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Different associations of albuminuria with total and cardiovascular mortality by concentrations of persistent organic pollutants in the elderly

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ABSTRACT

Epidemiologic studies have indicated that albuminuria is associated with mortality from all causes and cardiovascular disease (CVD), with substantial heterogeneity. We evaluated if the associations of urine albumin creatinine ratio (ACR) with all-cause and CVD mortality differed depending on serum concentrations of persistent organic pollutants (POPs), strong lipophilic chemical mixtures with very long half-lives, which are recently linked to many degenerative diseases. Study subjects were participants of the National Health and Nutrition Examination Survey 1999–2004 who were 60 years or older at baseline (n=1215 and 1067 for organochlorine pesticides (OCPs) and other POPs, respectively). They were followed-up through 2011 (mean follow-up periods: 8.1 and 8.0 years for OCPs and other POPs, respectively). The associations between the ACR and all-cause mortality significantly differed by the serum levels of POPs, especially organochlorine pesticides (OCPs; $P_{interaction} < 0.01$). Stratified analyses indicated that the associations between ACR and all-cause mortality became stronger as the serum levels of OCPs increased. Among the elderly with the highest tertile of OCPs, the adjusted hazard ratios were 1.0, 1.1, and 2.9 ($P_{trend} < 0.01$) across the categories of ACR (< 10, 10– < 30, and ≥30 mg/g); however, ACR was not clearly related to mortality among the elderly with the lowest tertile of OCPs. CVD mortality showed similar interactions, as noted for all-cause mortality ($P_{interaction} < 0.01$). The different associations between albuminuria and mortality by the serum OCP levels and the little association among the elderly with low serum OCPs levels suggest that OCPs play an important role in albuminuria-related death risk. However, these findings need to be replicated in other cohort studies.

1. Introduction

A large body of evidence has shown that elevated albumin levels in urine are predictive of all-cause and cardiovascular disease (CVD) mortality both in groups at high risk for CVD as well as general population (Chronic Kidney Disease Prognosis et al., 2010; Fox et al., 2012; Mahmoodi et al., 2012). There was a graded relationship between the baseline albuminuria and the risk of mortality without any clear threshold (Chronic Kidney Disease Prognosis et al., 2010; Fox et al., 2012; Mahmoodi et al., 2012). Albuminuria has been suspected to be linked to various disease outcomes as a sensitive marker of widespread endothelial dysfunction (Abdelhafiz et al., 2011).

On the other hand, background exposure to low-dose persistent organic pollutants (POPs) has been recently linked to various diseases of the endocrine, immune, and reproductive systems (Carpenter and Carpenter, 2013). In particular, POPs reportedly increase the risk of common obesity-related diseases such as type 2 diabetes and metabolic syndrome in the general population (Lee et al., 2014b, 2014; Ruzzin et al., 2012). Supporting the epidemiological findings, chronic treatment of rats or mice with low-dose POPs mixtures led to the development of various insulin resistance-related phenotypes such as dyslipidemia and steatohepatitis (Mulligan et al., 2016; Ruzzin et al., 2010).

As typical 20th century man-made chemicals, POPs are halogenated organic compounds with common properties such as high lipophilicity and resistance to biodegradation (Fisher, 1999). These unique chemical/physical features lead to the concentration of POPs in the fatty tissues of living organisms and its biomagnification through food webs (Goerke et al., 2004). Hence, although most of the problematic chlorinated POPs have already been banned or are strictly regulated worldwide (Karlaganis et al., 2001), nearly all human beings may still be exposed to these chemicals throughout their lifetime. Fatty

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animal food contaminated with POPs is the most important external exposure source, whereas adipose tissue contaminated with POPs in our body is the most important internal exposure source (Lee et al., 2014b). The typical examples of POPs include organochlorine pesticides (OCPs), polychlorinated dibenzo-p-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and polychlorinated biphenyls (PCBs).

Although the underlying mechanisms remain unknown, certain POPs exhibit interesting interactions with traditional CVD risk factors, such as obesity and cigarette smoking, on the risk of total and CVD mortality among the elderly (Hong et al., 2012; Lee et al., 2014a, 2013). For example, the association between fat mass and mortality differed according to the serum concentrations of POPs (Hong et al., 2012). Furthermore, the well-known relationship between cigarette smoking and mortality were primarily noted in elderly individuals with high serum concentrations of POPs (Lee et al., 2014a, 2013).

In fact, the relationship between albuminuria and mortality has indicated substantial heterogeneity among studies in terms of the strength of the associations (Chronic Kidney Disease Prognosis et al., 2010); however, the reason for the variation in the associations across studies remains unclear. We hypothesized that POPs may modify the relationship between albuminuria and mortality. In present study, we aimed to assess whether association of albuminuria with all-cause and CVD mortality differed according to the serum concentrations of OCPs, PCDDs, PCDFs, and PCBs among the elderly.

2. Materials and methods

2.1. Data collection and study participants

Merged datasets of the 1999–2000, 2001–2002, and 2003–2004 National Health and Nutrition Examination Survey (NHANES) were used for this study. The NHANES is a continuous, 2-year cycle program conducted by the National Centers for Health Statics (NCHS) of the Centers for Disease Control and Prevention (CDC). The NHANES involves a stratified multistage probability sample, representative of the civilian non-institutionalized US population. The inclusion criteria were as follows: age ≥60 years, available information on the serum concentrations of OCP or other POP compounds and urine albumin creatinine ratio (ACR), and follow-up until the end of 2011. In the NHANES 1999–2002, the levels of all compounds were measured in the same subsample, whereas in the NHANES 2003–2004, OCP and other POP compounds were measured in different subsamples. Thus, the final sample sizes were 1215 for the analyses of OCPs and 1067 for the analyses of PCDDs, PCDFs, and PCBs. This study was approved by the NCHS Research Ethics Review Board and written informed consent was obtained from all participants.

2.2. Measurements

A detailed description of the sample collection and analytic procedures for all biochemical parameters is provided in previous reports (CDC, 2002a, 2002b). In brief, the serum concentrations of individual OCP, PCDD, PCDF, and PCB compounds were measured using high-resolution gas chromatography/high-resolution mass spectrometry with isotope dilution for quantification. We selected 5 OCPs (p,p′-DDE, trans-nonachlor, oxychlordane, heptachlor epoxide and β-hexachlorocyclohexane), 3 PCDDs (1,2,3,6,7,8-Hexachlorodibenzo-p-dioxin, 1,2,3,4,6,7,8-heptachlorodibenzo-p-dioxin and 1,2,3,4,6,7,8,9-octachlorodibenzo-p-dioxin), 3 PCDFs (2,3,4,7,8-pentachlorodibenzofuran, 1,2,3,4,7,8-hexachlorodibenzofuran and 1,2,3,4,6,7,8-heptachlorodibenzofuran), and 11 PCBs (PCB74, PCB99, PCB118, and PCB126, PCB146, PCB153, PCB156, PCB169, PCB170, PCB180 and PCB187) that exhibited concentrations greater than their respective detection limit in at least 80% of the study subjects.

Although we attempted to use both lipid-standardized concentrations and wet concentrations with lipid adjustment (including the serum concentrations of triglycerides and total cholesterol as covariates) in our analyses, only the results of lipid-standardized concentrations have been presented as they show similar associations. Lipid-standardized concentrations were calculated by dividing wet-weight concentrations by total lipids (total lipids (mg/dL)=2.27 × total cholesterol + triglycerides +62.3) (Phillips et al., 1989).

The urine ACR (mg/g) was computed based on the albumin and creatinine levels measured using the Jaffe rate method and solid-phase fluorescent immunoassay, respectively, from a random spot sample. Serum creatinine levels were measured using a kinetic rate Jaffe method. The glomerular filtration rate (GFR, mL/min/1.73 m^2) was estimated using the abbreviated Modification of Diet in Renal Disease (MDRD) Study formula (Levey et al., 2006).

2.3. Mortality follow-up

Probabilistic matching was used to link the NHANES participants with the National Death Index to ascertain the vital status. Matching was based on 12 identifiers for each participant (e.g., social security number, sex and date of birth). Subjects who survived the entire follow-up period were administratively censored on December 31, 2011. The follow-up duration for each subject was calculated as the difference between the NHANES examination date and the date on which the participant was last known to be alive or censored. The cause of death was determined using the underlying case listed on the death certificate, and was coded using the international classification of disease 10th revision (ICD-10). CVD mortality was classified as death due to heart disease (I00-I09, I11, I13, I20-I51) or cerebrovascular disease (I60-I69).

2.4. Statistical analysis

The urine albumin excretion levels were classified into 3 categories according to the urine ACR (< 10, 10 to < 30, and ≥30 mg/g). The serum levels of individual POPs were divided into tertiles; cutoff points for the tertiles of individual POPs are presented in S1 Table. Further categorizations of urine albumin excretion (< 10, 10 to < 30, 30–300, and ≥300 mg/g) and serum POPs levels (quartiles) did not yield different results.

In the present study, we primarily focused on the summary measures of POPs rather than on individual compounds, because the serum concentrations of individual POPs are highly correlated in general populations, particularly those belonging to the same subclasses of OCPs, PCDDs, PCDFs, and PCBs. In this situation, statistical analyses and interpretation focusing on individual compound would be misleading (Lee et al., 2014b). Among several methods to estimate the summary measures, we used the summary measure adding the rank orders of individual compounds belonging to each subclass. When molecular mechanisms are unknown, the rank-based summary measures which enable equal contributions from all the constituent compounds, are preferred over the biological pathway-based summary measures (Lee et al., 2014b). Also, even though absolute concentration-based summary measures can look intuitively more reasonable than rank-based summary measure (Lee et al., 2014b), they are mainly determined by a couple of compounds with high concentrations. In the case of PCBs, we further grouped them into low- and high- chlorinated PCBs (number of chlorination: < 6 vs. ≥6), because the patterns of associations were found to be different depending on the number of chlorination in an analysis of individual PCBs. The results of individual compounds, focusing on the results of the interaction analyses with urine ACR, are presented in S2 Table.

Using Cox proportional hazard models, we assessed whether the associations between urine ACR and all-cause and CVD mortality differed according to the serum concentrations of POPs at the baseline. Two methods were used to evaluate the interaction between urine ACR and POPs. First, we calculated the hazard ratios (HRs) of mortality