in 2003–2004 (see Table 4). Although not shown in tabular form, residents with less education, those who were not married, those with a history of farm work, or who had a garden or ate local produce generally had higher pesticide levels than those in the complementary categories for each of these variables.

In logistic regression modeling evaluating Σ35PCBs and metabolic syndrome, the unadjusted OR were significantly elevated in quintiles 2, 4 and 5; however, after adjustment for covariables including BMI, the observed effects were greatly attenuated, with none

remaining significant (see Table 5). Associations between the $\log_{10}$ transformed sum of the dioxin-like PCBs, a subgroup of non-dioxin-like congeners as well as the continuous individual PCB congeners (also $\log_{10}$ transformed) and metabolic syndrome exhibited a similar pattern, with significantly elevated ORs in bivariable models and attenuation of risk following covariable adjustment. As shown in the last column of Table 5, the addition of total lipids as a continuous variable (mg/dL) to all adjusted PCB models resulted in further attenuation or reversal of the effect estimates.

Results from logistic regression modeling of the OC pesticide levels and metabolic syndrome are shown in Table 6. Positive and significant associations between seven pesticides (*p,p′*-DDT, *p,p′*-DDE, HCB, β-HC-CH, oxychlor, tNONA, Mirex) and metabolic syndrome were observed across the majority of quintiles in each of the unadjusted models. Two dichotomous pesticides (*o,p′*-DDT and γ-HCCH) were observed to have non-significant inverse associations with metabolic syndrome in both the unadjusted and adjusted models. Following covariable adjustment, but without the addition of total lipids, the ORs for quintiles 2 through 4 of *p,p′*-DDT remained elevated while the quintile 5 odds ratio was greatly attenuated (Table 6). The ORs ranged from 1.61 to 2.36 with a non-significant trend ($p = 0.125$). The ORs in the adjusted model for tNONA were observed to be significantly elevated in quintiles 3 through 5, and ranged from 1.62 to 2.80. For *p,p′*-DDE, only the highest quintile remained significantly elevated in the multivariable model; that adjusted OR (95% CI) was 2.73 (1.09–6.88). Odds ratios for HCB remained elevated in all quintiles following adjustment, however significance was observed only in the highest quintile. Of note, the $\log_{10}$ HCB adjusted model was consistent with a significant upward trend in metabolic syndrome risk; that OR (95% CI) was 6.15 (1.66–22.88). In the adjusted quintile models for β-HCCH and oxychlor, the ORs were mostly elevated and increased with increasing quintile category; all confidence intervals included the null value however. Trends were more apparent in the adjusted $\log_{10}$ models for some of the pesticides; as shown in Table 6, significantly elevated odds ratios were observed for $\log_{10}$ oxychlor [OR of 2.09 (95% CI of 1.07–4.07)] and for $\log_{10}$ tNONA [OR of 3.19 (95% CI of 1.45–7.00)]. A similar but slightly weaker pattern (OR of 1.92, $p = 0.056$) was observed in the $\log_{10}$ β-HCCH model. Odds ratios for Mirex hovered near 1.0 or were reversed with the addition of covariables; this pattern was similar in both the adjusted quintile and $\log_{10}$ Mirex models. As shown in the last column of Table 6, the ORs for both the quintile and $\log_{10}$ models for all pesticides were further attenuated with the addition of total lipids as a continuous variable (mg/dL) to the wet weight adjusted models which included BMI. All ORs were non-significant, with the exception of quintile 2 for *p,p′*-DDT; that OR (95% CI) was 2.28 (1.13–4.59). As shown in Supplemental Table 1, the effect estimates from the final adjusted wet weight models with BMI and total lipids were similar to the lipid standardized models with identical covariables including BMI.

Effect modification by gender of several individual pesticide- and the Σ35PCBs-metabolic syndrome associations was observed, with females found to have higher risks of metabolic syndrome than males (Table 7). Significant interaction terms were observed in the total group models between sex and $Log_{10}$Σ35PCBs, $Log_{10}$β-HCCH, $Log_{10}$ Oxychlor and $Log_{10}$Mirex; the *p* value for the interaction term in the $Log_{10}$ *p,p′*-DDT was $p = 0.086$. In each of these adjusted sex-stratified analyses, the ORs for females were higher than for

males, but only significantly so for oxychlor. Although effect modification by gender was not observed for HCB and tNONA, significantly elevated ORs were observed among females for both these compounds (Table 7); in these stratified adjusted models, effect estimates for males also were elevated for HCB and tNONA, but the confidence intervals included 1.0.

None of the interaction terms for race and individual $\log_{10}$ pesticides or $\log_{10}\Sigma$35PCBs was significant (see Table 7). Nonetheless, nonwhites with exposure to *p,p′*-DDE, HCB and tNONA were observed to have significantly elevated risks of metabolic syndrome in each of these adjusted models. Odds ratios in the corresponding models for whites for HCB and tNONA also were elevated but included the null value. The OR associated with *p,p′*-DDE in whites was 0.99, and also consistent with no effect.

## 4. Discussion

Metabolic syndrome was found to be highly prevalent in this cohort of Anniston residents as were the individual components of this syndrome. People with the metabolic syndrome are at particularly high risk for the development of diabetes and cardiovascular disease and increased morbidity and mortality. Variability in POP levels across gender and racial groups was observed as were differing effects of specific compounds on metabolic syndrome risk.

Significant and positive associations with metabolic syndrome were observed in the Anniston study across one or more quintiles of exposure for *p,p′*-DDT quintile (Q 2–4), *p,p′*-DDE (Q 5), tNONA (Q3–5) and HCB (Q 4–5) following adjustment for standard risk factors, including demographics. Significant trends were observed in adjusted $\log_{10}$ oxychlor, tNONA, HCB and *β*-HCCH models ($p = 0.056$ in the latter) as well. Park et al. (2010) found a positive association between *β*-HCCH and metabolic syndrome in their case-control study; ORs (95% CI) across tertiles 2 and 3 of the compound were 3.2 (1.0–10.3) and 4.4 (1.4–13.5) in a model adjusted for age, sex, alcohol and smoking. The ORs were greatly attenuated when BMI was added to that model and consistent with the effect estimates observed in the Anniston population. Our findings for HCB are similar to those reported by Lee et al., 2007 for NHANES data with significant increases in higher quintile categories as well as for trend, a finding also reported by Tomar and colleagues in 2013. HCB was the only pesticide in the Anniston study in which the geometric mean value (0.058 ng/g whole weight) was below that of the NHANES geometric mean 2003–2004 HCB value (0.097 ng/ g whole weight) (see Table 4, http://www.cdc.gov/exposurereport/pdf/fourthreport.pdf). The observed associations for oxychlor and tNONA and metabolic syndrome were stronger in our study than those noted by Lee et al., 2007, as was the finding for *p,p′*-DDE. The geometric mean values for these pesticides in Anniston residents were between 20% and 100% higher than the background levels for the U.S. population as reported in NHANES 2003–2004 (Table 4). The increased risk of metabolic syndrome associated with *p,p′*-DDT in Anniston residents was consistent with a non-monotonic increase which declined in the highest exposure quintile, and demonstrated a non-significant *p* for trend. Although the 90th percentile value for Mirex was about 3 times higher in Anniston residents than in NHANES data, adjusted Mirex quintile ORs were all < 1.0 and consistent with no association with metabolic syndrome. Although individual pesticide

associations with metabolic syndrome were not reported in the nested case-control study of Lee et al., 2014b, a model including the sum of β-HCCH, HCB, oxychlor and heptachlor epoxide demonstrated a significantly elevated risk of metabolic syndrome for individuals with exposures in the 3rd and 4th quartiles; those ORs (95% CI) were 3.2 (1.1–9.1) and 3.1 (1.1–8.8) with a $p$ of 0.043.

Although PCBs were associated with diabetes in Anniston residents (Silverstone et al., 2012), no relationship with metabolic syndrome was observed for the Σ35 PCB variable, the Σdioxin-like PCBs or the subset of individual congeners after control for demographics, lifestyle factors (smoking and alcohol consumption) and family histories of heart disease and diabetes, even though all unadjusted odds ratios demonstrated positive and significant PCB effects. Our findings are in contrast to those from an analysis of 1999–2002 NHANES data in which dioxin-like PCBs (congeners 74, 118, 126) showed positive and significant associations with metabolic syndrome (Lee et al., 2007). Congener 126, the most active dioxin-like PCB was not measured in the Anniston cohort which may account for some of the inconsistencies in findings across studies. In the same analysis by Lee and colleagues, non-dioxin like PCBs (congeners 138, 153, 170, 180, 187) demonstrated significant inverted U relationships across quartiles with metabolic syndrome, also not observed in this analysis of Anniston residents. As in our study, individuals with diabetes were not included in the NHANES analyses so would not account for the differences observed. As noted by Lee et al. (2014a), the shape of the dose response curve is likely related to the concentration levels of a pollutant in a particular population as well as the age of that population. More highly exposed groups such as Anniston residents may not have an obvious gradient of exposure, resulting in a flatter curve overall when compared to the lower background levels observed in the general population. An inverted U shaped association was observed across quartiles of the 15 summed PCB congeners and metabolic syndrome in the nested case-control study of Lee et al., 2014b, with significance observed for quartile 3. Individuals with diabetes were included as part of the metabolic syndrome definition in this study although the actual numbers were not explicitly provided. Positive associations across quartiles of dioxin-like PCB toxic equivalents and metabolic syndrome also were observed in a cross-sectional study of the Japanese general population (Uemura et al., 2009).

Positive associations between PCBs, summed pesticides and individual components of metabolic syndrome, elevated blood pressure and triglycerides, were reported in the Anniston cohort (Goncharov et al., 2011; Aminov et al., 2013). In contrast to metabolic syndrome findings, no associations between chlorinated pesticides and blood pressure were observed (Goncharov et al., 2011). However, the analyses of elevated blood pressure and triglycerides were limited to subjects who were not taking anti-hypertensive medications or lipid lowering drugs. As these medications comprise part of the definition of metabolic syndrome, any participant taking hypertensive medications or lipid lowering drugs (but without diabetes) remained in the final analyses of OC pollutants and metabolic syndrome; these differences may partly explain the inconsistencies observed with PCBs and metabolic syndrome in this analysis.

The mechanisms by which OC pesticides and PCBs influence the development of metabolic syndrome are not well understood. Evidence suggests that obesity, insulin resistance and

endothelial cell damage leading to atherosclerosis are related to adipose tissue dysfunction and ensuing low level inflammation (Lyon and Hsueh, 2003; Shoelson et al., 2006; Howell and Mangum, 2011; Kim et al., 2012; Chang et al., 2014; Dalmas et al., 2014; Fabrizi et al., 2014; Lee et al., 2014a). Increases in levels of pro-inflammatory mediators such as interleukin-6, tumor necrosis factor-alpha and the adipokines, resistin and leptin, are thought to lead to this subacute inflammatory state (Shoelson et al., 2006). Changes in the targeting of genes specific to inflammatory pathways, changes in fatty acid uptake and cytokine levels in adipose tissue following exposure to PCBs and OC pesticides have been observed in both in vitro and animal studies (Wang et al., 2010; Howell and Mangum, 2011; Kim et al., 2012); these results support the view that OC compounds may play a role in adipose tissue dysfunction and the subsequent cascade of observed metabolic abnormalities.

Fat is the major storage compartment in the body for POPs and obesity is a major feature of the metabolic syndrome. With weight loss, overall body burden of POPs has been shown to decrease likely due to redistribution of pollutants to other body compartments, including serum, which may lead to greater availability for elimination (Kim et al., 2011). These findings are consistent with higher serum levels of POPs observed in individuals with long term weight loss or lower BMIs, compared to those with long term weight gain or those with higher BMIs (Lim et al., 2010; Dirinck et al., 2011). It also has been observed that variation in the number of chlorines in individual PCB congeners may impact the direction of the observed associations between POPs and weight change. Lind et al., 2013 demonstrated that long term weight gain was observed in older subjects with higher serum levels of summed OC pesticides and higher levels of low-chlorinated PCBs relative to those with lower serum levels of these compounds; in contrast, long term weight loss was observed in those with elevated levels of highly chlorinated PCBs. Lind and colleagues hypothesized that in addition to differences in body size, the pharmacokinetics of the POPs are complex due to differences in structure, and that the magnitude and timing of the exposure as well as the time since exposure likely influence the findings (Lind et al., 2013).

Metabolic syndrome was defined in this study using the NCEP-ATP III criteria in which the presence of any three of five factors (abdominal obesity, elevated blood pressure, elevated triglycerides, low HDL and elevated fasting glucose) constituted a positive ‘diagnosis’. Had the definition of metabolic syndrome employed by the International Diabetes Federation (IDF) been used (https://www.idf.org/e-library/consensus-statements/60-idfconsensus-worldwide-definitionof-the-metabolic-syndrome) in which abdominal obesity plus two additional factors indicated the presence of metabolic syndrome, the overall prevalence of metabolic syndrome among Anniston residents in this analysis would have been 50% rather than 49%. Using the IDF's lower waist circumference cut off values would have added 20 individuals to the positive metabolic syndrome group but the requirement for the presence of an enlarged waist circumference plus two additional factors would have eliminated 22 Anniston residents who otherwise had at least three of the NCEP-ATP III factors (data not shown). Because metabolic syndrome is a cluster of factors, differences in the definition employed or even in the mix of metabolic syndrome components present within specific study populations using the same definition could account for some of the inconsistencies observed in the literature. The Anniston study population was approximately half white and half African-American, with African-Americans making up about 40% of the participant

group with metabolic syndrome. Significantly higher age-adjusted mean levels of six of the nine pesticides were observed in nonwhites than in whites. Although effect modification by race/ethnicity of the pesticide-metabolic syndrome associations was not observed in any of the models, African Americans tended to have higher odds of metabolic syndrome than whites, with significant associations noted for *p,p′*-DDE, HCB and tNONA; of interest, higher *mean* levels of tNONA were not observed in nonwhites relative to whites even though the association with metabolic syndrome was stronger. As for the majority of the pesticides, PCB levels were significantly higher in African-Americans than whites; however, the odds of metabolic syndrome associated with PCB exposures were not significantly higher in this racial/ ethnic group. As reported by Pavuk et al. (2014b), African-Americans in the Anniston study population were significantly more likely to consume both local livestock and fish than whites although about 90% of both racial groups consumed local vegetables. African-Americans also were significantly more likely to live in West Anniston, the location of the former PCB production facility although whites had lived longer on average in Anniston than the African-Americans (data not shown).

Females comprised approximately 70% of the Anniston study population and the gender distributions across metabolic syndrome categories were similar to the overall study group. Significant effect modification by gender was observed for the log 10 transformedΣ35PCBs, *β*-HCCH, oxychlor and Mirex models even though significantly elevated odds ratios in females were observed only for oxychlor. The differential in sample size between males and females as well as the differences in mean levels of individual pesticides across gender makes the interpretation of the sex-stratified results more constrained.

Analyses highlighted in this paper were conducted with wet weight PCB and pesticide levels rather than with the lipid-standardized concentrations of these pollutants. In addition, highlighted final logistic models assessing POPs and metabolic syndrome excluded total lipids due to concern for over-adjustment and biased effect estimates (Schisterman et al., 2005; Lee et al., 2014a); however, estimates from identical models, but which included total lipids have been provided for comparison in the last column of Tables 5 and 6 as well as in Supplemental Table 1. Over-adjustment is particularly relevant to the assessment of POPs and metabolic syndrome; elevated triglycerides, a component of total lipids are part of the definition of the metabolic syndrome. Moreover, lipid levels are often reduced by medication used to treat components of metabolic syndrome. In order to control for ‘body fat’, BMI was used as a proxy measure of fat volume (Kahn and Cheng, 2008) and retained in all final models. The addition of BMI to the logistic regression models resulted in no particular pattern of changes in the odds ratios; effects were variable depending on the compound and included no change, an increase or a decrease, sometimes across quintiles or for one particular quintile only (data shown in Supplemental Table 1 for log $_{10}$ models only).

Limitations of the current study included self-reported health data via interview as well as the cross-sectional design, which precluded the assessment of temporality and possible causation. In addition, reverse causation cannot be ruled out since the causal pathway between POPs, adipose tissue dysfunction and metabolic syndrome remains poorly understand. Logistic regression models rather than log binomial models were fitted in this study and may have resulted in overestimates of the odds ratios since the prevalence of

metabolic syndrome was around 50% in the Anniston population. While there were 1110 individuals who completed the Anniston Community Health Survey, only about 75% of the group agreed to the additional clinic visit which included a blood draw for glucose, lipid, OC pesticide and PCB measurements, as well as blood pressure and physical measurements. While selection bias cannot be ruled out, there were no significant differences by sex or race for participants who attended and did not attend the clinic appointment; however, older residents and those who were retired or not employed were more likely to agree to the additional laboratory tests and procedures ($p < 0.05$). Finally, we are lacking data concerning the timing and duration of exposure to the OC pesticides in this population although the average duration of residency in Anniston for the cohort was 28.8 years (Silverstone et al., 2012).

Strengths of our study included the relatively large number of POP measurements which were performed (35 PCB congeners and 9 chlorinated pesticides/herbicides) from a single laboratory at the CDC in Atlanta, Georgia, with both serum wet weight and lipid-standardized values determined for all POPs. In-person interviews were used to collect survey data minimizing inconsistencies in understanding/question completion and missing information. Medication review and the measurement of height, weight, blood pressure and waist circumference, components of metabolic syndrome, as well as blood draws were undertaken by nurses following standardized protocols at a second in-person visit, improving study reliability and validity. In addition, fasting glucose measurements allowed us to distinguish individuals with prediabetes from those with normoglycemia as well as those with self-reported /diagnosed and undiagnosed diabetes.

## 5. Conclusion

In conclusion, metabolic syndrome, representing a combination of cardiovascular risk factors, was associated with exposure to several pesticides in Anniston, AL residents without diabetes. In contrast, PCB exposure was not associated with metabolic syndrome in this cohort. These data add to the evidence that environmental pollutants may be contributing to the development of metabolic syndrome.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Table 1

Demographic characteristics & health behaviors of participants with and without metabolic syndrome.

| Variable | Metabolic Syndrome | | Total Group | *p* value* |
|---|---|---|---|---|
| | No (*n* = 277) N (%) | Yes (*n* = 271) N (%) | (*n* = 548) N (%) | |
| Age in years: Mean (SD) | 49.1 (16.6) | 58.2 (14.3) | 53.6 (16.2) | < 0.001 |
| Median (range) | 48 (18–93) | 60 (20–87) | 54 (18–93) | |
| BMI in kg/m$^2$: Mean (SD) | 27.4 (6.6) | 32.9 (7.1) | 30.2 (7.4) | < 0.001 |
| Median (range) | 26.0 (16–64) | 31.8 (19–61) | 29.3 (16–64) | |
| Healthy weight: < 25 | 108 (39) | 23 (8) | 131 (24) | < 0.001 |
| Overweight: 25 to < 30 | 81 (29) | 75 (28) | 156 (29) | |
| Obese: ≥ 30 | 88 (32) | 171 (64) | 259 (47) | |
| Missing *n* = 2 | | | | |
| Sex: Female | 189 (68) | 183 (68) | 372 (68) | 0.86 |
| Male | 88 (32) | 88 (32) | 176 (32) | |
| Race: White | 141 (51) | 163 (60) | 304 (56) | 0.29 |
| Nonwhite | 136 (49) | 108 (40) | 244 (44) | |
| Education: Elementary | 23 (8) | 26 (10) | 49 (9) | 0.15 |
| Some High School | 53 (19) | 54 (20) | 107 (20) | |
| High School Grad | 100 (37) | 120 (45) | 220 (41) | |
| Some College or Technical | 67 (25) | 49 (18) | 116 (21) | |
| College Graduate | 30 (11) | 20 (7) | 50 (9) | |
| Missing *n* = 6 | | | | |
| Marital Status: Not Married | 153 (55) | 132 (49) | 285 (52) | 0.13 |
| Married/Partner | 124 (45) | 139 (51) | 263 (48) | |
| Current Smoker: No | 173 (63) | 190 (72) | 363 (67) | 0.26 |
| Yes | 103 (37) | 75 (28) | 178 (33) | |
| Missing *n* = 7 | | | | |
| Alcohol Consumption: [a] | | | | < 0.001 |
| Non Drinker | 161 (60) | 208 (78) | 369 (69) | |
| Light/Moderate Drinker | 58 (22) | 38 (14) | 96 (18) | |
| Heavy or Binge Drinker | 49 (18) | 20 (8) | 69 (13) | |
| Missing *n* = 14 | | | | |

[a] http://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/moderate-binge-drinking.

* *p* from *t*-test or Pearson Chi-square test.

## Table 2

Clinical characteristics of participants with and without metabolic syndrome.

| Variable | Metabolic Syndrome | | Total Group | *p* value* |
|---|---|---|---|---|
| | No (*n* = 277) N (%) | Yes (*n* = 271) N (%) | (*n* = 548) N (%) | |
| Family History Diabetes: No[a] | 113 (42) | 105 (40) | 218 (41) | 0.55 |
| Yes | 154 (58) | 159 (60) | 313 (59) | |
| Missing n = 17 | | | | |
| Family History Heart Disease: No[a] | 109 (41) | 84 (31) | 193 (36) | 0.027 |
| Yes | 159 (59) | 183 (69) | 342 (64) | |
| Missing n = 13 | | | | |
| Self-report - Liver Disease: No | 265 (96) | 260 (97) | 525 (96) | 0.69 |
| Yes | 11 (4) | 9 (3) | 20 (4) | |
| Missing n = 3 | | | | |
| Waist Circumference: cm | | | | < 0.001 |
| Normal | 184 (66) | 64 (24) | 248 (45) | |
| Increased (> 88 Female > 102 Male) | 93 (34) | 207 (76) | 300 (55) | |
| High Blood Pressure: mm Hg[b] | | | | < 0.001 |
| No | 181 (65) | 52 (19) | 233 (42) | |
| Yes | 96 (35) | 219 (81) | 315 (58) | |
| Prediabetes[c] | | | | < 0.001 |
| No | 253 (91) | 129 (48) | 382 (70) | |
| Yes | 24 (9) | 142 (52) | 166 (30) | |
| Low HDL: mg/dL[d] | | | | < 0.001 |
| No | 191 (69) | 34 (12) | 225 (41) | |
| Yes | 86 (31) | 237 (88) | 323 (59) | |
| High Triglycerides: mg/dL[e] | | | | < 0.001 |
| No | 250 (90) | 87 (32) | 337 (62) | |
| Yes | 27 (10) | 184 (68) | 211 (38) | |
| Total Lipids in mg/ dL; Mean (SD) | 593.8 (120.7) | 667.9 (177.5) | 630.5 (155.8) | < 0.001 |
| Insulin Resistance Assessment | | | | |
| HOMA; Mean (SD) | 2.1 (2.0) | 4.2 (4.0) | 3.1 (3.3) | < 0.001 |
| Missing n = 14 | | | | |

[a] Family history includes first and second degree blood relatives.

[b] Systolic ≥130 or Diastolic ≥85 or antihypertensive medication.

[c] Fasting glucose 100–125 mg/dL & no glycemic control medication or self-reported diagnosed diabetes.

[d] < 50 Females < 40 Males, or receiving lipid-lowering medication.

[e] ≥150 or receiving lipid-lowering medication.

* *p* from *t*-test or Pearson Chi-square test.

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## Table 3

**a Age-adjusted pesticides levels (pg/g wet weight) by metabolic syndrome status, gender and race: Anniston Community Health Survey. Geometric means (GM) and 95% confidence intervals (CI)**

| Pesticide & Trait | Metabolic Syndrome | | | | | | *p* value |
|---|---|---|---|---|---|---|---|
| | No (*n* = 277) | | Yes (*n* = 271) | | Total (*n* = 548) | | |
| | GM (95% CI) | | GM (95% CI) | | GM (95% CI) | | |
| HCB (ppt) | 52.4 | (49.7–55.1) | 59.4 | (56.4–62.7) | 55.7 | (53.7–57.8) | 0.001 |
| *Gender*: Female | 57.0 | (53.8–60.3) | 64.7 | (61.1–68.4) | 60.7 | (58.2–63.4) | < 0.01 |
| Male | 43.8 | (40.7–47.0) | 49.7 | (46.2–53.3) | 48.8 | (43.8–49.5) | |
| *Race/Eth*: White | 50.1 | (47.1–53.4) | 57.3 | (54.0–61.0) | 53.6 | (51.1–56.4) | 0.02 |
| Non-White | 54.7 | (51.3–58.3) | 62.5 | (58.5–67.0) | 58.5 | (55.5–61.8) | |
| *β*-HCCH (ppt) | 45.6 | (41.3–50.5) | 62.8 | (56.8–69.5) | 53.6 | (49.9–57.4) | < 0.001 |
| *Gender*: Female | 57.5 | (52.0–63.7) | 78.7 | (71.0–87.1) | 67.3 | (62.2–72.6) | < 0.001 |
| Male | 28.1 | (24.7–32.1) | 38.5 | (33.7–43.9) | 32.9 | (29.4–36.8) | |
| *Race/Eth*: White | 45.0 | (39.8–50.8) | 61.9 | (55.2–69.7) | 52.8 | (48.1–58.1) | 0.68 |
| Non-White | 46.3 | (40.9–52.5) | 63.8 | (56.0–72.9) | 54.5 | (49.0–63.9) | |
| Oxychlor (ppt) | 97.1 | (88.7–106.4) | 107.6 | (98.2–118.0) | 102.3 | (95.9–108.9) | 0.13 |
| *Gender*: Female | 104.0 | (94.0–114.8) | 115.0 | (103.9–127.4) | 109.4 | (101.4–118.0) | 0.003 |
| Male | 84.5 | (65.6–95.9) | 93.5 | (82.2–106.4) | 88.9 | (79.6–99.3) | |
| *Race/Eth*: White | 100.0 | (89.7–111.7) | 110.4 | (99.3–122.9) | 105.2 | (99.6–114.6) | 0.34 |
| Non-White | 94.2 | (84.1–105.4) | 103.8 | (92.0–116.9) | 90.2 | (89.7–108.6) | |
| tNONA (ppt) | 185.4 | (171.0–200.1) | 212.3 | (195.4–230.1) | 198.6 | (187.5–209.9) | 0.024 |
| *Gender*: Female | 190.1 | (173.8–208.0) | 218.8 | (198.6–238.2) | 203.2 | (190.1–217.8) | 0.21 |
| Male | 176.2 | (157.0–197.7) | 201.4 | (179.5–226.5) | 188.4 | (170.6–208.0) | |
| *Race/Eth*: White | 191.0 | (173.0–210.4) | 217.8 | (198.2–238.8) | 203.7 | (188.8–219.8) | 0.30 |
| Non-White | 179.9 | (162.6–198.6) | 204.6 | (184.1–227.5) | 191.9 | (176.2–208.9) | |
| *p,p′*-DDE | 1640 | (1469–1832) | 1820 | (1626–2037) | 1726 | (1600–1866) | 0.20 |
| *Gender*: Female | 1754 | (1549–1982) | 1945 | (1718–2198) | 1845 | (1683–2028) | 0.014 |
| Male | 1426 | (1219–1667) | 1581 | (1352–1854) | 1503 | (1312–1722) | |
| *Race/Eth*: White | 1180 | (1042–1337) | 1380 | (1225–1556) | 1276 | (1159–1406) | < 0.001 |
| Non-White | 2334 | (2051–2649) | 2723 | (2377–3119) | 2518 | (2259–2805) | |
| *p,p′*-DDT | 26.1 | (23.6–28.9) | 31.5 | (28.4–34.9) | 28.6 | (26.7–30.8) | 0.013 |

**a Age-adjusted pesticides levels (pg/g wet weight) by metabolic syndrome status, gender and race: Anniston Community Health Survey. Geometric means (GM) and 95% confidence intervals (CI)**

| Pesticide & Trait | Metabolic Syndrome | | | | | | *p* value |
|---|---|---|---|---|---|---|---|
| | No (*n* = 277) | | Yes (*n* = 271) | | Total (*n* = 548) | | |
| | GM (95% CI) | | GM (95% CI) | | GM (95% CI) | | |
| *Gender*: Female | 26.6 | (23.7–29.8) | 32.1 | (28.6–36.0) | 29.2 | (26.8–31.8) | 0.44 |
| Male | 25.1 | (21.6–29.0) | 30.2 | (26.1–35.0) | 27.5 | (24.3–31.2) | |
| *Race/Eth*: White | 19.4 | (17.3–21.8) | 24.6 | (22.0–27.5) | 21.9 | (20.0–23.9) | < 0.001 |
| Non-White | 35.7 | (31.8–40.3) | 45.3 | (33.9–51.4) | 40.3 | (36.4–44.5) | |
| Mirex | 57.9 | (52.0–64.6) | 48.1 | (43.2–53.7) | 52.8 | (49.0–57.0) | 0.02 |
| *Gender*: Female | 54.7 | (44.9–56.8) | 42.0 | (37.3–56.8) | 46.0 | (42.1–50.4) | < 0.001 |
| Male | 77.6 | (66.8–91.6) | 64.6 | (55.5–75.0) | 70.8 | (62.1–85.4) | |
| *Race/Eth*: White | 46.6 | (41.0–52.7) | 39.9 | (35.4–45.1) | 45.0 | (39.1–47.5) | < 0.001 |
| Non-White | 73.5 | (64.6–83.6) | 63.1 | (55.0–72.4) | 68.1 | (61.1–76.0) | |

**b Age adjusted sum 35 PCB levels (ng/g wet weight) by metabolic syndrome status, gender and race: Anniston Community Health Survey. Geometric means (GM) and 95% confidence intervals (CI)**

| POP&Trait | Metabolic Syndrome | | | | | | *p* value |
|---|---|---|---|---|---|---|---|
| | No (*n* = 277) | | Yes (*n* = 271) | | Total (*n* = 548) | | |
| | GM (95% CI) | | GM (95% CI) | | GM (95% CI) | | |
| Sum 35 PCB | 2.88 | (2.58–3.23) | 2.62 | (2.34–2.94) | 2.75 | (2.54–2.98) | 0.25 |
| *Gender*: Female | 2.76 | (2.44–3.13) | 2.51 | (2.21–2.85) | 2.64 | (2.39–2.90) | 0.12 |
| Male | 3.16 | (2.69–3.71) | 2.87 | (2.44–3.37) | 3.01 | (2.62–3.56) | |
| *Race/Eth*: White | 1.75 | (1.56–1.97) | 1.72 | (1.54–1.92) | 1.74 | (1.59–1.90) | < 0.001 |
| Non-White | 4.92 | (4.38–5.53) | 4.83 | (4.27–5.47) | 4.88 | (4.42–5.38) | |

## Table 4

Geometric mean serum pesticide levels (ng/g wet weight) in Anniston and in 2003–2004 NHANES data (adults 20 and older, all races).

| Pesticides (ng/g whole weight) | Anniston | | NHANES[a] | |
|---|---|---|---|---|
| | Geometric Mean | (95% CI) | Geometric Mean | (95% CI) |
| HCB | 0.058 | (0.056–0.060) | 0.097 | (0.092–0.102) |
| *β*-HCCH | 0.061 | (0.056–0.067) | 0.051 | (< LOD-0.058) |
| Oxychlor | 0.111 | (0.103–0.119) | 0.067 | (0.061–0.073) |
| tNONA | 0.213 | (0.199–0.228) | 0.106 | (0.095–0.119) |
| *p,p′*-DDE | 1.967 | (1.809–2.139) | 1.69 | (1.36–2.10) |
| *p,p′*-DDT | 0.032 | (0.030–0.034) | *b* | |
| Mirex | 0.055 | (0.051–0.059) | *b* | |

Lipid adjusted levels were similarly elevated in Anniston compared to NHANES (data not shown).

[a] http://www.cdc.gov/exposurereport/pdf/fourthreport.pdf

[b] Not calculated as proportion below limit of detection was too high for a valid result.

## Table 5

Sum 35PCBs, subsets and individual PCB congeners (ng/g wet weight) and metabolic syndrome; unadjusted and adjusted logistic regression models with odds ratios (OR) and 95% confidence intervals (CI).

| PCBs | MetSyn n (%) | Unadjusted OR (95% CI) | Adjusted[a] OR (95% CI) | Adjusted[a] & Lipids[b] OR (95% CI) |
|---|---|---|---|---|
| Σ35PCBs Quintiles (ng/g whole weight) | 247 (50%) | | | |
| Q1. 0.11–1.15 | 46 (37%) | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) |
| Q2. 1.16–2.42 | 52 (54%) | 1.98 (1.15–3.40) | 1.12 (0.51–2.46) | 0.94 (0.42–2.12) |
| Q3. 2.43–4.33 | 44 (49%) | 1.60 (0.92–2.78) | 0.69 (0.30–1.58) | 0.49 (0.21–1.17) |
| Q4. 4.34–9.33 | 55 (53%) | 1.88 (1.11–3.19) | 0.81 (0.33–1.98) | 0.57 (0.22–1.44) |
| Q5. 9.34–170 | 50 (59%) | 2.39 (1.36–4.21) | 0.78 (0.27–2.21) | 0.51 (0.17–1.50) |
| $Log_{10}$ Σ35PCBs per 1 ng/g increase | 247 (50%) | 1.83 (1.32–2.53) | 1.11 (0.57–2.16) | 0.78 (0.39–1.54) |
| $Log_{10}$ ΣDioxin-Like (#105, 118, 156, 157, 167, 189) per 1 ng/g increase | 247 (50%) | 1.94 (1.40–2.68) | 0.96 (0.51–1.78) | 0.74 (0.39–1.40) |
| $Log_{10}$ ΣNon Dioxin-Like (#138, 153, 170, 180, 187) per 1 ng/g increase | 247 (50%) | 1.74 (1.27–2.39) | 1.09 (0.58–2.06) | 0.79 (0.41–1.52) |
| $Log_{10}$ PCB congeners Each per 1 ng/g increase | | | | |
| #28 | 247 (50%) | 2.50 (1.54–4.05) | 1.18 (0.61–2.26) | 0.86 (0.43–1.70) |
| #66 | 247 (50%) | 1.93 (1.42–2.63) | 1.01 (0.63–1.61) | 0.86 (0.53–1.38) |
| #74 | 247 (50%) | 2.90 (2.08–4.05) | 1.29 (0.70–2.39) | 0.82 (0.43–1.58) |
| #99 | 247 (50%) | 1.62 (1.25–2.11) | 0.89 (0.56–1.40) | 0.72 (0.45–1.15) |
| #118 | 247 (50%) | 1.93 (1.50–2.48) | 0.95 (0.61–1.50) | 0.80 (0.50–1.28) |
| #153 | 247 (50%) | 1.69 (1.29–2.21) | 0.91 (0.55–1.52) | 0.68 (0.40–1.15) |
| #156 | 247 (50%) | 2.01 (1.50–2.69) | 1.29 (0.74–2.26) | 0.84 (0.46–1.51) |
| #170 | 247 (50%) | 1.84 (1.38–2.45) | 1.23 (0.70–2.15) | 0.79 (0.44–1.44) |
| #187 | 247 (50%) | 1.55 (1.21–1.98) | 0.91 (0.57–1.46) | 0.67 (0.41–1.10) |
| #194 | 247 (50%) | 1.58 (1.24–2.02) | 1.19 (0.74–1.92) | 0.81 (0.48–1.34) |
| #206 | 247 (50%) | 1.81 (1.42–2.31) | 1.28 (0.79–2.08) | 0.89 (0.54–1.48) |
| #209 | 247 (50%) | 1.71 (1.38–2.11) | 1.14 (0.72–1.79) | 0.82 (0.52–1.32) |

[a]Adjusted for age in yrs, family hx heart disease (no/yes), family hx diabetes (no/yes), liver disease (no/yes), sex, race (white/nonwhite), alcohol consumption (none, light/moderate, heavy/binge), current smoker (no/yes), marital status (not married, yes spouse/partner), grade (1–6 as interval; none to college grad), BMI (continuous).

[b]Total lipids (continuous) added to the adjusted models.

## Table 6

Logistic regression models: pesticides levels (pg/g wet weight) and metabolic syndrome (MetSyn). All $Log_{10}$ models; per log of 1 pg/g increase.

| Pesticides | MetSyn – n (%) | Unadjusted OR (95% CI) | Adjusted[a] OR (95% CI) | Adjusted[a] & Lipids[b] OR (95% CI) |
|---|---|---|---|---|
| 1. *p,p′*-DDT Quintiles (ppt) | | | | |
| Q1. 2.80–14.10 | 34 (30%) | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) |
| Q2. 14.11–22.90 | 51 (49%) | 2.17 (1.24–3.78) | 2.35 (1.19–4.64) | 2.28 (1.13–4.59) |
| Q3. 22.91–36.70 | 54 (52%) | 2.48 (1.42–4.32) | 1.95 (0.98–3.87) | 1.65 (0.81–3.34) |
| Q4. 36.71–66.50 | 55 (60%) | 3.41 (1.91–6.09) | 2.36 (1.11–5.01) | 1.82 (0.84–3.97) |
| Q5. 66.51–831.20 | 52 (62%) | 3.73 (2.05–6.77) | 1.61 (0.76–3.47) | 1.11 (0.50–2.48) |
| $Log_{10}$ *p,p′*-DDT | 246 (49%) | 3.50 (2.14–5.71) | 1.65 (0.87–3.12) | 1.14 (0.60–2.17) |
| 2. *p,p′*-DDE Quintiles (ppt) | | | | |
| Q1. 15.90–654.30 | 39 (33%) | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) |
| Q2. 654.31–1466.20 | 45 (43%) | 1.55 (0.90–2.67) | 1.56 (0.78–3.11) | 1.43 (0.70–2.91) |
| Q3. 1466.21–2755.60 | 51 (49%) | 1.95 (1.13–3.36) | 1.43 (0.69–2.97) | 1.13 (0.53–2.40) |
| Q4. 2755.61–5520.82 | 56 (60%) | 3.07 (1.74–5.40) | 1.64 (0.76–3.53) | 1.42 (0.65–3.11) |
| Q5. 5520.83–38,301.20 | 56 (71%) | 4.93 (2.66–9.16) | 2.73 (1.09–6.88) | 1.92 (0.75–4.92) |
| $Log_{10}$ *p,p′*-DDE | 247 (50%) | 2.80 (1.91–4.09) | 1.59 (0.88–2.85) | 1.14 (0.64–2.06) |
| 3. HCB Quintiles (ppt) | | | | |
| Q1. 15.20–38.10 | 35 (32%) | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) |
| Q2. 38.11–51.18 | 46 (43%) | 1.62 (0.93–2.83) | 1.39 (0.70–2.76) | 1.12 (0.55–2.25) |
| Q3. 51.19–66.52 | 53 (51%) | 2.24 (1.28–3.91) | 1.79 (0.88–3.66) | 1.27 (0.60–2.67) |
| Q4. 66.53–87.66 | 53 (53%) | 3.03 (1.69–5.42) | 2.09 (0.97–4.48) | 1.15 (0.51–2.60) |
| Q5. 87.67–1481.00 | 60 (67%) | 4.23 (2.33–7.67) | 2.31 (1.02–5.26) | 0.91 (0.35–2.32) |
| $Log_{10}$ HCB | 247 (50%) | 14.90 (5.93–37.45) | 6.15 (1.66–22.88) | 1.38 (0.34–6.61) |
| 4. *β*-HCCH Quintiles (ppt) | | | | |
| Q1. 3.60–17.98 | 30 (27%) | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) |
| Q2. 17.99–42.56 | 46 (41%) | 1.93 (1.10–3.38) | 1.24 (0.62–2.49) | 0.97 (0.47–2.00) |
| Q3. 42.57–91.14 | 51 (51%) | 2.82 (1.59–5.00) | 1.46 (0.67–3.19) | 1.00 (0.44–2.28) |
| Q4. 91.15–199.66 | 58 (66%) | 5.35 (2.92–9.82) | 1.87 (0.76–4.58) | 1.15 (0.44–2.95) |
| Q5. 199.67–1756.00 | 60 (74%) | 7.91 (4.14–15.13) | 1.84 (0.66–5.14) | 0.95 (0.32–2.82) |
| $Log_{10}$ *β*-HCCH | 245 (49%) | 4.06 (2.79–5.91) | 1.92 (0.98–3.74) | 1.28 (0.64–2.55) |
| 5. Oxychlor Quintiles (ppt) | | | | |
| Q1. 8.63–53.90 | 40 (34%) | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) |
| Q2. 53.91–100.70 | 37 (38%) | 1.20 (0.69–2.09) | 0.92 (0.45–1.88) | 0.80 (0.38–1.67) |
| Q3. 100.71–155.40 | 52 (54%) | 2.28 (1.32–3.96) | 1.57 (0.75–3.29) | 1.22 (0.57–2.63) |
| Q4. 155.41–247.80 | 55 (59%) | 2.79 (1.59–4.87) | 1.48 (0.65–3.37) | 0.79 (0.33–1.91) |
| Q5. 247.81–3104.20 | 63 (70%) | 4.61 (2.56–8.31) | 2.09 (0.83–5.26) | 1.02 (0.37–2.76) |
| $Log_{10}$ Oxychlor | 247 (50%) | 3.33 (2.15–5.14) | 2.09 (1.07–4.07) | 1.42 (0.71–2.84) |
| 6. tNONA Quintiles (ppt) | | | | |
| Q1. 8.91–102.20 | 33 (28%) | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) |

| Pesticides | MetSyn – n (%) | Unadjusted OR (95% CI) | Adjusted[a] OR (95% CI) | Adjusted[a] & Lipids[b] OR (95% CI) |
|---|---|---|---|---|
| Q2. 102.21–182.30 | 44 (44%) | 2.04 (1.16–3.58) | 1.62 (0.78–3.39) | 1.38 (0.64–2.96) |
| Q3. 182.31–277.40 | 51 (53%) | 2.89 (1.63–5.09) | 2.17 (1.00–4.73) | 1.66 (0.74–3.74) |
| Q4. 277.41–450.80 | 60 (63%) | 4.24 (2.38–7.55) | 2.54 (1.05–6.16) | 1.47 (0.57–3.77) |
| Q5. 450.81–7333.10 | 59 (67%) | 5.18 (2.84–9.43) | 2.80 (1.09–7.18) | 1.51 (0.55–4.16) |
| *Log*$_{10}$ tNONA | 247 (50%) | 4.52 (2.77–7.39) | 3.19 (1.45–7.00) | 1.96 (0.88–4.38) |
| 7. Mirex Quintiles (ppt) | | | | |
| Q1. 1.30–24.24 | 47 (41%) | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) |
| Q2. 24.25–48.44 | 45 (48%) | 1.35 (0.78–2.33) | 0.64 (0.30–1.36) | 0.59 (0.27–1.29) |
| Q3. 48.45–74.16 | 49 (52%) | 1.56 (0.91–2.70) | 0.96 (0.44–2.11) | 0.77 (0.34–1.74) |
| Q4. 74.17–128.96 | 48 (55%) | 1.81 (1.03–3.17) | 0.99 (0.42–2.33) | 0.64 (0.26–1.57) |
| Q5. 128.97–2574.40 | 58 (55%) | 1.77 (1.04–3.02) | 0.88 (0.37–2.11) | 0.58 (0.23–1.45) |
| *Log*$_{10}$ Mirex | 247 (50%) | 1.58 (1.11–2.25) | 1.06 (0.57–1.96) | 0.72 (0.38–1.36) |
| 8. *o,p′*-DDT (dichotomous) | | | | |
| Below Detection limit | 128 (51%) | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) |
| Detectable | 119 (48%) | 0.91 (0.64–1.29) | 0.66 (0.42–1.02) | 0.58 (0.36–0.91) |
| *Log*$_{10}$ *o,p′*-DDT | 247 (50%) | 1.00 (0.58–1.73) | 1.00 (0.52–1.91) | 0.81 (0.41–1.59) |
| 9. γ-HCCH (dichotomous) | | | | |
| Below Detection limit | 172 (53%) | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) |
| Detectable | 75 (44%) | 0.70 (0.49–1.02) | 0.92 (0.57–1.46) | 0.86 (0.53–1.39) |
| *Log*$_{10}$ γ-HCCH | 247 (50%) | 1.48 (0.75–2.91) | 0.89 (0.39–2.07) | 0.97 (0.41–2.30) |

[a]Adjusted for age in yrs, family hx heart disease (no/yes), family hx diabetes (no/yes), liver disease (no/yes), sex, race (white/nonwhite), alcohol consumption (none, light/moderate, heavy/binge), current smoker (no/yes), marital status (not married, yes spouse/partner), grade (1–5 as interval; elementary to college grad) and BMI (continuous).

[b]Total lipids (continuous) added to the adjusted models.

**Table 7**

$Log_{10}$ pesticides & PCB levels and metabolic syndrome: logistic regression models. Adjusted odds ratios (AOR) (95% CI) for the total group and stratified by gender or by race.[a]

| Pesticide/PCB | Total Group | Sex | | Race/Ethnicity | |
|---|---|---|---|---|---|
| | | Females (*n* = 338–339) | Males (*n* = 157–159) | Whites (*n* = 269–271) | Nonwhites (*n* = 226–227) |
| | AOR (95% CI) | AOR (95% CI) | AOR (95% CI) | AOR (95% CI) | AOR (95% CI) |
| $Log_{10}$ Σ35PCBs* | 1.11 (0.57–2.16) | 1.68 (0.69–4.11) | 0.50 (0.16–1.58) | 0.99 (0.37–2.68) | 1.23 (0.50–2.99) |
| $Log_{10}$ *p,p′*-DDT† | 1.65 (0.87–3.12) | 1.84 (0.79–4.27) | 1.07 (0.33–3.51) | 1.33 (0.57–3.10) | 2.36 (0.85–6.58) |
| $Log_{10}$ *o,p′*-DDT | 1.00 (0.52–1.91) | 0.82 (0.35–1.92) | 1.37 (0.44–4.22) | 1.22 (0.49–3.03) | 0.74 (0.28–1.93) |
| $Log_{10}$ *p,p′*-DDE | 1.59 (0.88–2.85) | 1.36 (0.64–2.89) | 1.22 (0.41–3.67) | 0.99 (0.45–2.16) | 3.06 (1.19–7.90) |
| $Log_{10}$ HCB | 6.15 (1.66–22.88) | 7.31 (1.00–53.37) | 1.51 (0.19–12.29) | 5.64 (0.88–36.07) | 8.10 (1.15–56.75) |
| $Log_{10}$ β-HCCH* | 1.92 (0.98–3.74) | 2.14 (0.80–5.75) | 0.77 (0.26–2.29) | 1.69 (0.66–4.35) | 2.28 (0.85–6.08) |
| $Log_{10}$ γ-HCCH | 0.89 (0.39–2.07) | 0.85 (0.27–2.72) | 1.09 (0.28–4.19) | 1.10 (0.36–3.37) | 0.81 (0.21–3.14) |
| $Log_{10}$ Oxychlor* | 2.09 (1.07–4.07) | 2.68 (1.05–6.81) | 0.99 (0.32–3.04) | 2.11 (0.82–5.47) | 2.19 (0.84–5.67) |
| $Log_{10}$ tNONA | 3.19 (1.45–7.00) | 3.14 (1.10–9.00) | 2.39 (0.63–9.11) | 2.59 (0.93–7.26) | 4.64 (1.29–16.61) |
| $Log_{10}$ Mirex* | 1.06 (0.57–1.96) | 1.14 (0.50–2.56) | 1.01 (0.36–2.81) | 0.86 (0.39–1.94) | 1.56 (0.57–4.23) |

None of the interaction terms were significant for race X pesticide/PCBs.

[a]Adjusted for age in yrs, family hx heart disease (no/yes), family hx diabetes (no/yes), liver disease (no/yes), alcohol consumption (none, light/moderate, heavy/binge), current smoker (no/yes), marital status (not married, yes spouse/partner), grade (1–5 as interval; elementary to college grad) and BMI (continuous). Total group models also include sex and race. Models stratified by sex include race and models stratified by race include sex.

*$p < 0.05$ for interaction term total group model, sex X individual pesticide or Σ35PCBs.

†$0.05 < p < 0.10$ for interaction term sex X *p,p′*-DDT.