Relationships among Exposure to Environmental Pollutants, Endogenous Hormones, and Kidney Disease Risk

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THESIS

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LIST OF ABBREVIATIONS

ACE	Angiotensin-Converting-Enzyme
ARIC	Atherosclerosis Risk in Communities Study
BB-153	2,2' ,4,4' ,5,5'-hexabromobiphenyl
BMI	Body Mass Index
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CYP1A	Cytochrome P450, family 1, subfamily A
CYP2B	Cytochrome P450, family 2, subfamily B
CV	Coefficient of Variation
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
DDD	Dichloro-diphenyl-dichloroethane
DDE	1,1-dichloro-2,2-bis(4-chlorophenyl)-ethene
DDT	2,2-bis(p-chlorophenyl)-1,1,1-trichloroethane
DHEAS	Dehydroepiandrosterone Sulfate
eGFR	Estimated Glomerular Filtration Rate
ESRD	End-Stage Renal Disease
FSH	Follicle Stimulating Hormone
FT3	Free Triiodothyronine
FT4	Free Thyroxine
LDL	Low-density Lipoprotein
LH	Luteinizing Hormone

LIST OF ABBREVIATIONS (continued)

HCB	Hexachlorobenzene
HCHS/SOL	Hispanic Community Health Study / Study of Latinos
HDL	High-density Lipoprotein
IQR	Interquartile Range
NCHS	National Center for Health Statistics
NHANES	National Health and Nutrition Examination Survey
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
OR	Odds Ratio
PBDEs	Polybrominated Diphenyl Ethers
PCBs	Polychlorinated Biphenyls
PCDD	Polychlorinated dibenzo-p-dioxin
PCDF	Dibenzofurans
POPs	Persistent Organic Pollutants
SBP	Systolic Blood Pressure
SHBG	Sex Hormone-Binding Globulin
TCDD	2,3,7,8-tetrachlorodibenzo-p-dioxin
TEQ	Total Toxic Equivalents
TSH	Thyrotropin
T3	Total Triiodothyronine
T4	Total Thyroxine
UACR	Urinary Albumin to Creatinine Ratio
95% CI	95% Confidence Interval

SUMMARY

Chronic kidney disease (CKD) and its related comorbidities are significant public health problems both in the United States and globally. Environmental factors may have a significant impact on the development and progression of CKD; however, neither the factors related to progression nor have the mechanisms of action been well elucidated. This dissertation examined associations among measured levels of multiple persistent organic pollutants (POPs), endogenous thyroid, pituitary, and sex steroid hormones and multiple parameters of kidney function using cross-sectional and longitudinal data from the National Health and Nutrition Examination Survey (NHANES) and the Hispanic Community Health Study/Study of Latinos (HCHS/SOL).

Using data from an ancillary study in HCHS/SOL, we showed that circulating levels of thyroid stimulating hormone (TSH) were inversely associated with estimated glomerular filtration rate (eGFR) cross-sectionally and over an average six-year follow up period in a diverse cohort of Hispanic/Latino participants free of diabetes at baseline. In this cohort, TSH levels were also positively associated with incident albuminuria. We additionally showed that luteinizing hormone (LH) and follicle stimulating hormone (FSH) concentrations appeared to be inversely associated with eGFR among post-menopausal females cross-sectionally. However, when we looked at the odds of incident albuminuria and CKD at visit 2 among the post-menopausal females who were not categorized as having albuminuria or CKD at visit 1, we again saw associations with the pituitary hormones. Among females, we observed an inverse association between LH and odds of incident albuminuria, which remained after mutual adjustment for FSH, but we did not observe a similar association when we modeled the odds of incident

CKD composite. It is possible that LH may be positively associated with urinary albumin excretion over time, but not with eGFR over time, hence the discordance with the two outcomes. Among the male participants, LH was inversely associated with eGFR at baseline and positively associated with urinary albumin to creatinine ratio (UACR) and odds of albuminuria. However, there was no association with LH and any outcome at Visit 2. Also among males, FSH concentration appeared to be positively associated with UACR and odds of albuminuria at baseline. However, the associations with eGFR and UACR among males observed at baseline using cross-sectional data were not observed when we examined hormone associations with levels of eGFR and UACR at visit 2 after the six year follow-up. When we evaluated the associations with free and bound testosterone, we observed an inverse association with free testosterone and UACR cross-sectionally, and an inverse association between testosterone and visit 2 eGFR.

In regard to pollutant measurements, using the HCHS/SOL data we showed that circulating levels of polychlorinated biphenyl (PCB) concentrations may be associated with small increases in UACR over time. We also showed that concentrations of 1,1-dichloro-2,2-bis(4-chlorophenyl)-ethene (DDE) may be associated with lower levels of UACR over time. When we evaluated these associations using cross-sectional data from the NHANES, we found that PCB concentrations may be associated with small increases in eGFR, particularly among males, but it is uncertain if these associations are real or due to bias. We also showed that PCB concentrations were positively associated with eGFR and UACR among males, and that concentrations of heptachlor epoxide may be associated with increased odds of low eGFR. Most other associations with pesticide concentrations were not independent of diabetes status, indicating that

diabetes may play a large role in the causal pathway connecting these analytes to poor kidney outcomes among adults in the general population. Our findings to support the need for additional investigation into these exposures with longitudinal endpoints to fully understand their impact on renal health.

Future analyses are planned using the HCHS/SOL data to incorporate measures from a second batch of analyte measurements and use multiple imputation methods to impute data for exposure concentrations that are missing for various analyte measures. Advanced methods specially designed to evaluate pollutant mixtures will then be applied to assess the associations between the POPs mixtures and kidney function parameters. This planned additional investigation into these exposures with both our cross-sectional and longitudinal endpoints is warranted to fully understand the impact, if any, of these pollutants on renal health. Our results require further validation and reproduction in additional cohorts, but suggest that particular legacy pollutants are involved in the pathology of CKD and that endogenous hormones may also play a role. Further analyses to evaluate associations between POPs and endogenous hormones should be completed, with mediation analyses to evaluate the mechanism of action with respect to renal health if deemed necessary.

I. INTRODUCTION AND SPECIFIC AIMS

In the United States CKD affects approximately 14.8% of the population (Saran et al. 2017). The consequences of CKD include kidney failure requiring dialysis or a transplant, cardiovascular disease (CVD), disability, and premature death (Go et al. 2014). The proportion of CKD patients who progress to end-stage renal disease (ESRD) increases each year (Saran et al. 2017); however, the factors related to progression have not been well elucidated. Recognized risk factors for CKD include diabetes and hypertension, but a better understanding of other risk factors that contribute to kidney disorders is needed. Furthermore, evidence suggests that significant racial/ethnic and sex-related disparities in CKD and related comorbidities exist, indicating a need for studies that examine novel risk factors in populations that are racially/ethnically diverse and inclusive of both sexes.

Thyroid disorders are common among people with CKD, and alterations in thyroid function have been linked to CVD and death among CKD patients. Many studies of these associations have been cross-sectional, and few have investigated whether thyroid dysfunction is involved in the development or progression of CKD. Additionally, the existing studies of thyroid disorders and kidney function were not designed to assess sex-differences and did not include racially or ethnically diverse samples of participants.

Several studies suggest sex-specific differences in the mechanisms and epidemiology of CKD (Neugarten, Acharya, and Silbiger 2000, Neugarten and Golestaneh 2013, Silbiger and Neugarten 2008). Male sex has been associated with

higher morbidity and mortality among patients with CKD, and males may experience more rapid CKD progression relative to females. This may be attributed to the influence of testosterone on renal dynamics (Carrero et al. 2018, Silbiger 2011), but this is not well understood or agreed upon. Endogenous estradiol is considered nephroprotective (Ahmed and Ramesh 2016), however, it is unclear if female use of exogenous estradiol in the form of oral contraceptives and postmenopausal hormone therapy has any effect on kidney function. Female protection via estrogen may no longer be present in cases of comorbid diabetes (Maric and Sullivan 2008), where evidence of sex differences and the effects of sex hormones on kidney function is less conclusive.

There is increasing evidence that low-level environmental exposures may contribute to the development of endocrine disorders and/or impaired cardiorenal function in the general population. Persistent organic pollutants are synthetic compounds with the ability to persist in the environment and act as endocrine disruptors in the human body. Used heavily in the 20th century and later banned, POPs entered the environment as herbicides, pesticides, plastics, and electrical equipment. Common POPs include PCBs and organochlorine pesticides. Total concentrations of PCBs, DDE, and hexachlorobenzene (HCB) in the human body have been declining over time (Hagmar et al. 2006), but continue to persist due to the long half-life of these chemicals (Hopf et al. 2013) and continuous exposure from certain foods such as fatty fish sourced from contaminated water, meat, and dairy products (Knutsen et al. 2011, Malisch and Kotz 2014). Polychlorinated biphenyls, dioxins, and chlorinated pesticides have been implicated in these the development of chronic diseases (Kataria, Trasande,

and Trachtman 2015), may have estrogenic or anti-estrogenic properties, and have been implicated in thyroid hormone disruption.

Exposure to POPs as a risk factor for CKD is largely underexplored, particularly in the context of normal glucose parameters. Persistent organic pollutants that are excreted primarily via the urinary tract may be more likely to accumulate in the kidneys. Evidence suggests that these exposures may impact kidney function, indicating a need for studies that examine these risk factors longitudinally and in populations that are racially diverse and inclusive of both sexes. Mechanistically, POPs and their metabolites may interfere with endocrine processes by affecting the hypothalamic-pituitary-gonadal (Diamanti-Kandarakis et al. 2009) and hypothalamo–pituitary–thyroid (Fisher et al. 2006, Khan et al. 2002) axes in the pathway to kidney disease, leading to disease development and/or progression.

The collective aim of this thesis intends to contribute to the understanding of the relationships among environmental exposure to persistent pollutants, endogenous hormones, and risk of kidney disease. This will be done following four specific aims and accompanying sub aims:

1. To examine the cross-sectional and prospective associations between thyroid hormones and measures of kidney function in an ethnically diverse Hispanic/Latino population, using data from the parent HCHS/SOL study and the Persistent Organic Pollutants, Endogenous Hormones and Diabetes in Latinos Ancillary Study.

    1.1. Describe the relationships of endogenous thyroid hormones measured at baseline, with baseline prevalence of CKD and measures of eGFR and UACR.

1.2. Determine if levels of endogenous thyroid hormones measured at baseline are associated with changes in eGFR and UACR from Visit 1 to Visit 2.

1.3. Explore the relationships of baseline levels of endogenous thyroid hormones with the subsequent development of CKD at Visit 2.

2. To examine the cross-sectional and prospective associations among pituitary and sex steroid hormones with measures of kidney function in an ethnically diverse Hispanic/Latino population, using data from the parent HCHS/SOL and the Persistent Organic Pollutants, Endogenous Hormones and Diabetes in Latinos Ancillary Study.

   2.1. Describe the relationships of endogenous pituitary and sex hormones measured at baseline, with baseline prevalence of CKD and measures of eGFR and UACR.

   2.2. Determine if levels of endogenous pituitary and sex hormones measured at baseline are associated with changes in eGFR and UACR from Visit 1 to Visit 2.

   2.3. Explore the relationships of baseline levels of endogenous pituitary and sex hormones with the subsequent development of CKD at Visit 2.

3. To examine the cross-sectional and prospective associations among several classes of POPs (PCBs, organochlorine pesticides, polybrominated diphenyl ethers (PBDEs), and 2,2' ,4,4' ,5,5'-hexabromobiphenyl (BB-153)) and measures of kidney function in an ethnically diverse Hispanic/Latino population, using data from the

parent HCHS/SOL study and the Persistent Organic Pollutants, Endogenous Hormones and Diabetes in Latinos Ancillary Study.

3.1. Describe the relationships of persistent organic pollutants measured at baseline, with baseline prevalence of CKD and measures of eGFR and UACR.

3.2. Determine if levels of persistent organic pollutants measured at baseline are related to changes in eGFR and UACR from Visit 1 to Visit 2.

3.3. Explore the relationships of baseline levels of persistent organic pollutants with the subsequent development of CKD (Visit 2), among individuals without CKD at baseline (Visit 1).

4. To examine the cross-sectional associations between concentrations of polychlorinated biphenyls and organochlorine pesticides with kidney function using data from the NHANES.

4.1. Evaluate sex as a modifier of these associations.

II. BACKGROUND AND LITERATURE REVIEW

A. Prevalence of Chronic Kidney Disease in the United States

Chronic kidney disease affects approximately 14.8% of the United States population (Saran et al. 2017). The consequences of CKD include kidney failure requiring dialysis or a transplant, CVD, disability, and premature death (Go et al. 2014). Chronic kidney disease is also associated with infertility and disorders of bone and mineral metabolism. The proportion of CKD patients who progress to ESRD increases each year (Saran et al. 2017); however, the factors related to progression have not been well elucidated. Recognized risk factors for CKD include diabetes and hypertension, but a better understanding of other risk factors that contribute to kidney disorders is needed. Furthermore, evidence suggests that significant racial/ethnic and sex-related disparities in CKD, ESRD, and related comorbidities exist (Derose et al. 2013, McClellan et al. 2010, Nicholas, Kalantar-Zadeh, and Norris 2015), indicating a need for studies that examine novel risk factors in populations that are racially/ethnically diverse and inclusive of both sexes.

B. Thyroid Hormones and Kidney Function

Thyroidal status influences kidney function, inducing both glomerular and tubular changes in the kidney. In turn, kidney disease may induce thyroid dysfunction, suggesting that reverse causality must be considered in the investigation of the associations among measures of thyroid hormones and kidney function. Thyroid disorders are common among people with CKD, and alterations in thyroid function have been linked to CVD and death among CKD patients. Although mechanisms have not yet

been elucidated (Rhee 2016), animal studies have shown hypothyroidism to be associated with detriments in kidney structure and size (Mariani and Berns 2012). Epidemiologic studies of these associations have mostly been cross-sectional, and few have investigated whether thyroid dysfunction is involved in the development or progression of CKD. In a cross-sectional population-based study of adults ages 40 and older without previously diagnosed thyroid disease, subclinical or overt hypothyroidism defined using measured TSH was associated with low eGFR (<60ml/min/1.73 m^2) prevalence (Asvold, Bjoro, and Vatten 2011). In another cross-sectional study of adults 60 and older, those with serum TSH levels in the third (odds ratio (OR) 1.83 (95% CI 1.15-2.92)) and fourth (OR 1.96 (95% CI 1.23-3.13)) quartiles relative to the first quartile had higher odds of low eGFR (<60ml/min/1.73 m^2) (Gopinath et al. 2013). This same study showed that persons with serum free thyroxine (FT4) levels in the fourth quartile (≥14.6 pmol/l) relative to the first quartile (≤11.9 pmol/l) had higher odds of low eGFR (<60ml/min/1.73 m2), OR 1.64 (95% CI 1.10, 2.45) (Gopinath et al. 2013). In cross-sectional analyses, the Atherosclerosis Risk in Communities (ARIC) study found FT4 and TSH (TSH Q4 (2.68-227 mIU/l) versus Q1 (0.005-1.23 mIU/l) OR= 1.87 (95% CI 1.25–2.81)) to be positively associated with reduced kidney function, in addition to total triiodothyronine (T3) concentrations being inversely associated (T3 Q4 (140.6-614.5 ng/dl) versus Q1 (19.5-13.0 ng/dl) OR= 0.19 (95% CI 0.12–0.31)) with reduced kidney function (Schultheiss et al. 2017).

When the ARIC study investigators assessed the association of incident CKD after a median follow-up time of 19.6 years, none of the measures of thyroid function were associated with incident CKD (Schultheiss et al. 2017). Other studies of the

association of incident CKD with markers of thyroid function include a cohort of middle-aged and older Chinese participants in which higher FT4, but not TSH nor free triiodothyronine (FT3), was associated with increased risk of incident CKD over a four year follow-up period (Huang, Ding, et al. 2016). Compared to those with FT4 levels <13.60 pmol/l, those with FT4 levels >14.83 pmol/l had 1.88-fold higher (95% CI 1.27–2.77) increased risk of incident CKD, and each 1-pmol/l increase in FT4 was associated with 12% increased risk of incident CKD (Huang, Ding, et al. 2016). In a sample of 558 participants ages 85 and older from the Leiden 85-plus Study, neither TSH, FT4, nor FT3 were associated with change in eGFR over a five-year follow-up period (Meuwese et al. 2014). In a prospective cohort study of South Korean men and women who were free of CKD and proteinuria at baseline, high levels of TSH and low levels of FT3, but not FT4 was associated with an increased risk of incident CKD (Zhang et al. 2014). After a median follow-up of 3.5 years, 1,032 of the 104,633 participants in the study developed CKD. The hazard ratio for CKD comparing the highest (2.85-5.0 mIU/l) versus the lowest (0.25–1.18mIU/l) quintile of TSH was HR=1.59 (95% CI 1.29-1.95). When modeled using a spline, levels of FT3 less than 3 pg/ml were associated with increased risk of incident CKD (Zhang et al. 2014).

The Kangbuk Samsung Health Study did not show evidence of sex differences in their analyses of the prospective associations of TSH, FT3 and FT4 with incident CKD (Zhang et al. 2014), however, no other studies have evaluated sex differences in the association between thyroid hormones and kidney function. Furthermore, many of the studies of endogenous hormones and kidney function have been conducted in cohorts of white, black, or Asian populations, with few to zero Hispanic/Latino participants.

Given that disease patterns may vary by race/ethnicity and ancestral background, it is important to conduct studies that examine the associations between endogenous hormones and kidney function in diverse racial and ethnic groups. There is a clear need for more studies to assess the potential association between endogenous hormones and kidney function using epidemiologic data.

C. Sex Hormones and Kidney Function

Several studies suggest sex -specific differences in the mechanisms and epidemiology of CKD (Neugarten, Acharya, and Silbiger 2000, Neugarten and Golestaneh 2013, Silbiger and Neugarten 2008). The prevalence of CKD in the United States may be greater among females (Zhang and Rothenbacher 2008), but male sex has been associated with more rapid CKD progression and higher morbidity and mortality among patients with CKD (Carrero et al. 2018). Evidence from animal studies suggests that sex steroid hormones play a role in CKD (Chen, Naftilan, and Oparil 1992, Klett et al. 1993, Ji et al. 2007, Rogers et al. 2007, Sandberg 2008, Yanes, Sartori-Valinotti, and Reckelhoff 2008).

In humans, the mechanisms for sex differences in CKD may include the influence of estradiol and/or testosterone on renal function, but this is not well understood or agreed upon, and few studies have objectively examined sex steroid hormone levels in relation to CKD endpoints. Generally, estradiol is considered protective in relation to kidney function. Many studies evaluating the effects of exogenous estradiol administered as part of hormone replacement therapy on kidney function have been conducted in samples of postmenopausal women. Results from these studies have

varied from null association (Manning et al. 2003) to both positive (Szekacs et al. 2000, Agarwal et al. 2005) and negative associations (Ahmed et al. 2008). In the Rancho Bernardo Study, current use of postmenopausal estrogen therapy was associated with lower odds of CKD at baseline, but there was no association with eGFR across the 10-year follow-up period (Fung et al. 2011). Another study of 5,845 women ages 66 and older found oral estrogen therapy to be associated with a dose dependent decrease in eGFR across a two-year period (Ahmed et al. 2008). These studies have varied in the endpoints examined, information available on duration and dose of hormone use, and in the inclusion, exclusion, or adjustment for comorbid diabetes. Female protection via estrogen may no longer be present in cases of comorbid diabetes (Maric and Sullivan 2008), where evidence of sex differences and the effects of sex hormones on kidney function is even less conclusive. To the best of our knowledge, only one study has objectively evaluated the association between sex hormone levels and kidney function in pre- and postmenopausal women, and results indicated no association at baseline (cross-sectionally) nor after 11 years of follow-up (Kim et al. 2019).

Among men, a limited number of studies have investigated the association between sex hormone levels and eGFR or albuminuria. In a study of 101 Swedish men without diabetes aged 18 to 50 years old, total and free testosterone levels were negatively associated with eGFR-based CKD stage (Hylander and Lehtihet 2015). In these same men, average levels of luteinizing hormone were positively associated with eGFR-based CKD stage and there was no association with sex hormone-binding globulin (SHBG) (Hylander and Lehtihet 2015). Among men with CKD stage 1 (eGFR ≥90 ml/min per 1.73 m^2) the average serum LH level was 4.16 U/L, whereas among

men with CKD stage 5 (eGFR <15 ml/min per 1.73 m^2) the average serum LH level was 9.43 U/L. In a subsample of overweight and glucose intolerant men from the Diabetes Prevention Program and the follow-up Diabetes Prevention Program Outcomes Study, cross-sectional analyses showed inverse associations between estradiol and dehydroepiandrosterone sulfate (DHEAS) with eGFR and a positive association between DHEAS and UACR. In longitudinal analyses, higher levels of SHBG at baseline were associated with lower risk for low eGFR (HR per SD: 0.80 95% CI, 0.57 to 0.90) across the 11 year follow-up period (Kim et al. 2019). Yi and colleagues evaluated the associations between sex hormones and kidney function among male participants in the Third National Health and Nutrition Examination Survey (NHANES III), finding that average concentrations of free testosterone were higher in men with low eGFR relative to those with eGFR ≥ 60 mL/min/1.73m^2 (Yi et al. 2009). After multivariable adjustment, only free estradiol was associated with the odds of low eGFR (OR tertile 3 versus tertile 1=3.04, 95% CI (1.22, 7.57)).

D. Persistent Organic Pollutants

Persistent organic pollutants are synthetic compounds with the ability to persist in the environment and act as endocrine disruptors in the human body. These compounds can act within the body by mimicking, blocking, or interfering with the hormones the human body makes naturally (Diamanti-Kandarakis E, Bourguignon JP, Giudice LC, Hauser R, Prins GS, Soto AM, Zoeller RT, Gore AC Endocr Rev. 2009). Used heavily in the 20th century and later banned, POPs entered the environment as herbicides, pesticides, plastics, and electrical equipment. Common POPs include PCBs and

organochlorine pesticides, many of which have long half-lives of at least 10-15 years (Tee et al. 2003, Ritter et al. 2011, Axmon and Rignell-Hydbom 2006).

1. Polychlorinated biphenyls

Polychlorinated biphenyls are well known for their fire-resistant properties and as such were used in electrical equipment until the late 1970s when their use was discontinued in the United States. These substances are stored in fat, have the capacity to bioaccumulate, and are persistent in the food chain (Beyer and Biziuk 2009). Total concentrations in the human body have been declining over time (Hagmar et al. 2006), but continue to persist due to long half-lives (Hopf et al. 2013) and continuous exposure from certain foods such as fatty fish, meat, and dairy products (Knutsen et al. 2011, Malisch and Kotz 2014). Contemporary exposure is also possible through contact or spills from old electrical equipment and from PCB-containing building materials such as caulk used in buildings constructed prior to the ban (Herrick et al. 2004).

The PCB chemical structure consists of two benzene rings connected by a carbon-carbon bond, with one to ten chlorine atoms attached to it. Exposure to PCBs generally occurs in mixtures because there are 209 different PCB congeners that have variable degrees of chlorination. The health effects of exposure depend on the number and position of each chlorine on the biphenyl ring, the combination of congeners, and their interactions. In general, the variation in PCB structure and chlorination leads to variation in the mechanism of action and known biological activity of individual congeners. Although the literature has not been consistent, in general non-planar PCBs with chlorines placed in the ortho position and/or their metabolites may be estrogenic as

demonstrated in various in vitro and in in vivo studies and are considered to be non-dioxin-like (Arcaro et al. 1999, Gierthy, Arcaro, and Floyd 1997, Jansen et al. 1993). This is in contrast to coplanar PCBs with non- and mono-ortho chlorines, which are structurally similar to 2,3,7,8-tetrachlorodibenzo-p-dioxin and are considered anti-estrogenic and dioxin-like (Krishnan and Safe 1993, Ahlborg et al. 1995). Inconsistencies in associations between various PCBs and health effects and the large number of analytes available to measure and evaluate has led to numerous studies which have investigated strategies to group various PCB congeners (McFarland and Clarke 1989, Moysich et al. 1999), including constructing a summary measure of total PCBs, and creating groupings of hypothesized estrogenic, anti-estrogenic, and mixed analytes (Wolff et al. 1997) or groupings by mechanism of action relative to altered gene expression (Warner et al. 2012).

2. Organochlorine pesticides

Organochlorines such as 2,2-bis(p-chlorophenyl)-1,1,1-Trichloroethane (DDT), the metabolite DDE, hexachlorobenzene, β-hexachlorocyclohexane, oxychlordane (a metabolite of chlordane), and *trans*-nonachlor (a component of chlordane) have previously been used as pesticides or insecticides. Before being banned in the United States in 1973, DDT was used as a pesticide on agricultural crops (Agency for Toxic Substances and Disease Registry (ATSDR) 2019). Hexachlorobenzene was manufactured and used as a fungicide in the United States until 1984. At present it is created as a waste product when chlorinated hydrocarbons are produced (Agency for Toxic Substances and Disease Registry (ATSDR) 2015). β-

hexachlorocyclohexane is one of eight isomers of hexachlorocyclohexane, which was used as an insecticide on crops and animals. Although no longer produced in the United States, gamma-hexachlorocyclohexane can be imported for use as an insecticide and is commonly used in medications to treat mites and head lice (Agency for Toxic Substances and Disease Registry (ATSDR) 2005). Chlordane was used as a pesticide on agricultural crops, lawns, gardens, and in fumigation in the United States from 1948 to 1978. In the early 1980's it was used in homes to control termites.

Prior analyses of serum levels of organochlorine pesticides from the NHANES indicate that serum levels are detectable in a majority of persons aged 12 years and older in the United States and are especially high among older adults ages 60 and older (Sjodin et al. 2014, Patterson et al. 2009). High levels among older adults is likely due to exposure particularly during times when use of these compounds was high.

E. Persistent Organic Pollutants and Thyroid Hormones

Exposure to PCBs and pesticides has been linked to alterations in levels of thyroid hormones in multiple studies in both animal models and in humans. Several studies in rats have shown a decrease in peripheral thyroid hormones after exposure to various classes of POPs (Hallgren and Darnerud 2002, Hallgren et al. 2001). In a study of rats, PCB, but not DDT, exposure was inversely associated with T3 uptake (Bastomsky 1974). Another study of rats was suggestive of an inverse association between PCBs and total thyroxine (T4) (Ness et al. 1993). In a study of birds, DDT exposure was associated with lower levels of T3 and T4 (Scollon, Carr, and Cobb 2004), but this was not observed in a study of rats (Desaulniers et al. 2005).

Hexachlorobenzene has been inversely associated with T4 and T3 (Foster et al. 1993, Alvarez et al. 2005, den Besten et al. 1993). Postulated mechanisms of action include interference with thyroid hormones binding to receptors, altered binding with serum transport proteins such as thyroid-binding globulin (Cheek et al. 1999), and/or induction of altered thyroid hormone metabolism (Boas et al. 2006, Khan et al. 2002).

The magnitude and direction of associations between these chemicals and thyroid hormones in human studies have not been consistent and have frequently differed by sex. Among adults in Brazil, associations between exposure to DDT, hexachlorobenzene, and β-hexachlorocyclohexane with thyroid function differed by sex (Freire et al. 2013). Persky et al. (Persky et al. 2012) found an inverse association between PCB exposure and TSH and T3 among men, and an inverse association between PCB exposure and T3 uptake but not TSH among post-menopausal women (Persky et al. 2011). Sex differences have been observed in other studies as well. A Canadian study that examined these associations among men and women found PCB levels to be inversely associated with T4 but not T3 among men (Abdelouahab et al. 2008). In this same study, PCB levels were inversely associated with T3 but not T4 among women (Abdelouahab et al. 2008). In the NHANES 1999-2002 cycle, analyses among older women showed that PCB exposure was positively associated with TSH, however, among older men, PCB exposure was inversely associated with TSH (Turyk, Anderson, and Persky 2007). Turyk et al. also found total PCBs to be inversely associated with T3, T4, and TSH among male participants from a cohort of people that consumed sport caught fish (Turyk et al. 2006). A study of adult men recruited from an infertility clinic found positive associations between DDE and both free T4 and total T3,

and inverse associations between DDE and TSH, PCB 138, PCB 153, sum of PCBs and HCB with T3 (Meeker, Altshul, and Hauser 2007). A positive association between total PCBs and PCB 153 was observed with FT3, and no association with TSH among a population in Italy, but sex-specific analyses were not conducted (Donato et al. 2008). Among participants of the Anniston Community Health Survey, thyroid-like PCBs (sum of PCBs 28, 52, 74, 101, 105, and 118), HCB, and DDE were inversely associated with total T3, but not associated with TSH or T4 (Benson et al. 2018). These differences could be due to variation in study populations and/or in sources and levels of exposure.

F. Persistent Organic Pollutants and Sex Hormones

Animal studies provide supportive evidence of effects on sex hormones following exposure to POPs. Female and male rat offspring had decreased testosterone levels after maternal prenatal oral chlordane administration (Cassidy et al. 1994), however, plasma testosterone level was unchanged in male rats fed 19.5 mg/kg/day chlordane for 90 days (Shain, Shaeffer, and Boesel 1977). In a study of male mice, treatment with chlordane resulted in degeneration of spermatogenic epithelium (Balash, Al-Omar, and Abdul Latif 1987). Young female goats exposed to PCB 153 had lower levels of luteinizing hormones, delayed puberty, and higher progesterone levels relative to unexposed goats (Lyche et al. 2004).

Endocrine disrupting chemicals like PCBs and pesticides may influence levels of sex steroid hormones in humans, yet few epidemiologic studies have utilized sex hormones as endpoints. Among postmenopausal women, occupational PCB exposure was inversely associated with FSH and SHBG (Persky et al. 2011). A cross-sectional

study of 77 peri- and postmenopausal women in Brazil found inverse associations between LH and hexachlorobenzene, DDT, and dichloro-diphenyl-dichloroethane (DDD) (Freire et al. 2014). An inverse association was also observed for DDD and FSH among these women, but no associations were observed with estradiol (Freire et al. 2014). Testosterone was measured among 304 men in the same area, and heptachlor and DDT concentrations were inversely associated with testosterone levels (Freire et al. 2014). Among 178 men living near the Great Lakes with measurements of PCB and DDE, PCB exposure from fish consumption was inversely associated with SHBG-bound testosterone, but not associated with SHBG or levels of free testosterone (Persky et al. 2001). Among the same men, neither exposure to PCBs nor DDE was associated with estrone sulfate, FSH, LH, nor DHEAS (Persky et al. 2001). In a subsample of 56 frequent and infrequent Great Lakes fish consumers with measurements of total noncoplanar PCBs, total toxic equivalents (TEQs) from dioxin-like organochlorines, and DDE measurements, PCB exposure was inversely associated with SHBG-bound testosterone and DDE exposure was inversely associated with estrone sulfate (Turyk et al. 2006). No association was observed between concentrations of PCBs, TEQs, or DDE with any measure of FSH, LH, free testosterone, nor SHBG (Turyk et al. 2006). When modeled in combination, PCBs were inversely associated with both estrone sulfate and SHBG, and TEQs were positively associated with estrone sulfate and SHBG (Turyk et al. 2006). Among 305 Swedish men, PCB 153 concentration was inversely correlated with free testosterone, but no correlation was observed for FSH, SHBG, LH, or estradiol (Richthoff et al. 2003). In a pooled study of men living in Greenland, Poland, Sweden, and Ukraine DDE was associated with FSH, and other associations varied by

study site (Giwercman et al. 2006). This included positive associations between PCB 153 and DDE with SHBG and LH among the men from the Ukraine, but among men from Greenland only PCB 153 was associated with LH (Giwercman et al. 2006). A study of men in Norway observed a positive association between PCB 153 and SHBG (Haugen et al. 2011). Pesticides and PCBs may alter binding and activity of endogenous sex hormones at the level of the estrogen, androgen, and aryl hydrocarbon receptors (Craig, Wang, and Flaws 2011, Whitehead and Rice 2006) in addition to altering their metabolism and affecting their excretion.

G. Persistent Organic Pollutants and Kidney Function

Existing evidence from animal and human studies suggest POPs may be a risk factor for CKD. A study in the artic fox found a higher prevalence of glomerular, tubular and interstitial renal lesions in animals fed a diet high in POPs relative to those on the control diet (Sonne et al. 2008). A study in rats showed that treatment with dioxins and PCBs resulted in increases in serum creatinine and injury to the kidney, and that the chemicals had a synergistic effect (Lu et al. 2009). The few studies that assessed the relationship between POPs and kidney function in humans were largely cross-sectional and focused on diabetic nephropathy with mixed results (Everett and Thompson 2016, 2015, Everett, Thompson, and Dismuke 2017). One study using the 1999-2004 NHANES cycles, analyses restricted to Mexican American participants showed that p,p'-DDT levels above 0.086 ng/g compared to levels less than or equal to 0.086 ng/g were associated with increased odds of diabetes and UACR >30 mg/g (OR= 4.42, 95% CI 2.23-8.76) (Everett, Thompson, and Dismuke 2017). In this same study, levels of DDE in the fourth quartile relative to the first quartile were associated with higher odds of

diabetes with UACR >30 mg/g (OR= 14.95, 95% CI 2.96-75.48). This study did not examine other pesticides or associations with eGFR. Another study of the NHANES 1999-2004 cycles showed levels of heptachlor epoxide to be associated with odds of diabetes with UACR >30 mg/g (OR= 1.75, 95% CI 1.05-2.93) (Everett and Thompson 2015). This study did not examine associations with eGFR, nor did it use sex-specific cut points for UACR categorization.

Few studies have examined these associations among persons without diabetes. One cross-sectional study in a non-diabetic population suggested that exposure to POPs may be associated with kidney disease independent of diabetes status (Huang, Ding, et al. 2016). In a small (n=149) longitudinal study of patients with diabetes, exposure to non-dioxin-like PCBs (PCB 28, PCB 49, PCB 44) was associated with as much as 75% higher risk of ESRD (Grice et al. 2017). More recently, investigations into the origins of CKD in agricultural communities in Central and South America, and in Asia have shown inverse associations between pesticide exposures and eGFR and positive association with urinary albumin levels among CKD patients (Siddarth et al. 2014, Siddharth et al. 2012, Ghosh et al. 2017).

Exposure to POPs as a risk factor for CKD is largely underexplored, particularly in the context of normal glucose parameters. Persistent organic pollutants that are excreted primarily via the urinary tract may be more likely to accumulate in the kidneys. Evidence suggests that these exposures may impact kidney function, indicating a need for studies that examine these risk factors longitudinally and in populations that are racially diverse and inclusive of both sexes. Further study may also provide evidence to support or reject the hypothesis that associations between POPs and kidney function

are largely the result of reverse causation (Everett and Thompson 2014), an argument that has been made in response to associations seen among participants with diabetic nephropathy. Mechanistically, POPs and their metabolites may interfere with endocrine processes by affecting the hypothalamic-pituitary-gonadal (Diamanti-Kandarakis et al. 2009) and hypothalamo–pituitary–thyroid (Fisher et al. 2006, Khan et al. 2002) axes in the pathway to kidney disease, leading to disease development and/or progression.

H. Metabolism and Toxicity of Persistent Organic Pollutants in the Kidney

Humans are exposed to PCBs and pesticides through dermal, inhalation, and oral exposure routes. Once they enter the body, the rate with which PCBs are metabolized is dependent on the number and positions of the chlorine molecules that are present (Mathews and Anderson 1975). Highly chlorinated PCBs and pesticides accumulate in tissues rich in lipids such as the liver, adipose tissue, or plasma due to their lipophilic disposition (Kutz, Wood, and Bottimore 1991, Fangstrom et al. 2002).

The biological pathways through which exposure to POPs may increase the risk of chronic disease outcomes such as kidney disease are not completely understood. Different POPs may be estrogenic or anti-estrogenic and have the potential to synergistically disrupt the endocrine system (McFarland and Clarke 1989, Wolff et al. 1997, Moysich et al. 1999, Safe 1994b, a). Numerous studies provide evidence suggesting that endocrine pathways may be involved (Mostafalou and Abdollahi 2013, 2017); however, specific hormonal pathways have not been explored fully.

III. RELATIONSHIPS BETWEEN ENDOGENOUS THYROID HORMONES AND KIDNEY FUNCTION: FINDINGS FROM THE HISPANIC COMMUNITY HEALTH STUDY/STUDY OF LATINOS (HCHS/SOL)

A. Rationale

Impaired kidney function is a growing public health issue affecting a large proportion of adults in the United States and globally. Identification of factors related to kidney disease that are amenable to intervention is necessary to decrease the burden of disease. Altered states of thyroid function have been connected to reduced kidney function in prior studies, but these studies have primarily been conducted in samples of persons with advanced kidney disease. In a sample representative of the U.S. population, the proportion of individuals with hypothyroidism was larger in those with lower levels of eGFR (Lo et al. 2005). This cross-sectional finding has been replicated in other studies of adults with and without diagnosed CKD (Asvold, Bjoro, and Vatten 2011, Chonchol et al. 2008), suggesting that alterations in thyroid hormone levels may be associated with CKD. To date, no study has assessed the associations of endogenous thyroid hormones and CKD using prospective data from a diverse cohort of Hispanics/Latinos. There is a clear need for more studies to evaluate factors related to kidney disease in diverse populations using epidemiologic data. Prior analysis of the HCHS/SOL cohort showed the overall prevalence of CKD among Hispanics/Latinos at baseline was 13.7% with significant variation among different Hispanic/Latino background groups (Ricardo et al. 2015). The overall goal of this study was to examine the relationships of endogenous thyroid hormones with CKD in an ethnically diverse Hispanic/Latino population who were enrolled in a community-based cohort study and

who did not have diabetes at baseline. Our specific aims were to 1) describe the relationships of endogenous thyroid hormones measured at baseline, with baseline prevalence of CKD and measures of eGFR and UACR; 2) determine if levels of endogenous thyroid hormones were associated with changes in eGFR and UACR from Visit 1 to Visit 2; and 3) examine the relationships of baseline levels of endogenous thyroid hormones with the subsequent development of CKD at Visit 2.

B. Methods

1. Study population

This study used baseline and prospective data from HCHS/SOL. In brief, HCHS/SOL is a multisite prospective cohort study designed to identify risk and protective factors for chronic disease among persons from diverse Hispanic/Latino background groups living across the United States. The cohort included 16,415 men and women between 18 to 74 years of age at the time of recruitment. Participants were recruited from 2008 until 2011 from randomly selected households in San Diego, CA; Bronx, NY; Chicago, IL; and Miami, FL. The HCHS/SOL included first through third generation participants of Mexican, Cuban, Puerto Rican, Dominican Republic, Central and South-American background. Details of the study design and sampling methods are previously published (Lavange et al. 2010, Sorlie et al. 2010). The Persistent Organic Pollutants, Endogenous Hormones and Diabetes in Latinos Ancillary Study oversampled from middle-aged and older participants ages 45-74 in the HCHS/SOL study using a case-cohort study design. To select the random sample, participants were stratified by baseline glucose measurements (1,176 with prediabetes at baseline and

1,174 with normal baseline glucose measurements) and approximately equally divided between men and women ages 45 -74 years (1,148 men and 1,202 women), and with only one participant per household within each sex and blood glucose subgroup. Participants who transitioned from pre-diabetes to diabetes during the follow up period were oversampled to ensure that approximately half of those in this category had transitioned to diabetes. The final ancillary study sample consisted of 2,350 HCHS/SOL males and females who either had prediabetes or normal glucose parameters at Visit 1.

Of the 2,342 HCHS/SOL ancillary study participants with hormone measurements available, 2,019 (86%) were included in the cross-sectional analyses and 1,980 (84%) in the longitudinal analyses comparing eGFR and UACR at visits 1 and 2. A total of 323 participants (14%) were excluded because of missing data on at least one serum hormone (n=4), serum cystatin C (n=12) or urine albumin/creatinine ratio (n=115) or due to be excluded a priori (values are not mutually exclusive). We excluded participants who reported using oral/inhalantable glucocorticosteroid medications (n=33), thyroid medications (n=112), and/or any hormone replacement therapy (including androgens) (n=45). An additional 39 participants were excluded due to missing serum cystatin C (n=10) or urine albumin/creatinine ratio (n=54) data at Visit 2. For analyses of incident albuminuria and/or CKD composite, participants with low eGFR or albuminuria at visit 1 were excluded.

2. Variable definitions

a. Measures of kidney function

Urine albumin was measured on the ProSpec nephelometric analyzer (Dade Behring GMBH, Marburg, Germany) using an immunoturbidometric method. Urine creatinine was measured in both serum and urine on a Roche Modular P Chemistry Analyzer (Roche Diagnostics, Indianapolis, IN) using a creatinase enzymatic method. We defined albuminuria using sex-specific cutoffs (urine albumin/creatinine ratio ≥17 mg/g in males and ≥25 mg/g in females) (Mattix et al. 2002). Glomerular filtration rate (GFR) was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine-cystatin C equation ($eGFR_{creat-cyst}$) (Inker et al. 2012). Serum creatinine measurements were traced by isotope dilution mass spectrometry. Serum cystatin C was measured using a turbidimetric method on the Roche Modular P Chemistry Analyzer (Gentian AS, Moss, Norway). Low eGFR was defined as $eGFR_{creat-cyst}$ <60 ml/min per 1.73 m2. At baseline, CKD was defined by either a low eGFR or the presence of albuminuria using sex-specific cutoffs. We defined incident low eGFR as eGFR <60 ml/min per 1.73 m2 with eGFR decline ≥1 ml/min per 1.73 m2 per year of follow –up. We defined incident CKD as low eGFR <60 ml/min per 1.73 m2 with eGFR decline ≥1 ml/min per 1.73 m2 per year of follow -up or presence of new onset albuminuria (sex-specific) at Visit 2 among those who did not have low eGFR or albuminuria at Visit 1.

b. Hormone measurements and definitions of thyroid disease

Serum samples for thyroid hormone measurements were collected at the baseline HCHS/SOL examination visit. All hormones were measured using a Roche COBAS 6000 chemistry analyzer (Roche Diagnostics, Indianapolis, IN). Thyroid-stimulating hormone (TSH, thyrotropin) was measured using a TSH reagent/sandwich immunoassay method/electrochemiluminescence (Roche Diagnostics, Indianapolis, IN). This method has been standardized against the 2nd IRP WHO Reference Standard 80/558. Interassay coefficient of variation (CV) was 2.1% at 1.596 mlU/L and 2.9% at 9.037 mlU/L. Free thyroxine was measured using a FT4 reagent/competitive immunoassay/electrochemiluminesence (Roche Diagnostics, Indianapolis, IN). This method has been standardized by isotope dilution gas chromatography/mass spectrometry. Interassay CV was 2.5% at 1.16 ng/dL and 2.6% at 2.64 ng/dL. Triiodothyronine (total T3) was measured using a T3 reagent/competitive immunoassay/electrochemiluminescence (Roche Diagnostics, Indianapolis, IN). This method has been standardized against reference standards by weighing T3 into analyte-free human serum matrix. Interassay CV was 6.0% at 152.4 ng/dL and 7.2% at 353.00 ng/dL. The lower limits of detection for TSH, FT4, and T3 were 0.005 mIU/L, 0.023 ng/dL, and 19.5 ng/dL, respectively. All hormone assays are FDA approved and independently assessed with external proficiency testing materials. All assays are performed by the Advanced Research & Diagnostics Laboratory at the University of Minnesota, which is a CAP/CLIA certified laboratory.

We defined euthyroid as having both TSH and FT4 levels in the normal reference range as defined by the laboratory. For TSH normal reference ranges were

0.27-4.20 mIU/L and for FT4 normal reference ranges were 0.93-1.70 ng/dL. All participants with TSH or FT4 levels outside these ranges were considered noneuthyroid. We defined hypothyroidism using ranges for both subclinical and overt hypothyroidism (Garber et al. 2012). Subclinical hypothyroidism was defined as serum TSH concentrations above the reference range of >4.20 mIU/L, and FT4 concentrations within the reference range of 0.93-1.70 ng/dL. Overt hypothyroidism was defined as TSH concentrations above the reference range of >4.20 mIU/L, and FT4 concentrations below the reference range of <0.93 ng/dL. We also defined categories of subclinical and overt hyperthyroidism. Subclinical hyperthyroidism was defined as TSH concentrations below the reference range <0.27 mIU/L with FT4 concentrations within the reference range of 0.93-1.70 ng/dL. Overt hyperthyroidism was defined as TSH concentrations below the reference range <0.27 mIU/L with FT4 concentrations above the reference range >1.70 ng/dL.

c. Covariates

Study participants reported their age, sex, years of education (less than high school, high school, more than high school), Hispanic/Latino heritage, household income (<10k, 10k-20k, 20k-40k, 40k-75k, 75k+), health insurance status (yes/no), nativity (born in U.S. (yes/no)), heritage group (Central American, Cuban, Dominican, Mexican, Puerto Rican, and South American), language (Spanish/English), and current smoking status (never, former, or current smoker). Anthropometric measurements of weight (kilograms), height (centimeters), and waist circumference (centimeters) were performed by trained study staff following a standard protocol. Body mass index (BMI) was calculated as weight in kilograms divided by height in squared meters.

Questionnaire, examination, and laboratory data was used to classify diabetes status (normal or prediabetes at baseline) and hypertension status (yes/no). Systolic and diastolic blood pressure measurements (mmHg; continuous) were taken using a standardized study protocol. Total, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol (continuous, mg/dL) and triglycerides (continuous, mg/dL) were measured. At the study visit, participants brought their medications with them, and medication labels were scanned. Medication use was reported for: antihypertensives, angiotensin-converting-enzyme (ACE) inhibitors, angiotensin II receptor antagonists, Nonsteroidal anti-inflammatory drugs (NSAIDs), diuretics, hormone replacement medications, statins, and thyroid medications.

Among females, menopause status was derived by a series of steps that included evaluation of the participant's age (≥62 years old determined to be post-menopausal) and menstruation status (among those who reported absence of menses, if FSH was >25.8 mIU/mL or LH >7.7 mIU/mL, the participant was determined to be post-menopausal (n=677); among with FSH < 25.8 mIU/mL and LH < 7.7 mIU/mL, the participant was determined to be peri-menopausal). If the participant reported current menses or did not answer the question regarding menstruation status, if FSH was >25.8 mIU/mL or LH >7.7 mIU/mL, the participant was determined to be peri-menopausal (n=182) and for those with FSH < 25.8 mIU/mL and LH < 7.7 mIU/mL, the participant was determined to be pre-menopausal (n=117).

3. Statistical analysis

All analyses used SAS Version 9.4 (Cary, NC) and Stata Statistical Software, Release 13 (StataCorp LP, College Station, TX) and followed methodology for complex survey data, taking the appropriate ancillary study sampling weights into account. The analyses were conducted in a series of three steps. Distributions of all continuous outcomes and covariates were examined, and the natural log transformation was applied to those that were skewed. Then descriptive statistics using baseline data from the HCHS/SOL ancillary study were produced to show the proportions of study participants with low eGFR, albuminuria, and the composite CKD overall and by demographic characteristics such as age, sex, education, income, language preference, and specific Hispanic/Latino background. The Rao-Scottt Chi-square test was used to compare weighted proportions, and the t-test was used to compare weighted means. Geometric means for each thyroid hormone with 95% confidence intervals (95% CIs) were produced overall and by covariates. For descriptive purposes, continuous covariates were categorized or dichotomized using clinically relevant cut points that included LDL ≥160 mg/dL, HDL < 40 mg/dL, and triglyericides ≥200 mg/dL (Expert Panel on Detection 2001).

Cross-sectional associations between each continuous thyroid hormone (TSH, FT4, and T3) and measures of eGFR and log UACR were estimated using linear regression models. Logistic regression models were estimated for the dichotomous outcomes albuminuria and the CKD composite. Due to the small number of cases, odds of low eGFR was not evaluated. We also evaluated associations of euthyroid vs. noneuthryoid and hypothyroid (subclinical and overt) vs. not hypothyroid. Multivariable linear and

logistic models were built for each hormone concentration or disease state with a forward approach, first evaluating the linearity assumption by adding a quadratic term to the model. In the presence of significant quadratic terms, the natural log transformation of the hormone was modeled. Hormones were also modeled as quartiles to evaluate non-linear relationships. Quartiles were modeled as an ordinal variable to evaluate linear trend. Evaluation of the presence of effect modification was conducted by adding an interaction term between the hormone and the covariate to the model. Effect modification was assessed for sex (male vs. female), prediabetes (normal vs. prediabetes), and hypertension (present vs. absent). For effect modification, a p-value < 0.05 was considered statistically significant. Significant and meaningful interaction terms are presented as stratified results. The forward approach was used to assess confounding by adding potential confounding variables to the model one at a time and evaluating a > 10% change in the estimate.

Linear regression models were used to prospectively assess changes in eGFR and log UACR from visit 1 to visit 2. The relationships of both continuous and ranked quartile values of each thyroid hormone was evaluated after controlling for baseline eGFR and UACR values, time elapsed between study visits, and relevant confounders. In addition to examining baseline characteristics as potential confounders, differences in covariates comparing visit 2 to baseline levels were considered as confounders. We assessed potential confounding by time varying factors in our prospective analyses for diabetes status (normal, pre, or diabetes at Visit 2), systolic and diastolic blood pressure measurements (mmHg; continuous), body mass index (continuous, kg/m^2), total, LDL & HDL cholesterol (continuous, mg/dL), and triglycerides (continuous, mg/dL) by adding

the visit 2 variable to the model for categorical characteristics or by adding the difference between visit 1 and visit 2 values to the model for continuous characteristics. Effect modification was assessed for sex (male vs. female), and baseline diabetes (normal vs. prediabetes) and hypertension (present vs. absent) status in a manner consistent with the methods used on the cross-sectional analyses. For effect modification, a p-value < 0.05 was considered statistically significant.

Logistic regression models were used to explore risk for incident CKD, as previously defined, and new onset albuminuria at Visit 2 among those who did not have low eGFR or albuminuria at Visit 1. In these models, associations were evaluated between both continuous and ranked quartile hormone values. Evaluation of effect modification by sex, diabetes, and hypertension (at Visit 1) and adjustment for confounders was determined as in previous models.

C. Results

Among the 2,019 sample participants with cross-sectional data, the median age was 55 years (IQR 48 to 62), mean eGFR was 93.5 mL/minute/1.73m^2 (95% CI 92.2 to 94.8), and median UACR was 6.2 mg/g (IQR 4.6 to 11.0). Overall, 44 participants had low eGFR (weighted proportion 2.6% (95% CI 1.6, 3.7%), 225 participants had albuminuria (10.8% (95% CI 8.7, 13.0%)), and 250 had CKD (12.4% (10.1, 14.7%)). Tables I and II present the overall baseline demographic and clinical characteristics of the sample, in addition to the characteristics by low eGFR, albuminuria, and CKD status. Participants with low eGFR tended to be older and have lower total cholesterol levels compared to participants without low eGFR, but there was no age or difference in

lipids with respect to albuminuria. Compared to those without, a larger proportion of those with low eGFR, albuminuria, and the CKD composite had hypertension, and levels of systolic and diabetes blood pressure were higher on average.

In our sample of participants not using thyroid medications there were 1729 participants (86.5%) who had normal thyroid levels without any sign of overt or subclinical disease. There were 6 cases (0.3%) of subclinical hyperthyroidism, and 6 cases (0.3%) of overt hyperthyroidism. In total, there were 141 cases of hypothyroidism, including 101 (4.4%) subclinical and 40 (2.3%) overt cases. Although the proportion of participants with low eGFR was smaller among those with hypothyroidism compared to non-hypothyroid (Table 1), the number of cases with low eGFR and hypothyroidism was small (n=2). The proportions with albuminuria and the CKD composite did not differ by thyroid disease status.

Geometric mean levels of TSH, FT4, and T3 are presented in Table III overall and by select covariates. The average level for each hormone did not vary with age, and only T3 levels appeared to vary by sex. Among females, hormone levels were similar among pre, peri, and postmenopausal women. The most marked differences in hormone levels were among the contrasts of cigarette use, with never smokers having higher TSH and lower T3 levels relative to current smokers. Although TSH and T3 levels appeared lower among those with low eGFR, albuminuria, or the CKD composite, differences were not statistically significant. FT4 levels were slightly higher among those with low eGFR (1.22 ng/dL), compared to those with eGFR ≥ 60 (1.12 ng/dL).

Cross-sectional associations between the thyroid hormone concentrations and eGFR are shown in Table IV. When modeled as a continuous variable, TSH levels were inversely associated with eGFR after multivariable adjustment (continuous β=-0.13 (95% CI -0.18, -0.08), p<0.0001). A similar inverse trend was observed with ranked quartiles of TSH (p for trend<0.0001, Q4 vs. Q1 β=-6.3 (95% CI –8.9, -3.7), p<0.0001). We observed significant interaction terms between both TSH and baseline prediabetes status (p-interaction=0.007) and TSH and sex (p-interaction=0.001). The interaction terms remained significant when both were added to the same model, but the three-way interaction term between sex, prediabetes, and TSH was not statistically significant. In models for TSH stratified by prediabetes status, the magnitude of the inverse association was larger among those with normal glucose levels (continuous β=-0.89 (95% CI -1.5, -0.31), p=0.003) relative to those with prediabetes (continuous β=-0.13 (95% CI -0.17, -0.09), p<0.0001). A similar difference in the magnitude of the association was observed comparing the association among males (continuous β=-1.2 (95% CI -1.8, -0.61), p<0.0001) to that of females (continuous β=-0.13 (95% CI -0.16, -0.10), p<0.0001). Relative to those without hypothyroid, participants with subclinical or overt hypothyroidism had lower average eGFR levels.

When modeled as a continuous variable, levels of FT4 appeared to be inversely associated with eGFR, but the associations were not statistically significant. When modeled using ranked quartiles, FT4 concentrations in the highest quartile (levels ranging from 1.25 to 4.38 ng/dL) were inversely associated with eGFR compared to the lowest quartile (levels < 1.03 ng/dL). T3 did not appear to be associated with eGFR at baseline in any of the models.

Cross-sectional associations between the thyroid hormone concentrations and continuous UACR are shown in Table V. Concentrations of TSH, FT4, and T3 were not associated with UACR in crude or multivariable adjusted models. When the odds of albuminuria were modeled as shown in Table VI, neither TSH nor FT4 concentrations were associated with odds of albuminuria. When T3 concentration was modeled, the association did not appear to be linear (p-value quadratic=0.02), and log T3 was associated with lower odds of albuminuria when modeled as a continuous variable (p=0.0004). Estimated odds using ranked quartiles of T3 showed lower odds of albuminuria comparing Q4 to Q1, but estimates were not statistically significant. A similar pattern was observed with odds of the CKD composite, which was comprised mostly of cases of albuminuria. There was no association with hypothyroidism.

In total 1,980 participants in this study had data available to compare kidney health parameters at visit 1 and visit 2. Characteristics of participants at each visit are presented in Table VII. Across an average 6 year follow up period, a large proportion of participants at visit 2 enrolled in health insurance. The proportion of participants at visit 2 with hypertension, diabetes, and taking related medications was larger relative to that at visit 1. Average lipid profiles at visit 2 were better relative to visit 1, and average eGFR and UACR decreased slightly. The proportion of participants with low eGFR was 4.6% at visit 2, which is higher than the 2.6% with low eGFR at visit 1.

In regards to the associations between thyroid hormone concentrations measured at visit 1 (baseline) and eGFR measurements at visit 2, results are presented in Table VIII. TSH did not appear to be associated with eGFR at visit 2 in pooled analysis, however, we observed significant interaction terms between TSH and baseline hypertension

status (p-interaction=0.02) and TSH and sex (p-interaction=0.001). The interaction terms remained significant when both were added to the same model, but the three-way interaction term between sex, hypertension, and TSH was not statistically significant. In models for TSH stratified by hypertension status, an inverse association was observed among those with hypertension (log TSH β=-2.3 (95% CI -4.1, -0.62), p=0.008) with no association among those without hypertension (log TSH β=-0.05 (95% CI -1.9, 1.8), p=0.95). When stratified by sex, the association with TSH was positive among males, and inverse among females. A similar difference in the magnitude of the association was observed comparing the association among males (continuous β=1.8 (95% CI 0.39, 3.1), p=0.01) to that of females (continuous β=-2.1 (95% CI -3.5, -0.78), p=0.002). There was no association between hypothyroidism and eGFR (data not shown). There were no associations between FT4 and eGFR (data not shown), nor did we observe associations between T3 concentrations when modeled as a continuous or ranked quartile variable (data not shown). We did, however, observe an inverse association when T3 concentration was categorized using the clinical reference ranges available and dichotomized into high concentration vs. normal/low concentration (β=-6.8 (95% CI -12.5, -1.0), p=0.02)) indicating that those with T3 levels greater than 181 ng/dL had lower eGFR at visit 2 relative to those with levels less than 181 ng/dL (data not shown). This association was observed even after multivariable adjustment for eGFR at visit 1, time from Visit 1 to Visit 2, age (continuous, years), self-reported ethnicity/background, sex (male/female), systolic blood pressure (at visit 1), fasting blood glucose (at visit 1), triglycerides (at visit 1), and antihypertensive medication use (at visit 1). Visit 2 eGFR levels were not different comparing those with hypothyroidism to those without.

When associations between thyroid hormone concentrations measured at visit 1 and UACR measurements at visit 2 were assessed, we did not observe associations with TSH or T3 concentrations. There was no association between hypothyroidism and UACR (data not shown). When FT4 was modeled as a continuous variable, the estimated inverse association with UACR was not statistically significant, as presented in Table IX. When FT4 was modeled as a categorical variable, the contrast between Q4 vs. Q1 was significant indicating those with the highest FT4 levels at visit one had lower average UACR levels at visit 2 (Q4 GM=5.5 (95% CI 4.8, 6.3) vs. Q1 GM=6.7 (95% CI 5.9, 7.6), p=0.01).

After restricting to the 1,733 participants who had information on eGFR and UACR at visit 2 and who did not have low eGFR or albuminuria at visit 1, a total of 107 participants (5.6% (95% CI 3.7 to 7.4%)) had incident albuminuria and 141 participants (8.1% (95% CI 5.9 to 10.3%)) had incident CKD. We observed a positive association between TSH and odds of both incident albuminuria (OR=1.1 (95% CI 1.06, 1.18), p=0.001) and incident CKD composite (OR=1.2 (95% CI 1.05, 1.31), p=0.004). As presented in in Table X, estimates for increasing quartiles of TSH appeared associated with higher odds of both outcomes, but were not statistically significant. Visit 1 concentrations of FT4 were not associated with either outcome, and levels of T3 did not appear to be associated with incident albuminuria but there was a statistically significant positive association between T3 and the odds of the CKD composite. This discordance is concordant with the findings that high T3 levels are associated with worsening eGFR and not associated with UACR, and indicates that the association between T3 levels and incident CKD composite may be driven by the small numbers of cases of low eGFR and hence should be interpreted with caution.

TABLE I.
WEIGHTED BASELINE DEMOGRAPHIC AND CLINICAL UNIVARIATE (OVERALL) AND BIVARIATE (BY LOW EGFR, ALBUMINURIA, AND CKD STATUS) CATEGORICAL CHARACTERISTICS OF MALE AND FEMALE PARTICIPANTS (N=2,019)

	Overall	**eGFR <60** n=44 2.6% (95% CI 1.6, 3.7%)	**p-value**	**Albuminuria** n=225 10.8% (95% CI 8.7, 13.0%)	**p-value**	**CKD** n=250 12.4% (95% CI 10.1, 14.7%)	**p-value**
	N (weighted %)	**% (95% CI)**	<0.0001	**% (95% CI)**		**% (95% CI)**	
Male, %	1043 (47.5)	3.3 (1.5, 5.1)	0.23	12.9 (9.9, 15.9)	0.09	14.7 (11.5, 17.9)	0.07
Female, %	976 (52.5)	2.0 (0.7, 3.2)		9.0 (5.7, 12.3)		10.3 (6.9, 13.7)	
Menopause Status							
Pre	117 (8.5)	0.9 (0.0, 2.6)	0.04	12.4 (4.2, 20.6)	0.67	12.4 (4.2, 20.6)	0.65
Peri	182 (14.3)	0.3 (0.0, 1.0)		7.8 (2.7, 12.9)		7.8 (2.7, 12.9)	
Post	677 (77.2)	2.4 (0.8, 4.0)		8.9 (4.8, 12.9)		10.6 (6.4, 14.8)	
Hispanic/Latino background							
Central American	192 (7.0)	2.4 (0.0, 5.2)		7.2 (3.1, 11.2)	0.21	8.6 (3.7, 13.4)	0.10
Cuban	347 (28.1)	3.0 (0.4, 5.6)		10.1 (6.4, 13.7)		11.6 (7.4, 15.7)	
Dominican	190 (8.8)	3.0 (0.0, 6.1)		11.2 (5.1, 17.4)		13.8 (7.2, 20.4)	
More than one/Other heritage	44 (4.1)	3.5 (0.0, 10.4		11.2 (0.8, 21.6)		11.2 (0.8, 21.6)	
Puerto Rican	332 (15.4)	3.3 (0.6, 6.0)		16.7 (9.9, 23.4)		19.2 (12.2, 26.3)	
South American	162 (5.0)	0		4.6 (0.3, 8.9)		4.6 (0.3, 8.9)	
Mexican (ref)	752 (31.6)	2.2 (0.6, 3.7)		10.4 (5.8, 15.0)		11.6 (6.9, 16.3)	
Study Center, Bronx	455 (27.2)	3.2 (1.1, 5.3)	0.79	15.0 (8.8, 21.2)	0.11	17.3 (11.0, 23.6)	0.06
Chicago	514 (13.1)	2.2 (0.3, 4.2)		10.5 (6.8, 14.2)		11.4 (7.5, 15.3)	
Miami	539 (37.7)	2.8 (0.8, 4.7)		9.2 (6.4, 12.0)		10.6 (7.5, 13.7)	
San Diego	511 (22.0)	1.8 (0.0, 3.7)		8.7 (5.3, 12.0)		9.9 (6.3, 13.6)	
Born in United States, %	430 (20.2)	3.3 (1.0, 5.6)	0.53	15.3 (9.8, 20.9)	0.07	18.1 (12.2, 23.9)	0.03
<10 years living in US, %	398 (22.6)	2.8 (0.5, 5.0)	0.80	9.9 (6.2, 13.6)	0.68	10.3 (6.5, 14.1)	0.64
< High school education, %	790 (37.9)	2.6 (1.0, 4.1)	0.99	11.1 (6.7, 15.5)	0.38	13.0 (8.5, 17.6)	0.53

TABLE I (continued).
WEIGHTED BASELINE DEMOGRAPHIC AND CLINICAL UNIVARIATE (OVERALL) AND BIVARIATE (BY LOW EGFR, ALBUMINURIA, AND CKD STATUS) CATEGORICAL CHARACTERISTICS OF MALE AND FEMALE PARTICIPANTS (N=2,019)

	Overall	**eGFR <60** n=44 2.6% (95% CI 1.6, 3.7%)	**p-value**	**Albuminuria** n=225 10.8% (95% CI 8.7, 13.0%)	**p-value**	**CKD** n=250 12.4% (95% CI 10.1, 14.7%)	**p-value**
	N (weighted %)	**% (95% CI)**	<0.0001	**% (95% CI)**		**% (95% CI)**	
Income <$30,000 (annually), %	1293 (63.5)	2.8 (1.4, 4.2)	0.33	12.8 (9.8, 15.9)	0.04	14.5 (11.3, 17.7)	0.05
Have health insurance, %	970 (44.6)	3.7 (2.0, 5.4)	0.01	11.8 (8.8, 14.7)	0.41	14.3 (11.1, 17.6)	0.09
Current cigarette use, %	430 (21.0)	2.8 (0.8, 4.8)	0.73	10.4 (6.6, 14.2)	0.66	12.2 (8.1, 16.3)	0.78
Never drink alcohol, %	998 (54.4)	2.9 (1.5, 4.3)	0.56	9.8 (6.4, 13.1)	0.26	11.2 (7.8, 14.6)	0.35
Cardiovascular disease, %	146 (7.3)	7.8 (2.8, 12.8)	0.03	13.7 (6.7, 20.6)	0.40	18.8 (10.7, 26.9)	0.10
Hypertension (BP>=140/90 and Med Use)**, %**	655 (37.0)	5.9 (3.3, 8.5)	<0.0001	17.1 (13.2, 20.9)	<0.0001	20.7 (16.3, 25.1)	<0.0001
Body mass index (BMI), Norm/Und, %	374 (20.9)	2.4 (0.4, 4.5)	0.77	11.5 (6.2, 16.8)	0.59	12.8 (7.3, 18.3)	0.67
Overweight (25 ≤BMI<30), %	872 (43.7)	3.0 (1.2, 4.8)		9.5 (6.8, 12.1)		11.1 (8.1, 14.1)	
Obese (BMI ≥ 30), %	770 (35.4)	2.2 (0.7, 3.7)		12.1 (7.8, 16.5)		13.6 (9.1, 18.2)	
Prediabetes, %	1025 (60.0)	2.8 (1.5, 4.2)	0.60	12.6 (9.2, 15.9)	0.04	14.3 (10.9, 17.7)	0.03
Normal glucose, %	994 (40.0)	2.3 (0.5, 4.0)		8.3 (6.1, 10.5)		9.5 (6.9, 12.2)	
Medication use, %, ACEi/ARB	304 (18.0)	6.6 (3.0, 10.3)	0.01	13.6 (8.2, 19.0)	0.26	17.2 (11.2, 23.3)	0.08
NSAIDs	410 (19.7)	1.7 (0.2, 3.2)	0.26	7.9 (4.9, 10.9)	0.08	8.6 (5.4, 11.7)	0.03
Statins	202 (10.5)	10.3 (4.2, 16.4)	0.01	18.6 (6.7, 30.4)	0.18	24.1 (12.2, 36.0)	0.05
Antidepressants	134 (6.4)	6.3 (0.5, 12.0)	0.19	7.4 (2.2, 12.6)	0.21	12.2 (4.9, 19.6)	0.96
Low Physical activity, %	896 (46.6)	2.2 (1.0, 3.5)	0.73	12.4 (8.7, 16.1)	0.37	13.5 (9.7, 17.3)	0.57
Thyroid Disease:							
Noneuthyroid	290 (13.5)	1.5 (0.3, 2.7)	0.14	11.7 (2.4, 21.1)	0.83	13.0 (3.7, 22.3)	0.88
Euthyroid (normal)	1729 (86.5)	2.8 (1.6, 4.0)		10.7 (8.6, 12.8)		12.3 (10.1, 14.5)	
Hypothyroid	141 (6.7)	0.8 (0.0, 2.1)	0.04	14.9 (0.0, 32.3)	0.64	15.5 (0.0, 32.8)	0.71
Not hypothyroid	1878 (93.3)	2.7 (1.6, 3.9)		10.6 (8.6, 12.5)		12.2 (10.0, 14.3)	

TABLE II.
WEIGHTED BASELINE DEMOGRAPHIC AND CLINICAL UNIVARIATE (OVERALL) AND BIVARIATE (BY LOW EGFR, ALBUMINURIA, AND CKD STATUS) CONTINUOUS CHARACTERISTICS OF MALE AND FEMALE PARTICIPANTS (N=2,019)

	Overall	**eGFR <60** n=44 2.6% (95% CI 1.6, 3.7%)	**p-value**	**Albuminuria** n=225 10.8% (95% CI 8.7, 13.0%)	**p-value**	**CKD** n=250 12.4% (95% CI 10.1, 14.7%)	**p-value**
	Mean (95% CI)[a]	**Mean (95% CI)[a]**		**Mean (95% CI)[a]**		**Mean (95% CI)[a]**	
Age, yr[b]	55 (48-62)	64 (58-68)	<0.0001	55 (49-63)	0.67	57 (49-64)	0.07
Average systolic BP (mmHg)	128 (127, 129)	143 (133, 153)	0.003	140 (136, 144)	<0.0001	141 (137, 144)	<0.0001
Average diastolic BP (mmHg)	75 (74, 76)	81 (75, 87)	0.06	81 (78, 83)	<0.0001	81 (78, 83)	<0.0001
Glucose, fasting (mg/dL)	96 (95, 96)	96 (93, 100)	0.65	97 (95, 99)	0.11	97 (95, 99)	0.07
% Glycosylated Hemoglobin	5.6 (5.5, 5.6)	5.6 (5.3, 5.8)	0.69	5.6 (5.5, 5.6)	0.94	5.6 (5.5, 5.6)	0.94
Total cholesterol, mg/dl	212 (208, 215)	194 (177, 211)	0.04	216 (209, 222)	0.28	214 (207, 221)	0.49
LDL cholesterol, mg/dl	133 (130, 136)	120 (106, 133)	0.06	136 (131, 141)	0.37	135 (130, 140)	0.51
HDL cholesterol, mg/dl	51 (50, 52)	46 (41, 52)	0.15	53 (49, 57)	0.24	52 (48, 56)	0.37
Triglycerides, mg/dl[b]	118 (85-169)	121 (90-154)	0.84	112 (85-159)	0.41	114 (85-160)	0.53
C-reactive protein, mg/L[b]	1.9 (1.0-4.0)	2.5 (1.5-5.0)	0.09	2.2 (1.1-4.2)	0.14	2.2 (1.1-4.2)	0.06

[a]For continuous variables, weighted mean (95% confidence interval) values are presented unless otherwise specified
[b]Weighted median (25th-75th percentile)

TABLE III.
WEIGHTED BIVARIATE ASSOCIATIONS OF GEOMETRIC MEAN (GM) AND 95% CONFIDENCE INTERVALS (95% CI) FOR THYROID HORMONES WITH BASELINE (VISIT 1) COVARIATES AMONG STUDY PARTICIPANTS

	Thyrotropin (TSH), mIU/L		**Free thyroxine** (Free T4) ,ng/dL		**Total triiodothyronine** (T3), ng/dL	
	GM (95% CI)	**p-value**	**GM (95% CI)**	**p-value**	**GM (95% CI)**	**p-value**
Overall	1.68 (1.58, 1.79)		1.12 (1.09, 1.15)		123 (121, 126)	
Age in years						
65+	1.67 (1.46, 1.90)	0.81	1.15 (1.11, 1.19)	0.28	122 (117, 127)	0.65
55-64	1.66 (1.56, 1.77)	0.73	1.13 (1.11, 1.15)	0.48	123 (121, 126)	0.92
45-54 (ref)	1.70 (1.52, 1.90)	ref	1.11 (1.05, 1.17)	ref	124 (119, 129)	ref
Sex, Male	1.61 (1.51, 1.71)	0.17	1.15 (1.13, 1.17)	0.11	126 (124, 129)	0.04
Female	1.75 (1.58, 1.94)		1.10 (1.05, 1.16)		121 (116, 125)	
Menopause Status						
Pre	1.62 (1.24, 2.11)	0.46	1.06 (0.99, 1.14)	0.44	120 (113, 127)	0.99
Peri	1.55 (1.33, 1.80)	0.14	1.14 (1.11, 1.17)	0.32	125 (121, 129)	0.17
Post (ref)	1.81 (1.58, 2.06)	ref	1.1 (1.03, 1.17)	ref	120 (114, 126)	ref
Hispanic/Latino background						
Central American	1.89 (1.63, 2.20)	0.96	1.11 (1.08, 1.14)	0.81	126 (121, 132)	0.09
Cuban	1.54 (1.38, 1.72)	0.03	1.15 (1.12, 1.19)	0.25	127 (122, 131)	0.05
Dominican	1.41 (1.28, 1.54)	0.001	1.13 (1.11, 1.16)	0.44	124 (120, 129)	0.16
More than one/other	1.30 (0.99, 1.73)	0.02	1.12 (1.04, 1.2)	0.75	127 (116, 138)	0.21
Puerto Rican	1.67 (1.55, 1.79)	0.12	1.14 (1.11, 1.16)	0.41	125 (122, 129)	0.09
South American	1.83 (1.63, 2.07)	0.71	1.12 (1.08, 1.15)	0.68	121 (117, 125)	0.57
Mexican	1.90 (1.63, 2.22)	ref	1.1 (1.02, 1.19)	ref	118 (112, 126)	ref
Study Center, Bronx	1.73 (1.45, 2.06)	0.99	1.07 (0.98, 1.17)	0.14	122 (114, 130)	0.98
Chicago	1.76 (1.65, 1.89)	0.69	1.15 (1.13, 1.17)	0.92	124 (122, 126)	0.31
Miami	1.60 (1.45, 1.75)	0.21	1.14 (1.11, 1.17)	0.58	125 (122, 129)	0.15
San Diego	1.73 (1.59, 1.87)	ref	1.15 (1.13, 1.17)	ref	122 (119, 125)	ref
Born in United States	1.63 (1.51, 1.74)	0.42	1.14 (1.12, 1.17)	0.25	127 (123, 130)	0.09
Non-US Born	1.70 (1.57, 1.83)		1.12 (1.08, 1.16)		122 (119, 126)	
<10 years living in US	1.83 (1.65, 2.02)	0.05	1.15 (1.11, 1.19)	0.53	124 (120, 128)	0.19
Non-US Born and YRS US 10-19	1.78 (1.39, 2.30)	0.34	1.08 (0.95, 1.21)	0.20	120 (109, 131)	0.17

TABLE III (continued).
WEIGHTED BIVARIATE ASSOCIATIONS OF GEOMETRIC MEAN (GM) AND 95% CONFIDENCE INTERVALS (95% CI) FOR THYROID HORMONES WITH BASELINE (VISIT 1) COVARIATES AMONG STUDY PARTICIPANTS

	Thyrotropin (TSH), mIU/L		**Free thyroxine** (Free T4) ,ng/dL		**Total triiodothyronine** (T3), ng/dL	
	GM (95% CI)	**p-value**	**GM (95% CI)**	**p-value**	**GM (95% CI)**	**p-value**
Non-US Born and YRS US ≥20	1.60 (1.51, 1.70)	0.71	1.12 (1.11, 1.14)	0.05	123 (121, 125)	0.06
US Born	1.56 (1.39, 1.76)	ref	1.17 (1.13, 1.21)	ref	129 (123, 134)	ref
Education						
> High school grad	1.59 (1.48, 1.70)	0.21	1.13 (1.11, 1.15)	0.51	123 (121, 126)	0.57
High school graduate	1.77 (1.58, 1.99)	0.88	1.14 (1.11, 1.18)	0.28	127 (124, 131)	0.10
< High school	1.75 (1.53, 1.99)	ref	1.11 (1.04, 1.18)	ref	121 (115, 128)	ref
Income ≥$30,000	1.64 (1.54, 1.75)	0.93	1.13 (1.1, 1.15)	0.28	124 (121, 127)	0.08
Less than $30,000	1.71 (1.56, 1.87)	0.68	1.12 (1.08, 1.17)	0.29	124 (120, 128)	0.10
Missing/not reported	1.62 (1.30, 2.03)	ref	1.16 (1.11, 1.21)	ref	115 (105, 125)	ref
Have health insurance	1.63 (1.54, 1.74)	0.35	1.14 (1.12, 1.16)	0.38	125 (122, 127)	0.35
No health insurance	1.74 (1.55, 1.96)		1.11 (1.05, 1.17)		122 (117, 127)	
Current cigarette use	1.40 (1.30, 1.51)	0.0004	1.14 (1.12, 1.16)	0.36	134 (131, 137)	<0.0001
Former	1.70 (1.55, 1.86)	0.51	1.15 (1.12, 1.17)	0.25	122 (118, 125)	0.70
Never	1.78 (1.60, 1.97)	ref	1.11 (1.06, 1.17)	ref	120 (116, 125)	ref
High alcohol use	1.44 (1.21, 1.71)	0.04	1.12 (1.08, 1.16)	0.81	121 (116, 125)	0.33
Low	1.57 (1.48, 1.67)	0.05	1.14 (1.12, 1.16)	0.30	123 (122, 125)	0.91
Never	1.78 (1.60, 1.98)	ref	1.11 (1.06, 1.17)	ref	124 (119, 129)	ref
Cardiovascular disease	1.87 (1.59, 2.19)	0.18	1.15 (1.11, 1.19)	0.29	123 (117, 128)	0.76
No	1.66 (1.55, 1.77)		1.12 (1.09, 1.16)		123 (121, 126)	
Hypertension (BP>=140/90/Meds), Yes	1.66 (1.54, 1.79)	0.75	1.14 (1.11, 1.17)	0.35	123 (121, 126)	0.94
No	1.69 (1.55, 1.85)		1.11 (1.07, 1.16)		123 (119, 127)	
Body mass index (BMI), kg/m²						
Obese	1.82 (1.58, 2.10)	0.02	1.09 (1.02, 1.17)	0.26	124 (117, 131)	0.55
Overweight	1.67 (1.55, 1.80)	0.06	1.14 (1.13, 1.16)	0.84	124 (121, 126)	0.40
Normal/Underweight	1.49 (1.36, 1.63)	ref	1.14 (1.11, 1.17)	ref	122 (118, 125)	ref
Prediabetes	1.64 (1.49, 1.81)	0.30	1.11 (1.07, 1.16)	0.32	124 (120, 128)	0.51
Normal glucose	1.74 (1.65, 1.84)		1.14 (1.12, 1.16)		122 (120, 125)	

TABLE III (continued).
WEIGHTED BIVARIATE ASSOCIATIONS OF GEOMETRIC MEAN (GM) AND 95% CONFIDENCE INTERVALS (95% CI) FOR THYROID HORMONES WITH BASELINE (VISIT 1) COVARIATES AMONG STUDY PARTICIPANTS

	Thyrotropin (TSH), mIU/L		**Free thyroxine** (Free T4) ,ng/dL		**Total triiodothyronine** (T3), ng/dL	
	GM (95% CI)	**p-value**	**GM (95% CI)**	**p-value**	**GM (95% CI)**	**p-value**
Medication use						
ACEi/ARB, Yes	1.59 (1.45, 1.74)	0.24	1.15 (1.12, 1.19)	0.17	124 (119, 128)	0.91
No	1.70 (1.58, 1.83)		1.12 (1.08, 1.15)		123 (120, 126)	
NSAIDs, Yes	1.62 (1.42, 1.84)	0.53	1.15 (1.12, 1.18)	0.17	122 (119, 126)	0.64
No	1.70 (1.58, 1.82)		1.12 (1.08, 1.15)		123 (120, 127)	
Statins, Yes	2.07 (1.36, 3.15)	0.28	1.03 (0.83, 1.28)	0.37	113 (96, 133)	0.25
No	1.64 (1.56, 1.72)		1.14 (1.12, 1.15)		125 (123, 126)	
Antidepressants, Yes	1.69 (1.37, 2.09)	0.95	1.1 (1.07, 1.14)	0.39	121 (116, 125)	0.30
No	1.68 (1.57, 1.79)		1.13 (1.09, 1.16)		123 (121, 126)	
Antianxiety, Yes	1.62 (1.17, 2.25)	0.82	1.19 (1.12, 1.26)	0.07	128 (121, 135)	0.20
No	1.68 (1.58, 1.79)		1.12 (1.09, 1.15)		123 (120, 126)	
Antipsychotics, Yes	1.26 (0.98, 1.62)	0.02	1.14 (1.06, 1.22)	0.69	117 (101, 137)	0.52
No	1.69 (1.59, 1.80)		1.12 (1.09, 1.15)		123 (121, 126)	
Physical activity level, Low	1.87 (1.66, 2.11)	0.009	1.1 (1.04, 1.16)	0.58	121 (116, 127)	0.62
Moderate	1.54 (1.45, 1.64)	0.79	1.15 (1.13, 1.16)	0.09	126 (123, 128)	0.33
High	1.51 (1.37, 1.68)	ref	1.12 (1.1, 1.15)	ref	123 (119, 128)	ref
High LDL ≥160 mg/dl	1.72 (1.55, 1.90)	0.66	1.11 (1.08, 1.14)	0.43	121 (119, 124)	0.31
No	1.67 (1.54, 1.80)		1.13 (1.09, 1.17)		124 (120, 127)	
Low HDL <40 mg/dl	1.82 (1.68, 1.98)	0.08	1.13 (1.11, 1.16)	0.61	128 (125, 131)	0.008
No	1.65 (1.53, 1.78)		1.12 (1.09, 1.16)		122 (119, 125)	
High triglycerides ≥200 mg/dl	1.95 (1.78, 2.14)	0.003	1.11 (1.08, 1.14)	0.46	125 (121, 128)	0.56
No	1.63 (1.52, 1.76)		1.13 (1.09, 1.16)		123 (120, 126)	
C-reactive protein ≥2 mg/L	1.69 (1.51, 1.89)	0.90	1.11 (1.05, 1.17)	0.28	125 (120, 131)	0.19
No	1.67 (1.58, 1.78)		1.14 (1.12, 1.16)		121 (119, 124)	
Low eGFR < 60, Yes	1.56 (1.32, 1.84)	0.41	1.22 (1.16, 1.28)	0.005	119 (111, 127)	0.31
No	1.68 (1.58, 1.80)		1.12 (1.09, 1.15)		123 (121, 126)	

TABLE III (continued).
WEIGHTED BIVARIATE ASSOCIATIONS OF GEOMETRIC MEAN (GM) AND 95% CONFIDENCE INTERVALS (95% CI) FOR THYROID HORMONES WITH BASELINE (VISIT 1) COVARIATES AMONG STUDY PARTICIPANTS

	Thyrotropin (TSH), mIU/L		**Free thyroxine** (Free T4) ,ng/dL		**Total triiodothyronine** (T3), ng/dL	
	GM (95% CI)	**p-value**	**GM (95% CI)**	**p-value**	**GM (95% CI)**	**p-value**
Albuminuria, Yes	1.99 (1.30, 3.04)	0.38	1.02 (0.82, 1.26)	0.31	112 (96, 131)	0.17
No	1.65 (1.57, 1.72)		1.14 (1.12, 1.15)		125 (123, 127)	
CKD, Yes	1.93 (1.32, 2.81)	0.42	1.04 (0.86, 1.26)	0.37	113 (99, 130)	0.16
No	1.65 (1.57, 1.73)		1.14 (1.12, 1.15)		125 (123, 127)	

TABLE IV.
CROSS-SECTIONAL ASSOCIATIONS BETWEEN CONTINUOUS AND RANKED QUARTILES OF SERUM THYROID HORMONE CONCENTRATIONS AND EGFR AT BASELINE AMONG STUDY PARTICIPANTS

	Continuous eGFR (mL/minute/1.73m^2)		
	Crude β (95% CI)	**Model 1 β (95% CI)[b]**	**Model 2 β (95% CI)[c]**
Thyroid hormones:			
Thyrotropin (TSH), mIU/L	-0.07 (-0.12, -0.02)	-0.14 (-0.20, -0.09)	-0.13 (-0.18, -0.08)
p-value (continuous)	0.008	<0.0001	<0.0001
TSH Q1 (0.004-1.18)	ref	ref	ref
TSH Q2 (1.19-1.73)	-5.4 (-9.2, -1.5)[a]	-3.3 (-6.2, -0.33)[a]	-3.2 (-6.2, -0.23)[a]
TSH Q3 (1.74-2.46)	-3.4 (-6.7, -0.15)[a]	-2.8 (-5.5, -0.08)[a]	-2.6 (-5.4, 0.08)
TSH Q4 (2.47-255)	-6.1 (-9.4, -2.9)[a]	-6.5 (-9.0, -3.9)[a]	-6.3 (-8.9, -3.7)[a]
p-value trend	0.002	<0.0001	<0.0001
Using reference limits			
TSH Low (<0.27 mIU/L)	0.5 (-10.3, 11.3)	1.6 (-5.1, 8.3)	1.6 (-5.1, 8.3)
TSH Normal (0.27–4.2 mIU/L)	3.8 (0.12, 7.4)[a]	4.8 (1.7, 8.0)[a]	4.7 (1.5, 7.8)[a]
TSH High (>4.2 mIU/L)	ref	ref	ref
Free thyroxine (Free T4) ,ng/dL	-4.5 (-9.0, 0.04)	-2.4 (-7.3, 2.6)	-2.7 (-7.4, 2.0)
p-value (continuous)	0.05	0.35	0.26
Free T4 Q1 (0.18-1.03)	ref	ref	ref
Free T4 Q2 (1.04-1.13)	-3.3 (-7.1, 0.4)	-1.5 (-4.0, 1.0)	-1.4 (-3.9, 1.1)
Free T4 Q3 (1.14-1.24)	-1.2 (-3.9, 1.5)	-1.1 (-3.8, 1.5)	-1.0 (-3.7, 1.8)
Free T4 Q4 (1.25-4.38)	-4.0 (-7.1, -0.9)[a]	-3.2 (-6.1, -0.4)[a]	-2.9 (-5.8, -0.02)[a]
p-value trend	0.06	0.05	0.08
Total triiodothyronine (T3), ng/dL	-0.02 (-0.08, 0.03)	-0.03 (-0.07, 0.02)	-0.03 (-0.07, 0.01)
p-value (continuous)	0.34	0.26	0.15
T3 Q1 (32-111)	ref	ref	ref
T3 Q2 (112-124)	-0.94 (-4.1, 2.2)	-0.78 (-3.5, 1.9)	-1.1 (-3.8, 1.5)
T3 Q3 (125-137)	2.5 (-0.4, 5.4)	2.2 (-0.47, 5.0)	2.1 (-0.59, 4.8)
T3 Q4 (138-393)	-1.7 (-5.5, 2.0)	-2.3 (-5.4, 0.83)	-2.5 (-5.6, 0.60)
p-value trend	0.74	0.40	0.34
Thyroid Disease States:			
Hypothyroid	-3.8 (-7.4, -0.10)	-4.8 (-8.0, -1.6)	-4.7 (-7.9, -1.5)
Not hypothyroid	ref	ref	ref
p-value	0.04	0.003	0.004

[a] p<0.05; [b] Model 1 is adjusted for age (continuous, years), self-reported ethnicity/background, sex (male/female), systolic blood pressure (continuous), body mass index (continuous), fasting blood glucose (continuous), nativity (US born, yes/no)

[c] Model 2 is adjusted for age (continuous, years), self-reported ethnicity/background, sex (male/female), systolic blood pressure (continuous), body mass index (continuous), fasting blood glucose (continuous), nativity (US born, yes/no), statin medication use (yes/no), and ACE/ARB medication use (yes/no)

TABLE V.
CROSS-SECTIONAL ASSOCIATIONS BETWEEN CONTINUOUS AND RANKED QUARTILES OF SERUM THYROID HORMONE CONCENTRATIONS AND UACR AT BASELINE AMONG STUDY PARTICIPANTS

	Continuous log UACR (mg/g)		
	Crude β (95% CI)	**Model 1 β (95% CI)[c]**	**Model 2 β (95% CI)[d]**
Thyroid hormones:			
Thyrotropin[b] (TSH), mIU/L	0.20 (-0.16, 0.57)	0.18 (-0.16, 0.53)	0.16 (-0.13, 0.46)
p-value (continuous)	0.27	0.29	0.27
TSH Q1 (0.004-1.18)	ref	ref	ref
TSH Q2 (1.19-1.73)	0.03 (-0.13, 0.19)	0.001 (-0.16, 0.16)	-0.001 (-0.16, 0.16)
TSH Q3 (1.74-2.46)	-0.08 (-0.23, 0.07)	-0.13 (-0.29, 0.03)	-0.14 (-0.30, 0.01)
TSH Q4 (2.47-255)	0.10 (-0.23, 0.43)	0.05 (-0.25, 0.35)	0.03 (-0.23, 0.30)
p-value trend	0.74	0.98	0.84
Free thyroxine (Free T4) ,ng/dL	-0.54 (-1.8, 0.74)	-0.40 (-1.6, 0.84)	-0.35 (-1.4, 0.72)
p-value (continuous)	0.40	0.53	0.52
Free T4 Q1 (0.18-1.03)	ref	ref	ref
Free T4 Q2 (1.04-1.13)	-0.12 (-0.41, 0.17)	-0.08 (-0.34, 0.18)	-0.09 (-0.33, 0.16)
Free T4 Q3 (1.14-1.24)	0.03 (-0.27, 0.33)	0.08 (-0.20, 0.35)	0.08 (-0.17, 0.33)
Free T4 Q4 (1.25-4.38)	0.06 (-0.23, 0.36)	0.13 (-0.15, 0.42)	0.12 (-0.14, 0.38)
p-value trend	0.46	0.20	0.19
Total triiodothyronine (T3), ng/dL	-0.005 (-0.01, 0.004)	-0.004 (-0.01, 0.005)	-0.004 (-0.01, 0.004)
p-value (continuous)	0.30	0.35	0.35
T3 Q1 (32-111)	ref	ref	ref
T3 Q2 (112-124)	-0.09 (-0.37, 0.19)	-0.09 (-0.35, 0.17)	-0.06 (-0.30, 0.17)
T3 Q3 (125-137)	-0.02 (-0.30, 0.26)	-0.02 (-0.27, 0.23)	-0.02 (-0.26, 0.23)
T3 Q4 (138-393)	-0.09 (-0.38, 0.19)	-0.02 (-0.26, 0.22)	-0.002 (-0.22, 0.21)
p-value trend	0.62	0.99	0.93
Thyroid Disease States:			
Hypothyroid	0.26 (-0.65, 1.2)	0.28 (-0.57, 1.1)	0.25 (-0.47, 0.98)
Not hypothyroid	ref	ref	ref
p-value	0.57	0.51	0.49

[a] $p<0.05$

[b] Continuous TSH concentration modeled after log transformation

[c] Model 1 is adjusted for age (continuous, years), self-reported ethnicity/background, sex (male/female), systolic blood pressure (continuous), body mass index (continuous), fasting blood glucose (continuous), nativity (US born, yes/no)

[d] Model 2 is adjusted for age (continuous, years), self-reported ethnicity/background, sex (male/female), systolic blood pressure (continuous), body mass index (continuous), fasting blood glucose (continuous), nativity (US born, yes/no), statin medication use (yes/no), and ACE/ARB medication use (yes/no)

TABLE VI.
CROSS-SECTIONAL ASSOCIATIONS BETWEEN SERUM THYROID HORMONE CONCENTRATIONS AND ALBUMINURIA AND CKD STATUS AT BASELINE AMONG STUDY PARTICIPANTS

	Albuminuria			CKD		
	% (95% CI)	Model 1	Model 2	% (95% CI)	Model 1	Model 2
Thyroid hormones:		OR (95% CI)[c]	OR (95% CI)[d]		OR (95% CI)[c]	OR (95% CI)[d]
Thyrotropin[b] (TSH), mIU/L (Log)		1.5 (0.79, 2.9)	1.4 (0.85, 2.5)		1.5 (0.76, 2.8)	1.4 (0.82, 2.3)
p-value (continuous)		0.21	0.17		0.25	0.22
TSH Q1 (0.004-1.18)	11.6 (7.4, 15.7)	ref	ref	12.4 (8.2, 16.6)	ref	ref
TSH Q2 (1.19-1.73)	12.3 (8.1, 16.6)	0.98 (0.55, 1.7)	0.98 (0.55, 1.8)	14.7 (9.9, 19.6)	1.1 (0.62, 1.9)	1.1 (0.62, 1.9)
TSH Q3 (1.74-2.46)	6.6 (4.1, 9.2)	0.50 (0.28, 0.89)[a]	0.48 (0.27, 0.86)[a]	8.6 (5.5, 11.7)	0.60 (0.34, 1.1)	0.58 (0.32, 1.0)
TSH Q4 (2.47-255)	12.6 (6.4, 18.8)	1.0 (0.49, 2.2)	1.0 (0.49, 2.2)	13.4 (7.2, 19.6)	1.0 (0.49, 2.1)	0.97 (0.49, 1.9)
p-value trend	0.23	0.65	0.51	0.30	0.64	0.47
Free thyroxine (Free T4) ,ng/dL		0.27 (0.01, 5.0)	0.33 (0.03, 3.3)		0.42 (0.02, 9.2)	0.50 (0.05, 5.4)
p-value (continuous)		0.38	0.35		0.58	0.57
Free T4 Q1 (0.18-1.03)	10.3 (4.8, 15.8)	ref	ref	11.3 (5.7, 16.8)	ref	ref
Free T4 Q2 (1.04-1.13)	8.6 (5.3, 11.8)	0.89 (0.41, 1.9)	0.86 (0.40, 1.8)	9.3 (5.8, 12.7)	0.84 (0.40, 1.7)	0.80 (0.39, 1.6)
Free T4 Q3 (1.14-1.24)	14.6 (9.8, 19.3)	1.6 (0.74, 3.5)	1.6 (0.76, 3.4)	16.3 (11.4, 21.2)	1.6 (0.78, 3.4)	1.6 (0.79, 3.3)
Free T4 Q4 (1.25-4.38)	9.7 (5.9, 13.5)	1.1 (0.49, 2.6)	1.1 (0.50, 2.5)	12.4 (7.9, 16.9)	1.3 (0.59, 2.8)	1.3 (0.60, 2.7)
p-value trend	0.25	0.44	0.42	0.20	0.84	0.86
Total triiodothyronine[b] (T3), ng/dL		0.09 (0.02, 0.34)	0.11 (0.03, 0.36)		0.10 (0.02, 0.40)	0.13 (0.04, 0.44)
p-value (continuous)		0.0005	0.0004		0.001	0.001
T3 Q1 (32-111)	12.3 (6.6, 18.0)	ref	ref	13.7 (7.9, 19.5)	ref	ref
T3 Q2 (112-124)	11.6 (7.6, 15.7)	0.93 (0.46, 1.9)	0.97 (0.49, 1.9)	14.1 (9.3, 18.9)	1.0 (0.52, 2.0)	1.1 (0.57, 2.1)
T3 Q3 (125-137)	12.1 (7.4, 16.8)	0.86 (0.42, 1.8)	0.86 (0.42, 1.7)	13.0 (8.2, 17.8)	0.82 (0.42, 1.6)	0.82 (0.41, 1.6)
T3 Q4 (138-393)	7.5 (4.8, 10.2)	0.53 (0.27, 1.1)	0.55 (0.29, 1.1)	8.9 (5.8, 11.9)	0.59 (0.30, 1.2)	0.62 (0.32, 1.2)
p-value trend	0.39	0.09	0.09	0.39	0.11	0.11

[a] $p<0.05$; [b]Continuous TSH and T3 concentrations modeled after log transformation; [c]Model 1 is adjusted for age (continuous, years), sex (male/female), systolic blood pressure (continuous), fasting blood glucose (continuous), nativity (US born, yes/no); [d]Model 2 is adjusted for age (continuous, years), sex (male/female), systolic blood pressure (continuous), fasting blood glucose (continuous), nativity (US born, yes/no), and statin medication use (yes/no)

TABLE VII.
CHANGE IN CHARACTERISTICS FROM VISIT 1 TO VISIT 2 AMONG ANCILLARY STUDY PARTICIPANTS

Characteristic	**Visit 1**	**Visit 2**
	N (weighted %)	**N (weighted %)**
Income <$40,000 (annually), %	359 (18.6)	474 (24.8)
Have health insurance, %	1029 (55.1)	1567 (83.5)
Current cigarette use, %	427 (21.3)	340 (17.4)
Hypertension (BP>=140/90 and Med Use)**, %**	645 (37.6)	988 (56.2)
Average systolic BP (mmHg)[a]	128 (127, 130)	130 (129, 132)
Average diastolic BP (mmHg)[a]	75 (74, 76)	73 (72, 74)
Waist to hip ratio[a]	0.93 (0.92, 0.93)	0.94 (0.93, 0.94)
Diabetes, %	--	510 (17.4)
Prediabetes, %	1006 (59.7)	943 (56.2)
Normal glucose (no diabetes), %	974 (40.3)	527 (26.4)
Glucose, fasting (mg/dL)[a]	96.0 (95.3, 96.6)	102.0 (100.6, 103.2)
% Glycosylated Hemoglobin (%)[a]	5.6 (5.5, 5.6)	5.8 (5.7, 5.8)
Medication use, %		
Hypertension	321 (20.2)	752 (56.3)
Diabetes	6 (0.14)	182 (9.1)
Cholesterol	220 (12.3)	438 (32.3)
Total cholesterol (mg/dl)[a]	212 (208, 216)	199 (196, 201)
Triglycerides (mg/dl) (geometric mean)	123 (119, 128)	111 (107, 115)
eGFR (ml/min per 1.73 m^2)[a]	93 (92, 94)	88 (87, 89)
UACR (mg/g) (geometric mean)	8.4 (7.7, 9.1)	5.6 (5.1, 6.1)
Low eGFR[b]	43 (2.6)	78 (4.6)
Albuminuria	223 (11.0)	246 (11.9)
CKD	247 (12.6)	290 (14.9)

[a]For continuous variables, weighted mean (95% confidence interval) values are presented unless otherwise indicated.
[b]Low eGFR was defined as <60 at visit 1 and at visit 2 <60 w/ decline ≥1 ml/min per 1.73 m^2 per year of follow –up.

TABLE VIII.
PROSPECTIVE ASSOCIATIONS BETWEEN THYROID HORMONE LEVELS AT BASELINE AND EGFR LEVELS AT VISIT 2 (OVER SIX YEAR FOLLOW-UP) AMONG HCHS/SOL ANCILLARY STUDY PARTICIPANTS

	Continuous eGFR (mL/minute/1.73m²) at Visit 2					
	Crude β (95% CI)[d]	p-value	**Adjusted β (95% CI)[e]**	p-value	**Adjusted β (95% CI)[f]**	p-value
Thyroid hormones:						
Thyrotropin[a] (TSH)	-0.12 (-1.3, 1.1)	0.84	-0.57 (-1.9, 0.71)	0.38	-0.72 (-2.0, 0.56)	0.27
TSH Q2 vs. Q1	-0.14 (-1.9, 1.7)		0.001 (-1.9, 1.9)		-0.05 (-1.9, 1.8)	
TSH Q3 vs. Q1	-0.10 (-2.5, 2.3)	0.57[b]	-0.23 (-2.6, 2.1)	0.85[b]	-0.44 (-2.7, 1.8)	0.66[b]
TSH Q4 vs. Q1	0.62 (-1.2, 2.5)		-0.13 (-2.0, 1.7)		-0.36 (-2.2, 1.5)	
Males: Thyrotropin[a] (TSH)	1.9 (0.56, 3.4)	0.006	1.8 (0.43, 3.2)	0.01	1.8 (0.39, 3.1)	0.01
TSH Q2 vs. Q1	-0.08 (-2.2, 2.1)		0.96 (-1.1, 3.1)		0.86 (-1.2, 3.0)	
TSH Q3 vs. Q1	1.7 (-0.37, 3.9)	0.002[b]	1.9 (-0.29, 4.1)	0.007[b]	1.8 (-0.37, 4.1)	0.006[b]
TSH Q4 vs. Q1	3.5 (1.0, 5.9)[c]		3.2 (0.79, 5.7)[c]		3.2 (0.77, 5.6)[c]	
Females: Thyrotropin[a] (TSH)	-1.4 (-2.6, -0.08)	0.04	-2.0 (-3.4, -0.61)	0.005	-2.1 (-3.5, -0.78)	0.002
TSH Q2 vs. Q1	-0.24 (-3.1, 2.6)		-0.54 (-3.4, 2.3)		-0.34 (-3.1, 2.5)	
TSH Q3 vs. Q1	-2.1 (-6.0, 1.8)	0.09[b]	-2.1 (-5.6, 1.4)	0.02[b]	-2.1 (-5.3, 1.0)	0.01[b]
TSH Q4 vs. Q1	-1.9 (-4.5, 0.67)		-3.1 (-5.7, -0.52)[c]		-3.4 (-5.9, -0.84)[c]	
Hypertensive: Thyrotropin[a] (TSH)	-2.2 (-3.9, -0.43)	0.01	-2.1 (-3.9, -0.35)	0.02	-2.3 (-4.1, -0.62)	0.008
TSH Q2 vs. Q1	-2.4 (-5.3, 0.43)		-2.9 (-5.9, 0.08)		-2.7 (-5.5, 0.12)	
TSH Q3 vs. Q1	-4.1 (-8.7, 0.42)	0.06[b]	-4.0 (-8.6, 0.51)	0.09[b]	-4.3 (-8.7, 0.05)	0.06[b]
TSH Q4 vs. Q1	-2.7 (-6.0, 0.56)		-2.9 (-6.3, 0.47)		-3.1 (-6.4, 0.21)	
Normotensive: Thyrotropin[a] (TSH)	0.54 (-1.4, 2.4)	0.57	-0.001 (-1.9, 1.9)	0.99	-0.05 (-1.9, 1.8)	0.95
TSH Q2 vs. Q1	1.1 (-0.90, 3.2)		1.6 (-0.22, 3.5)		1.5 (-0.33, 3.4)	
TSH Q3 vs. Q1	2.3 (0.35, 4.2)[c]	0.03[b]	2.0 (0.17, 3.8)[c]	0.26[b]	1.9 (-0.07, 3.8)	0.35[b]
TSH Q4 vs. Q1	2.0 (-0.15, 4.2)		1.0 (-0.99, 3.1)		0.92 (-1.2, 3.0)	

[a] Continuous TSH concentration modeled after log transformation
[b] p for trend
[c] $p<0.05$
[d] Adjusted for eGFR at visit 1 and time from Visit 1 to Visit 2

[e] Adjusted for eGFR at visit 1, time from Visit 1 to Visit 2, age (continuous, years), self-reported ethnicity/background, sex (male/female), systolic blood pressure (at visit 1), and fasting blood glucose (at visit 1)
[f] Adjusted for eGFR at visit 1, time from Visit 1 to Visit 2, age (continuous, years), self-reported ethnicity/background, sex (male/female), systolic blood pressure (at visit 1), fasting blood glucose (at visit 1), triglycerides (at Visit 1), and antihypertensive medication use (at visit 1)

TABLE IX.
PROSPECTIVE ASSOCIATIONS BETWEEN THYROID HORMONE LEVELS AT BASELINE AND UACR LEVELS AT VISIT 2 (OVER SIX YEAR FOLLOW-UP) AMONG HCHS/SOL ANCILLARY STUDY PARTICIPANTS

	Continuous log UACR (mg/g) at Visit 2		
	Crude β (95% CI)[a]	**Adjusted β (95% CI)[b]**	**Adjusted β (95% CI)[c]**
Free thyroxine (Free T4), ng/dL	-0.22 (-0.50, 0.06)	-0.24 (-0.54, 0.05)	-0.25 (-0.54, 0.04)
p-value (continuous)	0.12	0.10	0.09
	Crude GM (95% CI)[a]	**Adjusted GM (95% CI)[b]**	**Adjusted GM (95% CI)[c]**
Free T4 Q1 (0.18-1.03)	6.4 (5.7, 7.1)	6.5 (5.8, 7.2)	6.7 (5.9, 7.6)
Free T4 Q2 (1.04-1.13)	5.4 (4.8, 6.1)	5.5 (4.9, 6.3)	5.7 (4.9, 6.5)
Free T4 Q3 (1.14-1.24)	5.5 (4.9, 6.2)	5.6 (5.0, 6.4)	5.8 (5.0, 6.6)
Free T4 Q4 (1.25-4.38)	5.2 (4.6, 5.9)[d]	5.3 (4.7, 6.0)[d]	5.5 (4.8, 6.3)[d]
p-value trend	0.02	0.03	0.02

[a] Adjusted for UACR at visit 1 and time from Visit 1 to Visit 2
[b] Adjusted for UACR at visit 1, time from Visit 1 to Visit 2, age (continuous, years), self-reported ethnicity/background, sex (male/female), systolic blood pressure (at visit 1), and fasting blood glucose (at visit 1)
[c] Adjusted for UACR at visit 1, time from Visit 1 to Visit 2, age (continuous, years), self-reported ethnicity/background, sex (male/female), systolic blood pressure (at visit 1), fasting blood glucose (at visit 1), triglycerides (at Visit 1), and antihypertensive medication use (at visit 1),
[d] $p<0.05$ (Q1 is the reference group)

TABLE X.
WEIGHTED PREVALENCE AND ODDS OF INCIDENT ALBUMINURIA AND CKD COMPOSITE BY BASELINE SERUM THYROID HORMONE CONCENTRATIONS AMONG HCHS/SOL ANCILLARY STUDY PARTICIPANTS

	Incident Albuminuria			Incident CKD		
Thyroid hormones:	**% (95% CI)**	**Inc. OR (95% CI)[a]**	**p-value**	**% (95% CI)**	**Inc. OR (95% CI)[a]**	**p-value**
Thyrotropin (TSH), mIU/L		1.1 (1.06, 1.18)	0.001		1.2 (1.05, 1.31)	0.004
TSH Q1 (0.004-1.18)	4.0 (1.5, 6.4)	ref		5.6 (2.9, 8.4)	ref	
TSH Q2 (1.19-1.73)	5.5 (2.6, 8.3)	1.2 (0.49, 2.9)	0.69	7.7 (4.2, 11.2)	1.1 (0.51, 2.5)	0.77
TSH Q3 (1.74-2.46)	5.9 (2.2, 9.5)	1.6 (0.60, 4.3)	0.34	8.7 (4.4, 13.0)	1.6 (0.72, 3.8)	0.23
TSH Q4 (2.47-255)	7.3 (2.2, 12.4)	1.8 (0.70, 4.8)	0.22	11.0 (5.0, 17.0)	2.0 (0.88, 4.4)	0.10
p-value trend		0.17			0.06	
Free thyroxine (Free T4) ,ng/dL		1.9 (0.65, 5.6)	0.24		1.8 (0.57, 5.6)	0.32
Free T4 Q1 (0.18-1.03)	4.5 (2.1, 6.8)	ref		8.1 (4.0, 12.2)	ref	
Free T4 Q2 (1.04-1.13)	3.9 (2.0, 5.8)	0.99 (0.48, 2.1)	0.99	6.0 (3.3, 8.7)	0.77 (0.42, 1.4)	0.42
Free T4 Q3 (1.14-1.24)	7.3 (3.8, 10.7)	1.6 (0.76, 3.3)	0.21	8.6 (4.9, 12.3)	1.0 (0.49, 2.1)	0.99
Free T4 Q4 (1.25-4.38)	6.5 (1.5, 11.4)	1.8 (0.64, 5.0)	0.26	9.6 (4.2, 14.9)	1.3 (0.57, 3.0)	0.52
p-value trend		0.20			0.46	
Total triiodothyronine (T3), ng/dL		1.00 (0.99, 1.01)	0.30		1.01 (1.00, 1.02)	0.04
T3 Q1 (32-111)	3.6 (1.5, 5.7)	ref		5.0 (2.5, 7.5)	ref	
T3 Q2 (112-124)	6.9 (1.9, 11.9)	2.0 (0.79, 5.2)	0.14	10.7 (4.7, 16.7)	2.4 (1.1, 5.5)	0.03
T3 Q3 (125-137)	4.8 (2.6, 7.0)	1.2 (0.54, 2.7)	0.64	6.5 (3.7, 9.3)	1.4 (0.64, 2.9)	0.42
T3 Q4 (138-393)	7.0 (3.4, 10.7)	1.6 (0.67, 3.9)	0.29	10.4 (6.0, 14.8)	2.1 (0.94, 4.8)	0.07
p-value trend		0.50			0.19	

[a] Adjusted for age (continuous, years), sex (male/female), systolic blood pressure (continuous), change in systolic blood pressure from Visit 1 to Visit 2, fasting blood glucose (continuous), change in fasting blood glucose from Visit 1 to Visit 2, and anti-hypertension medication use (yes/no)

D. Discussion

In this study, we evaluated the associations between circulating levels of TSH, FT4, and T3 with measures of kidney function using cross-sectional, longitudinal, and incident data sources. In our diverse sample of Hispanic/Latino adults, we found consistent results primarily with levels of TSH and eGFR. Cross-sectional findings indicated inverse associations between TSH concentrations and eGFR in pooled analyses, with effects that were larger in magnitude among those with normal glucose levels relative to those with prediabetes and among males relative to females. When eGFR at follow-up was modeled, TSH was not associated with eGFR in pooled analyses. Evidence of effect modification showed that TSH was inversely associated with eGFR at visit 2 among those with hypertension, and not associated with eGFR among those considered normotensive. Additionally, TSH was positively associated with visit 2 eGFR among males, and inversely associated with visit 2 eGFR among females. TSH was not associated with continuous UACR at visit 1 (cross-sectionally) or at visit 2, but we observed a positive association between TSH and odds of both incident albuminuria (OR=1.1 (95% CI 1.06, 1.18), p=0.001) and incident CKD composite (OR=1.2 (95% CI 1.05, 1.31), p=0.004).

Our results with TSH are similar to other cross-sectional studies that have found higher serum TSH levels to be associated with higher odds of low eGFR (<60ml/min/1.73 m^2) (Gopinath et al. 2013). In the ARIC study, information from 12,785 African American and white participants found TSH (TSH Q4 (2.68-227 mIU/l) versus Q1 (0.005-1.23 mIU/l) OR= 1.87 (95% CI 1.25–2.81)) concentrations to be associated with higher odds of low eGFR (<60ml/min/1.73 m^2) cross-sectionally (Schultheiss et al.

2017). In our study, we did not have enough cases of low eGFR to assess associations with the dichotomized outcome, but we did observe an inverse association with TSH and continuous eGFR.

Our analyses to evaluate associations with FT4 showed an inverse association between FT4 and eGFR in cross-sectional analyses that was borderline significant when FT4 was modeled as quartiles, but no association with eGFR at visit 2. Although we did not observe an association between continuous FT4 and eGFR in multivariable models, we did see an inverse association among those with the highest FT4 levels (fourth quartile 1.25 to 4.38 ng/dL) relative to the lowest quartile. One cross-sectional study done previously showed that serum FT4 levels in the fourth quartile (≥14.6 pmol/l) relative to the first quartile (≤11.9 pmol/l) had higher odds of low eGFR (<60ml/min/1.73 m2), OR 1.64 (95% CI 1.10, 2.45) (Gopinath et al. 2013). In the aforementioned ARIC study, FT4 (FT4 Q4 (1.23-5.94 ng/dL mIU/l) versus Q1 (0.03-1.01 ng/dL)) concentrations were associated with higher odds of low eGFR (<60ml/min/1.73 m^2) cross-sectionally (Schultheiss et al. 2017). In the ARIC study, contrasts of Q2 vs. Q1 and Q3 vs. Q1 were not statistically significant, similar to our findings. Although the direction of the association between continuous FT4 and UACR at visit 1 (cross-sectionally) was inverse, the association was not statistically significant after multivariable adjustment. Visit 1 FT4 levels were, however, inversely associated with UACR at visit 2. FT4 was not associated with any of the dichotomous endpoints cross-sectionally or in the incident analyses.

In their cross-sectional analyses, the ARIC study also found serum levels of T3 to be inversely associated (T3 Q4 (140.6-614.5 ng/dl) versus Q1 (19.5-13.0 ng/dl) OR=

0.19 (95% CI 0.12–0.31)) with low eGFR (<60ml/min/1.73 m^2) (Schultheiss et al. 2017). Our findings were in a similar direction but not statistically significant.

In our study, we did not observe consistent associations between T3 and kidney function parameters across the analyses conducted. When evaluating the associations between T3 levels and visit 1 continuous outcomes, all associations were null, but T3 levels were inversely associated with the dichotomous outcomes of albuminuria and the CKD composite. The associations between T3 levels at visit 1 and eGFR and UACR at visit 2 were also null, although we did observe that participants with T3 levels greater than 181 ng/dL had lower eGFR at visit 2 relative to those with levels less than 181 ng/dL. T3 levels at visit 1 were not associated with incident albuminuria, but were positively associated with the CKD composite. This should be interpreted cautiously due to the inconsistent associations with eGFR and this finding, in addition to the small number of cases of low eGFR that comprise the CKD composite endpoint.

Other studies that have conducted longitudinal analyses between thyroid hormones and kidney function parameters have had mixed findings. When the ARIC study investigators assessed the association of incident CKD after a median follow-up time of 19.6 years, none of the measures of thyroid function were associated with incident CKD (Schultheiss et al. 2017). This is in contrast to the associations we observed between TSH levels and eGFR, and TSH with incident albuminuria. In the ARIC study, continuous eGFR and the change in continuous eGFR over follow-up was not assessed as an outcome, nor was albuminuria used as an outcome in any of the analyses, indicating that the outcomes being compared in our study relative to the ARIC study represent different clinical endpoints. The ARIC study may not be the best suited

for comparison to the prospective outcomes assessed in our study. Other studies of the association of incident CKD with markers of thyroid function are available for comparison. One study that used a community-based cohort of middle-aged and older Chinese participants defined incident CKD as eGFR <60 ml/min/1.73 m2 or urinary albumin-to-creatinine ratio ≥30 mg/g, and found higher FT4, but not TSH, was associated with increased risk of incident CKD over a four year follow-up period (Huang, Ding, et al. 2016). In total, 198 participants developed incident CKD over the follow-up period, and compared to those with FT4 levels <13.60 pmol/l, those with FT4 levels >14.83 pmol/l had 1.88-fold higher (95% CI 1.27–2.77) increased risk of incident CKD (Huang, Ding, et al. 2016). When modeled as a continuous variable, each 1-pmol/l increase in FT4 was associated with 12% increased risk of incident CKD (Huang, Ding, et al. 2016). In a prospective cohort study of South Korean men and women who were free of CKD and proteinuria at baseline, high levels of TSH and low levels of free T3 (FT3), but not FT4 was associated with an increased risk of incident CKD defined as eGFR <60 ml/min/1.73 m^2 (Zhang et al. 2014). After a median follow-up of 3.5 years, 1,032 of the 104,633 participants in the study developed low eGFR (eGFR <60 ml/min/1.73 m^2). The hazard ratio for CKD comparing the highest (2.85-5.0 mIU/l) versus the lowest (0.25–1.18mIU/l) quintile of TSH was HR=1.59 (95% CI 1.29-1.95). When modeled using a spline, levels of FT3 less than 3 pg/ml were associated with increased risk of incident CKD (Zhang et al. 2014).

In our study, we observed evidence of sex differences in the cross-sectional and longitudinal analyses of eGFR. The Kangbuk Samsung Health Study is one of the only studies that evaluated sex differences in the associations under study, and they did not

show evidence of sex differences in their analyses of the prospective associations of TSH, FT3 and FT4 with incident CKD (Zhang et al. 2014). Our study is different from the Kangbuk study because of our low number of incident low eGFR cases, and use of albuminuria as the outcome for most of our incident cases. To our knowledge, however, no other studies have evaluated sex differences when assessing the association between thyroid hormones and kidney function.

Our findings may be explained by mechanisms related to glomerular and tubular functions of the kidney that are directly impacted by thyroid hormones. Animal models have shown hypothyroidism to be associated with smaller tubular mass and changes to the glomerulus (Vargas et al. 2006). Other animal studies have shown hypothyroid status to be associated vasoconstriction within the kidney that has the potential to decrease renal blood flow and may lead to kidney injury (Klein and Ojamaa 2001, Singer 2001). Experiments using hypothyroid dogs have shown that vasoconstriction may occur as a result of overload of proximal tubule filtrate if the tubules are unable to properly reabsorb water and sodium (Zimmerman et al. 1988). A study of hypothyroid rats showed that chloride filtrate overload can be caused by disturbance to the chloride channels which in turn can decrease GFR through feedback loops that occur between the tubules and glomeruli (van Hoek and Daminet 2009). This is consistent with our cross-sectional findings that showed higher TSH levels were associated with lower levels of eGFR. Hemodynamic changes resulting from TSH levels higher than the standard reference range, a hallmark characteristic of hypothyroidism, may also impact kidney function. These hemodynamic changes may include decreased blood volume

due to lower than normal levels of atrial natriuretic factor and erythropoietin (van Hoek and Daminet 2009, Vargas et al. 2006).

Our study used data from a well-characterized cohort of Hispanics/Latinos with detailed information on health conditions, medication usage, and objective laboratory measures of kidney function parameters. We used objective measures of thyroid hormones from stored samples, and had data to evaluate associations with kidney function parameters prospectively. The parent HCHS/SOL study collected detailed information on medications used by participants, allowing us to exclude participants using medications known to interfere with thyroid hormones such as glucocorticoids and thyroid medications (Burch 2019). Some limitations to our study should be taken into consideration. The definitions used for our outcomes were based on single measurements of serum or urine. A very small number of participants in our study had the low eGFR endpoint at any time point, precluding us from evaluating associations with that individual endpoint. This may limit our ability to generalize our study findings with other studies that used low eGFR as their primary endpoint. Although the weighted proportion of participants with albuminuria was similar to what was expected, the small number of cases these estimates were based on may have limited our statistical power to detect associations. We measured circulating thyroid hormones in serum, and cannot determine how circulating levels may act at the tissue level. Due to the design of the cohort study, we do not have information on when incident albuminuria or low eGFR occurred over the six year average follow up time. We also do not know the order of events in regard to changes in confounders over time. For example, we do not know the

timing of changes in metrics like blood pressure or lipids in relation to changes in GFR or urine albumin.

E. Conclusions

This is the first study to assess associations between circulating thyroid hormones and kidney function parameters in a diverse cohort of Hispanic/Latino adults with the unique opportunity to evaluate associations with kidney function parameters prospectively. Importantly, we observed associations that suggest alterations in thyroid hormones are associated with kidney function both cross-sectionally and over time. Levels of circulating thyroid hormones can be altered by a variety of factors, and additional research to investigate behavioral and environmental factors that impact thyroid hormone levels is warranted.

IV. RELATIONSHIPS BETWEEN ENDOGENOUS PITUITARY AND SEX STEROID HORMONES AND KIDNEY FUNCTION: FINDINGS FROM THE HISPANIC COMMUNITY HEALTH STUDY/STUDY OF LATINOS (HCHS/SOL)

A. Rationale

Several in-depth reviews of the impact of biological sex on the progression of kidney disease suggest sex -specific differences in the mechanisms and epidemiology of CKD (Neugarten and Golestaneh 2013, Silbiger and Neugarten 2008, Silbiger and Neugarten 1995). Multiple sources have contended that premenopausal women are protected from non-diabetic kidney disease relative to men of the same age (Neugarten, Acharya, and Silbiger 2000, Silbiger and Neugarten 2008, Silbiger and Neugarten 2003). This may be attributed to the influence of sex hormones in the pathogenesis of kidney disease. Animal studies have suggested that endogenous estrogen protects kidney function in both non-diabetic and diabetic disease states (Delle et al. 2012, Mankhey, Bhatti, and Maric 2005, Tanaka et al. 2012, Zimmerman et al. 2017). The data from human studies, however, is less clear. Studies have shown higher incidence of CKD in women relative to men, but male sex has been associated with higher morbidity and mortality among patients with CKD as well as quicker progression to ESRD relative to women (Hecking et al. 2014, Iseki et al. 2005, Ricardo et al. 2019). Male sex hormones may increase oxidative stress, activate the renin-angiotensin system, and worsen kidney fibrosis (Chen, Naftilan, and Oparil 1992, Ellison et al. 1989, Metzger et al. 1988, Chainy and Sahoo 2019, Fortepiani et al. 2003, Reckelhoff and Granger 1999, Yanes, Sartori-Valinotti, and Reckelhoff 2008) indicating that higher levels of testosterone in males may infer greater susceptibility to kidney disease. This

contrasts with decreased susceptibility provided by endogenous estrogen produced by premenopausal women, which is not observed among postmenopausal women (Silbiger and Neugarten 2008).

To our knowledge, few studies have assessed the associations of endogenous pituitary and sex steroid hormones and CKD using prospective data, and none have used data from a diverse cohort of Hispanics/Latinos. Understanding the role pituitary and sex steroid hormones play in the progression of CKD is important to inform strategies aimed at protecting kidney health. The HCHS/SOL ancillary study sample with its information on endogenous hormones, other risk factors, and large sample size that oversampled for middle-aged and older Hispanics/Latinos is uniquely suited to address our research question. The overall goal of this study was to examine the relationships of endogenous pituitary and sex steroid hormones with CKD in an ethnically diverse Hispanic/Latino population who were enrolled in a community-based cohort study and who did not have diabetes at baseline. Our specific aims were to 1) describe the relationships of endogenous pituitary and sex steroid hormones measured at baseline, with baseline prevalence of CKD and measures of eGFR and UACR; 2) determine if levels of endogenous pituitary and sex steroid hormones were associated with changes in eGFR and UACR from Visit 1 to Visit 2; and 3) examine the relationships of baseline levels of endogenous pituitary and sex steroid hormones with the subsequent development of CKD at Visit 2.

B. Methods

1. Study population

The HCHS/SOL is a multisite prospective cohort study designed to identify risk and protective factors for chronic disease among persons from diverse Hispanic/Latino background groups living across the United States. The cohort included 16,415 men and women between 18 to 74 years of age at the time of recruitment. Participants were recruited from 2008 until 2011 from randomly selected households in San Diego, CA; Bronx, NY; Chicago, IL; and Miami, FL. The HCHS/SOL included first through third generation participants of Mexican, Cuban, Puerto Rican, Dominican Republic, Central and South-American background. Details of the study design and sampling methods were previously published (Lavange et al. 2010, Sorlie et al. 2010). The Persistent Organic Pollutants, Endogenous Hormones and Diabetes in Latinos Ancillary Study oversampled from middle-aged and older participants ages 45-74 in the HCHS/SOL study using a case-cohort study design. To select the random sample, participants were stratified by baseline glucose measurements (1,176 with prediabetes at baseline and 1,174 with normal baseline glucose measurements) and approximately equally divided between men and women ages 45 -74 years (1,148 men and 1,202 women), and with only one participant per household within each sex and blood glucose subgroup. Participants who transitioned from pre-diabetes to diabetes during the follow up period were oversampled to ensure that approximately half of those in this category had transitioned to diabetes. The final ancillary study sample consisted of 2,350 HCHS/SOL males and females who either had prediabetes or normal glucose parameters at Visit 1.

Of the 2,342 HCHS/SOL ancillary study participants with hormone measurements available, 1,757 (75%) were included in the cross-sectional and longitudinal analyses (714 post-menopausal females and 1,043 males). A total of 585 participants (25%) were excluded because of missing data on at least one serum hormone (n=4), serum cystatin C (n=12) or urine albumin/creatinine ratio (n=115) or covariate (health insurance status (n=12); education (n=4)) (values are not mutually exclusive). We excluded pre- and peri-menopausal females (n=320) and participants who reported using oral/inhalantable glucocorticosteroid medications (n=33) and/or any hormone replacement therapy (including androgens) (n=45). An additional 64 participants were excluded due to missing serum cystatin C (n=10) or urine albumin/creatinine ratio (n=54) data at Visit 2.

2. Variable definitions

a. Measures of kidney function

Urine albumin was measured on the ProSpec nephelometric analyzer (Dade Behring GMBH, Marburg, Germany) using an immunoturbidometric method. Urine creatinine was measured in both serum and urine on a Roche Modular P Chemistry Analyzer (Roche Diagnostics, Indianapolis, IN) using a creatinase enzymatic method. We defined albuminuria using sex-specific cutoffs (urine albumin to creatinine ratio ≥17 mg/g in males and ≥25 mg/g in females) (Mattix et al. 2002). Glomerular filtration rate was estimated using the CKD-EPI creatinine-cystatin C equation ($eGFR_{creat\text{-}cyst}$) (Inker et al. 2012). Serum creatinine measurements were traced by isotope dilution mass spectrometry. Serum cystatin C was measured using a

turbidimetric method on the Roche Modular P Chemistry Analyzer (Gentian AS, Moss, Norway). Low eGFR was defined as $eGFR_{creat-cyst}$ <60 ml/min per 1.73 m^2. At baseline, CKD was defined by either a low eGFR or the presence of albuminuria using sex-specific cutoffs. We defined incident low eGFR as eGFR <60 ml/min per 1.73 m^2 with eGFR decline ≥1 ml/min per 1.73 m^2 per year of follow –up. We defined incident CKD as low eGFR <60 ml/min per 1.73 m^2 with eGFR decline ≥1 ml/min per 1.73 m^2 per year of follow -up or presence of new onset albuminuria (sex-specific) at Visit 2 among those who did not have low eGFR or albuminuria at Visit 1.

b. **Hormone measurements**

Serum samples for gonadotropin and steroid hormone measurements were collected at the baseline HCHS/SOL examination visit. All hormones were measured using a Roche COBAS 6000 chemistry analyzer (Roche Diagnostics, Indianapolis, IN). Luteinizing hormone was measured using a LH reagent/sandwich immunoassay (Roche Diagnostics, Indianapolis, IN). Follicle stimulating hormone was measured using a FSH reagent/sandwich immunoassay (Roche Diagnostics, Indianapolis, IN). Measures of SHBG used a SHBG reagent/sandwich immunoassay method/electrochemiluminescence (Roche Diagnostics, Indianapolis, IN). Estradiol was measured using an estradiol III reagent/competitive immunoassay method (Roche Diagnostics, Indianapolis, IN). Measures of DHEAS used a DHEA-S reagent/competitive immunoassay method/electrochemiluminescence (Roche Diagnostics, Indianapolis, IN). In male samples, testosterone was measured using a testosterone II reagent/competitive immunoassay/electrochemiluminescence (Roche Diagnostics, Indianapolis, IN). The

lower limits of detection for LH, FSH, SHBG, estradiol, DHEAS, and testosterone were 0.100 mIU/mL, <0.100 mIU/mL, 0.800 nmol/L, 18.4 pmol/L, 0.003 umol/L, and 2.5 ng/dL, respectively. All assays are performed by the Advanced Research & Diagnostics Laboratory at the University of Minnesota, which is a CAP/CLIA certified laboratory. Concentrations of testosterone (ng/dL), SHBG (nmol/L) and estradiol (pg/mL) were used to calculate concentrations of unbound (free) testosterone and estradiol according to the method supplied by Vermeulen (Vermeulen, Verdonck, and Kaufman 1999, Belgorosky, Escobar, and Rivarola 1987).

c. **Covariates**

Study participants reported their age, sex, years of education (less than high school, high school, more than high school), Hispanic/Latino heritage, current smoking status. Anthropometric measurements of weight (kilograms), height (centimeters), and waist circumference (centimeters) were performed by trained study staff following a standard protocol. Body mass index was calculated as weight in kilograms divided by height in squared meters. Among females, menopause status was derived by a series of steps that included evaluation of the participant's age (≥62 years old determined to be post-menopausal) and menstruation status (among those who reported absence of menses, if FSH was >25.8 mIU/mL or LH >7.7 mIU/mL, the participant was determined to be post-menopausal; among with FSH < 25.8 mIU/mL and LH < 7.7 mIU/mL, the participant was determined to be peri-menopausal). If the participant reported current menses or did not answer the question regarding menstruation status, if FSH was >25.8 mIU/mL or LH >7.7 mIU/mL, the participant was

determined to be peri-menopausal and for those with FSH < 25.8 mIU/mL and LH < 7.7 mIU/mL, the participant was determined to be pre-menopausal.

3. Statistical analysis

All analyses used SAS Version 9.4 (Cary, NC) and Stata Statistical Software, Release 13 (StataCorp LP, College Station, TX) and followed methodology for complex survey data, taking the appropriate ancillary study sampling weights into account. The analyses were conducted in a series of three steps. Distributions of all continuous outcomes and covariates were examined, and the natural log transformation was applied to those that were skewed. Then descriptive statistics using baseline data from the HCHS/SOL ancillary study were produced to show the proportions of study participants with low eGFR, albuminuria, and the composite CKD overall and by demographic characteristics such as age, sex, education, income, language preference, and specific Hispanic/Latino background. The Rao-Scottt Chi-square test was used to compare weighted proportions, and the t-test was used to compare weighted means. Geometric means for each hormone with 95% confidence intervals (95% CIs) were produced overall and by covariates, separately for males and females. The decision to conduct sex-specific analyses was made a priori. For descriptive purposes, continuous covariates were categorized or dichotomized using clinically relevant cut points.

Cross-sectional associations between each continuous pituitary and sex steroid hormone and measures of eGFR and log UACR were estimated using linear regression models. Logistic regression models were estimated for the dichotomous outcomes albuminuria and the CKD composite. Due to the small number of cases, odds of low eGFR was not evaluated. Multivariable linear and logistic models were built for each

hormone concentration with a forward approach, first evaluating the linearity assumption by adding a quadratic term to the model. In the presence of significant quadratic terms, the natural log transformation of the hormone was modeled. Hormones were also modeled as tertiles to evaluate non-linear relationships. Tertiles were modeled as an ordinal variable to evaluate linear trend. The forward approach was used to assess confounding by adding potential confounding variables to the model one at a time and evaluating a > 10% change in the estimate.

Linear regression models were used to prospectively assess changes in eGFR and log UACR from visit 1 to visit 2. The relationships of both continuous and ranked terrtile values of each hormone was evaluated after controlling for baseline eGFR and UACR values, time elapsed between study visits, and relevant confounders. In addition to examining baseline characteristics as potential confounders, differences in covariates comparing visit 2 to baseline levels were considered as confounders. We assessed potential confounding by time varying factors in our prospective analyses for diabetes status (normal, pre, or diabetes at Visit 2), systolic and diastolic blood pressure measurements (mmHg; continuous), body mass index (continuous, kg/m2), total, LDL & HDL cholesterol (continuous, mg/dL), and triglycerides (continuous, mg/dL) by adding the visit 2 variable to the model for categorical characteristics or by adding the difference between visit 1 and visit 2 values to the model for continuous characteristics.

Logistic regression models were used to explore risk for incident CKD, as previously defined, and new onset albuminuria at Visit 2 among those who did not have low eGFR or albuminuria at Visit 1. In these models, associations were evaluated between both continuous and ranked tertile hormone values. Evaluation of effect

modification by diabetes and hypertension (at Visit 1) and adjustment for confounders was determined as in previous models.

C. Results

At baseline, participant age ranged from 45 to 74, with a median age of 56 years (25th-75th percentiles= 50-63). Half of the 1,757 participants in the study sample were female (n=714). A total of 47 participants in our sample had eGFR < 60 (after weighting, 3.2% (95% CI 2.0, 4.5%)). Among those with low eGFR the median age was 66 years (59, 69) compared to 56 (50, 63) among those with eGFR ≥ 60, p<0.0001. Low eGFR was more prevalent among those with health insurance (4.5% (95% CI 2.5, 6.5%)) compared to those without (1.5% (95% CI 0.4, 2.6%), p=0.008). Compared to those with normal eGFR, participants with low eGFR also had higher average systolic blood pressure (SBP), waist to hip ratio, LDL cholesterol, and c-reactive protein levels, lower average total cholesterol levels, and a larger proportion was using medications such as ACE inhibitors and statins (Tables XI and XII). Using sex-specific cutoffs for urine albumin to creatinine ratio, 198 participants (11.2% (95% CI 8.7, 13.6%)) in our sample had albuminuria. Unlike low eGFR, the median age among those with albuminuria was 57 years (25th-75th percentiles= 50-64) compared to 56 (25th-75th percentiles= 50-63) among those without albuminuria. Compared to those without, participants with albuminuria had higher average SBP, diastolic blood pressure (DBP), and fasting glucose levels, and a larger proportion had prediabetes. Using our definition of CKD that included anyone with low eGFR or albuminuria using sex-specific cutoffs, 225 (13.0% (95% CI 10.4, 15.6)) participants met the definition of CKD at the baseline visit. Our composite measure of CKD was more prevalent among those with health

insurance compared to those without, and varied by self-reported income level. Compared to those without, participants with CKD were older, had higher average SBP, DBP, waist to hip ratio, fasting glucose, and c-reactive protein levels, and a large proportion had prediabetes.

As shown in Table XIII, among females, most average hormone levels differed by age, menopause status, and BMI. Among males (Tables XIV and XV), most average hormone levels differed by age, BMI, and to some degree by Hispanic background group. Average levels of SHBG, free estradiol, and free testosterone varied by nativity.

In analyses among post-menopausal females, tertiles of LH and FSH were inversely associated with eGFR after adjustment (Table XVI). When tertiles of LH and FSH were added to the linear regression model for eGFR together, only the association with LH remained (LH T3 vs. T1 β=-5.3 (95% CI -9.8, -0.81, p=0.02) statistically significant. Continuous log transformed LH was inversely associated with eGFR (β = -9.7 (95% CI -13.4, -5.9), p<0.0001). Continuous FSH was inversely associated with eGFR (β =-0.15 (95% CI -0.23, -0.09), p<0.0001). When both continuous log LH and continuous FSH were added to the same model, both inverse associations remained statistically significant (p=0.01 and p=0.02, respectively). Although we observed no association when assessing tertiles of estradiol with eGFR (p for trend=0.13, continuous estradiol was significantly positively associated with eGFR (β =0.01 (95% CI 0.01, 0.02), p<0.0001) but the magnitude of the association was small. A similar pattern was observed with free estradiol. There was no association in the tertile analysis (p for trend=0.33), but free estradiol was significantly positively associated with eGFR (β free

estradiol =0.82 (95% CI 0.49, 1.1), p<0.0001). There was no association between continuous or categorized SHBG or DHEAS with eGFR among postmenopausal females.

Among post-menopausal females, 66 participants had albuminuria (8.8% (95% CI 4.9 to 12.8%) and 79 participants had the composite CKD (10.7% (95% CI 6.6 to 14.9%). When we evaluated the associations between hormones and continuous UACR among post-menopausal females, we found that continuous FSH was positively associated with ln UACR but the magnitude was small (β =0.004 (95% CI 0.0001, 0.009), p=0.05). Continuous FSH was also associated with increased odds of albuminuria (OR=1.03 (95% CI 1.01, 1.04), p=0.0002) and the CKD composite (OR=1.03 (95% CI 1.01, 1.04), p=0.0001) among post-menopausal females, however this association was not observed when modeling FSH tertiles.

We did not observe an association between SHBG and UACR or albuminuria, but we did observe increased odds of the CKD composite when modeling continuous SHBG (OR=1.01 (95% CI 1.00, 1.02), p=0.01). Although we observed no association when assessing tertiles of estradiol with UACR, we observed a statistically significant but small inverse association with continuous estradiol and ln UACR (β =-0.0005 (95% CI -0.001, -0.00002), p=0.04). A similar pattern was observed with free estradiol. There was no association in the tertile analysis, but free estradiol was significantly inversely associated with ln UACR (β free estradiol=-0.03 (95% CI -0.06, -0.003), p=0.03). This association remained (p=0.02) when mutually adjusted for SHBG. There was no association between measured hormones and any other outcome in the cross-sectional analyses among post-menopausal females.

Among the male participants, only 28 individuals (3.7% (95% CI 1.8 to 5.6%) had low eGFR. When we evaluated model-based associations between hormones levels and continuous eGFR, tertiles of LH were inversely associated with eGFR after adjustment (Table XVII). This association remained when FSH tertiles were added to the same model. Continuous LH was significantly inversely associated with eGFR (β=-0.53 (95% CI -0.93, -0.13), p=0.009), and the association remained after mutual adjustment for FSH. There was no association between tertiles of FSH and eGFR (p for trend=0.86), and although continuous FSH was inversely associated with eGFR (β =-0.25 (95% CI -0.46, -0.005), p=0.04), the association was not statistically significant after mutual adjustment for LH. Untransformed FSH was inversely associated with eGFR (β =-0.21 (95% CI -0.44, -0.02), p=0.07). Tertiles of free testosterone were not associated with eGFR (p for trend=0.27), but continuous log transformed free testosterone was positively associated with eGFR (β =3.6 (95% CI 0.28, 7.0), p=0.03). The association between continuous ln free testosterone and eGFR was diminished when mutually adjusted for SHBG level (β =3.0 (95% CI -0.50, 6.7), p=0.09). There was no association between continuous estradiol (p=0.55), free estradiol (p=0.89), DHEAS (p=0.54), or testosterone (p=0.19) with eGFR (data not shown).

When we evaluated the associations with UACR among male participants, tertiles of LH and FSH were positively associated with UACR. Continuous LH was positively associated with ln UACR (β =0.04 (95% CI 0.02, 0.07), p=0.001), as was continuous FSH (β =0.02 (95% CI 0.01, 0.04), p=0.0001). Only the association between FSH and UACR remained significant when LH was mutually added to the adjusted model. There was no association between continuous SHBG (p=0.49), estradiol

(p=0.51), free estradiol (p=0.95), DHEAS (p=0.56), testosterone (p=0.73), or free testosterone (p=0.27) with UACR (data not shown). Evaluation of the associations between hormone concentrations and odds of albuminuria or CKD showed that tertiles of LH and FSH were positively associated with odds of both albuminuria and CKD among male participants. When both LH and FSH tertiles were added to the same model, associations between FSH with albuminuria remained. Continuous LH was positively associated with odds of albuminuria (OR=1.1 (95% CI 1.04, 1.2), p=0.003) and odds of CKD (OR=1.1 (95% CI 1.03, 1.2), p=0.003).

Continuous FSH was associated with increased odds of albuminuria (OR=1.09 (95% CI 1.05, 1.13), p<0.0001) and the CKD composite (OR=1.08 (95% CI 1.04, 1.12), p<0.0001) among males even after adjustment for age, body mass index, Hispanic/Latino background, hypertension medication use, and prediabetes status. When both LH and FSH were added to the same model, only FSH was significantly associated with odds of either outcome. Continuous SHBG appeared associated with increased odds of albuminuria (OR=1.01 (95% CI 1.00, 1.02), p=0.02). No other associations were statistically significant.

Table XVIII shows a comparison of select participant characteristics at visit 1 and at visit 2. On average, visit 2 took place 6 years after visit 1 (25th to 75th percentile 5.3 to 6.3 years). At visit 2, a larger proportion of participants reported having health insurance and among our sample participants who had either prediabetes or normal glucose status at visit 1, 18.3% had diabetes at visit 2.

The associations between pituitary and sex steroid hormone concentrations measured at visit 1 and eGFR measurements at visit 2 among post-menopausal females are presented in Table XIX. We did not observe any strong associations with any of the measured hormones. This was true both in minimally adjusted models controlling for eGFR at Visit 1 and time, and multivariable adjusted models that also included age, hypertension medication use, systolic blood pressure, body mass index, and fasting blood glucose at visit 1, plus visit 1 triglyceride levels and the difference in those levels from visit 1 to visit 2. When continuous DHEAS was modeled, we saw a suggestive positive association with Visit 2 eGFR (p=0.07), and we saw a similar positive association when DHEAS was modeled in tertiles (p for trend=0.06).

Examination of the associations between pituitary and sex steroid hormone concentrations measured at visit 1 and UACR measurements at visit 2 among post-menopausal females did not result in any observed associations. As presented in Table XX, there was a suggestive inverse association between continuous SHBG and UACR but it was not statistically significant and the magnitude was small. No other associations were observed.

The associations between pituitary and sex steroid hormone concentrations measured at visit 1 and eGFR measurements at visit 2 among males are presented in Table XXI. After multivariable adjustment, there was a suggestive inverse association between concentration of SHBG with eGFR at visit 2 (p continuous=0.16; p for trend=0.11), but it did not reach statistical significance and the magnitude of the association was small. When modeled as tertiles, the concentration of total testosterone was inversely associated with visit 2 eGFR (β T3 vs. T1=-2.6 (-4.8, -0.32), p=0.02, p for

trend=0.02) but the association was not observed when testosterone was modeled as a continuous variable (p continuous=0.39). No other hormone concentration was associated with eGFR at visit 2. When we assessed the associations between pituitary and sex steroid hormone concentrations measured at visit 1 and UACR measurements at visit 2 among males, we did not observe any associations between any measured hormone and UACR. The estimates are presented in Table XXII.

After restricting to the 1,532 participants (635 female and 897 male) who had information on eGFR and UACR at visit 2 and who did not have low eGFR or albuminuria at visit 1, a total of 42 female participants (5.7% (95% CI 2.5 to 8.8%)) had incident albuminuria and 61 female participants (10.2% (95% CI 6.2 to 14.2%)) had incident CKD. Multivariable adjusted associations between baseline hormone levels and odds of incident albuminuria and CKD among post-menopausal female participants are presented in in Table XXIII. We observed an inverse association between LH and odds of incident albuminuria when modeling LH both as a continuous variable (OR=0.94 (95% CI 0.88, 0.99), p=0.04) and as tertiles (OR T3 vs. T1 = 0.18 (95% CI 0.05, 0.66), p=0.01, p for trend=0.04). A similar association was suggestive with FSH, but the continuous hormone concentration was not significantly associated with odds of incident albuminuria, and the estimated association was null after mutual adjustment for LH. The associations with LH remained after mutual adjustment for FSH, but we did not observe a similar association when we modeled the odds of incident CKD composite and hence should be interpreted with caution. No other baseline hormone concentration appeared to be associated with incident albuminuria or CKD among post-menopausal female participants.

There were 60 male participants (5.7% (95% CI 3.6 to 7.8%)) who had incident albuminuria and 78 male participants (7.5% (95% CI 5.2 to 9.8%)) had incident CKD. Multivariable adjusted associations between baseline hormone levels and odds of incident albuminuria and CKD among male participants are presented in in Table XXIVI. We did not observe any strong associations between any baseline hormone concentration and incident albuminuria or CKD among male participants. When continuous SHBG was modeled, it was positively associated with odds of the CKD composite (p=0.05), however, there was no association when tertiles of SHBG were modeled.

TABLE XI.
WEIGHTED BASELINE DEMOGRAPHIC AND CLINICAL UNIVARIATE (OVERALL) AND BIVARIATE (BY EGFR, ALBUMINURIA, AND CKD STATUS) CATEGORICAL CHARACTERISTICS OF MALE AND POST-MENOPAUSAL FEMALE PARTICIPANTS WITH MEASURES OF PITUITARY AND SEX STEROID HORMONES

	Overall	**eGFR <60**	**p-value**	**Albuminuria**	**p-value**	**CKD**	**p-value**
	N (weighted %)	**% (95% CI)**		**% (95% CI)**		**% (95% CI)**	
Male, %	1043 (53.6)	3.7 (1.8, 5.6)		13.2 (10.1, 16.3)		15.0 (11.7, 18.2)	
Female, %	714 (46.4)	2.7 (1.0, 4.3)	0.41	8.8 (4.9, 12.8)	0.09	10.7 (6.6, 14.9)	0.12
Hispanic/Latino background							
Central American	155 (6.4)	3.0 (0.0, 6.3)		8.3 (3.4, 13.2)		10.0 (4.2, 15.8)	
Cuban	315 (28.3)	4.1 (0.9, 7.3)		10.8 (6.7, 15.0)		12.5 (7.8, 17.3)	
Dominican	167 (9.1)	3.2 (0.0, 6.6)		11.9 (5.3, 18.5)		14.7 (7.7, 21.8)	
More than one/Other heritage	38 (3.9)	4.1 (0.0, 12.1)		11.8 (0.0, 23.8)		11.8 (0.0, 23.8)	
Puerto Rican	304 (16.1)	3.6 (0.7, 6.5)		16.2 (9.1, 23.3)		19.1 (11.7, 26.5)	
South American	133 (4.9)	0		5.2 (0.3, 10.1)		5.2 (0.3, 10.1)	
Mexican (ref)	645 (31.3)	2.7 (0.9, 4.5)	--	10.1 (5.0, 15.2)	0.47	11.8 (6.5, 17.0)	0.27
Study Center, Bronx	395 (27.7)	3.5 (1.2, 5.8)		15.4 (8.6, 22.2)		18.1 (11.2, 24.9)	
Chicago	447 (12.7)	2.7 (0.4, 5.0)		9.8 (6.0, 13.5)		10.9 (6.9, 14.9)	
Miami	479 (37.3)	3.7 (1.3, 6.2)		10.5 (7.2, 13.8)		12.0 (8.4, 15.7)	
San Diego	436 (22.3)	2.4 (0.2, 4.6)	0.82	7.8 (4.3, 11.2)	0.11	9.5 (5.6, 13.5)	0.06
Born in United States, %	387 (20.5)	3.7 (1.1, 6.2)	0.72	13.9 (8.2, 19.7)	0.28	17.0 (11.0, 23.1)	0.14
<10 years living in US, %	342 (22.5)	3.1 (0.6, 5.7)	0.73	10.5 (6.4, 14.6)	0.70	11.0 (6.8, 15.1)	0.83
< high school education, %	705 (39.0)	3.7 (1.6, 5.7)	0.83	11.9 (7.1, 16.7)	0.67	14.3 (9.3, 19.2)	0.66
Income <$30,000 (annually), %	1111 (63.5)	3.7 (2.0, 5.4)	0.20	13.3 (9.9, 16.6)	0.04	15.4 (11.8, 18.9)	0.04
Have health insurance, %	939 (57.1)	4.5 (2.5, 6.5)	0.008	12.2 (9.0, 15.4)	0.39	15.1 (11.6, 18.6)	0.08
Current cigarette use, %	388 (21.5)	3.4 (1.2, 5.7)	0.38	10.7 (7.0, 14.4)	0.60	12.9 (8.8, 17.0)	0.77
Never drink alcohol, %	865 (54.6)	3.8 (2.0, 5.6)	0.35	93 (10.4 (6.7, 14.1)	0.28	12.2 (8.4, 16.0)	0.42
Cardiovascular disease, %	146 (8.6)	8.5 (3.3, 13.6)	0.03	13.1 (6.4, 19.8)	0.56	19.0 (11.0, 26.9)	0.12
Hypertension (BP>=140/90 and Med Use), %	620 (40.7)	6.4 (3.6, 9.3)	0.0003	17.0 (13.0, 21.1)	0.0002	20.7 (16.1, 25.2)	<0.0001

TABLE XI (continued).
WEIGHTED BASELINE DEMOGRAPHIC AND CLINICAL UNIVARIATE (OVERALL) AND BIVARIATE (BY EGFR, ALBUMINURIA, AND CKD STATUS) CATEGORICAL CHARACTERISTICS OF MALE AND POST-MENOPAUSAL FEMALE PARTICIPANTS WITH MEASURES OF PITUITARY AND SEX STEROID HORMONES

	Overall	**eGFR <60**	**p-value**	**Albuminuria**	**p-value**	**CKD**	**p-value**
	N (weighted %)	**% (95% CI)**		**% (95% CI)**		**% (95% CI)**	
Body mass index (BMI), Norm/Und	326 (20.7)	2.6 (0.3, 4.9)		12.8 (6.8, 18.7)		14.2 (8.1, 20.4)	
Overweight (25 ≤ BMI < 30), %	763 (45.1)	3.8 (1.6, 6.0)		9.3 (6.5, 12.2)		11.3 (8.0, 14.6)	
Obese (BMI ≥ 30), %	665 (34.2)	2.9 (1.1, 4.7)	0.69	12.5 (7.6, 17.5)	0.47	14.4 (9.3, 19.5)	0.55
Prediabetes, %	921 (61.6)	3.5 (1.9, 5.1)		13.1 (9.5, 16.7)		15.0 (11.3, 18.7)	0.06
Normal glucose, %	836 (38.4)	2.8 (0.8, 4.9)	0.62	8.1 (5.8, 10.4)	0.02	9.7 (6.8, 12.6)	0.03
Medication use, %							
ACEi/ARB	291 (19.9)	7.4 (3.2, 11.6)	0.02	14.1 (8.3, 19.9)	0.26	17.6 (11.2, 24.1)	0.11
Thyroid	67 (3.5)	11.0 (0.0, 23.4)	0.22	9.5 (0.0, 21.4)	0.78	13.3 (0.8, 26.0)	0.95
NSAIDs	355 (20.0)	3.6 (0.8, 6.4)	0.78	8.5 (4.8, 12.3)	0.18	9.9 (5.8, 14.0)	0.14
Statins	207 (12.3)	10.1 (4.2, 16.0)	0.01	17.2 (5.8, 28.6)	0.27	22.5 (10.9, 34.0)	0.09
Antidepressants	130 (7.1)	8.6 (2.3, 15.0)	0.08	8.9 (3.3, 14.4)	0.43	15.5 (7.5, 23.4)	0.53
Antipsychotics	36 (2.8)	1.4 (0.0, 4.3)	0.31	11.8 (0.0, 27.7)	0.94	11.8 (0.0, 27.7)	0.88
Low Physical activity level, %	766 (47.7)	2.6 (1.2, 4.1)	0.46	11.8 (7.9, 15.8)	0.84	13.2 (9.1, 17.3)	0.87

TABLE XII.
WEIGHTED BASELINE DEMOGRAPHIC AND CLINICAL UNIVARIATE (OVERALL) AND BIVARIATE (BY EGFR, ALBUMINURIA, AND CKD STATUS) CONTINUOUS CHARACTERISTICS OF MALE AND POST-MENOPAUSAL FEMALE PARTICIPANTS WITH MEASURES OF PITUITARY AND SEX STEROID HORMONES

	Overall	**eGFR <60**	**p-value**	**Albuminuria**	**p-value**	**CKD**	**p-value**
	Mean (95% CI)	**Mean (95% CI)**		**Mean (95% CI)**		**Mean (95% CI)**	
Age, yr[a]	56 (50, 63)	66 (59, 69)	<0.0001	57 (50, 64)	0.45	58 (52, 65)	0.04
Average systolic BP, mmHg	130 (129, 131)	142 (132, 151)	0.01	142 (138, 146)	<0.0001	142 (138, 146)	<0.0001
Average diastolic BP, mmHg	76 (75, 77)	79 (74, 85)	0.15	81 (78, 83)	<0.0001	81 (78, 83)	<0.0001
Glucose, fasting, mg/dL	96.5 (95.8, 97.1)	97.5 (94.2, 100.8)	0.54	98.1 (96.1, 100.1)	0.08	98.0 (96.3, 99.9)	0.06
Total cholesterol, mg/dl	214 (210, 218)	196 (181, 211)	0.02	216 (209, 223)	0.45	215 (207, 222)	0.84
LDL cholesterol, mg/dl	135 (131, 138)	121 (109, 133)	0.04	136 (131, 142)	0.51	135 (130, 141)	0.70
HDL cholesterol, mg/dl	50.6 (49.5, 51.7)	47 (42, 52)	0.18	53 (49, 58)	0.16	52 (48, 56)	0.27
Triglycerides, mg/dl[a]	123 (88, 171)	127 (101, 159)	0.95	112 (87, 156)	0.16	119 (87, 156)	0.25
C-reactive protein, mg/L[a]	1.9 (1.0, 3.8)	3.5 (2.1, 5.9)	0.03	2.1 (1.1, 4.0)	0.18	2.2 (1.1, 4.2)	0.07

[a]: Weighted median (25th-75th percentile) values are presented

TABLE XIII.
WEIGHTED AGE-ADJUSTED BIVARIATE ASSOCIATIONS OF GEOMETRIC MEAN AND 95% CONFIDENCE INTERVALS (95% CI) FOR SELECT HORMONES WITH BASELINE (VISIT 1) COVARIATES AMONG POST-MENOPAUSAL FEMALES (N=714)

	Luteinizing hormone (LH), mIU/mL		**Follicle stimulating hormone** (FSH), mIU/mL		**Sex hormone binding globulin** (SHBG), nmol/L		**Estradiol** (E2), pmol/L	
	GM (95% CI)	**p-value**	**GM (95% CI)**	**p-value**	**GM (95% CI)**	**p-value**	**GM (95% CI)**	**p-value**
Overall	30.6 (29.3, 31.8)		60.6 (57.6, 63.7)		54.5 (51.4, 57.7)	-	24.0 (22.4, 25.8)	
Age in years								
65+	27.7 (25.6, 30.1)	0.04	61.8 (55.9, 68.3)	0.12	59.7 (51.6, 69.2)	0.04	22.6 (19.4, 26.4)	0.01
55-64	32.0 (30.6, 33.5)	0.77	63.5 (59.7, 67.6)	0.02	54.4 (50.1, 59.2)	0.16	21.3 (19.7, 23.1)	<0.0001
45-54 (ref)	31.5 (28.8, 34.5)	ref	55.7 (50.6, 61.3)	ref	49.8 (45.7, 54.4)	ref	30.0 (25.8, 34.8)	ref
Hispanic/Latino background								
Central American	28.8 (24.8, 33.4)	0.78	56.2 (47.5, 66.6)	0.80	44.3 (39.3, 50.0)	0.009	22.6 (17.3, 29.5)	0.78
Cuban	33.7 (31.4, 36.1)	0.0006	71.9 (66, 78.4)	<0.0001	53.0 (45.5, 61.8)	0.91	22.7 (19.4, 26.5)	0.70
Dominican	32.0 (29.4, 34.8)	0.02	61.6 (55.2, 68.8)	0.10	55.8 (48.4, 64.3)	0.61	24.7 (21.0, 28.9)	0.61
More than one/other	34.0 (24.5, 47.1)	0.26	65.5 (45.1, 95.1)	0.37	60.1 (38.5, 93.8)	0.61	21.3 (15.1, 29.9)	0.58
Puerto Rican	29.5 (26.9, 32.3)	0.40	55.4 (48, 63.9)	0.92	61.9 (54.3, 70.7)	0.06	30.3 (23.9, 38.4)	0.05
South American	32.9 (28.5, 38.1)	0.06	62.7 (55.9, 70.4)	0.07	50.0 (41.6, 60.0)	0.50	18.2 (16.9, 19.6)	<0.0001
Mexican	28.1 (26, 30.3)	ref	54.9 (50.5, 59.7)	ref	53.5 (49.7, 57.7)	ref	23.5 (21.3, 25.9)	ref
Born in United States	28.7 (26.3, 31.4)	0.11	52.9 (46.1, 60.7)	0.02	58.0 (51.2, 65.8)	0.29	28.9 (23.6, 35.4)	0.03
Non-US Born	31.1 (29.7, 32.5)	ref	62.8 (59.9, 65.9)	ref	53.5 (50.0, 57.3)	ref	22.9 (21.2, 24.6)	ref
<10 years living in US	32.4 (29.9, 35.2)	0.09	66.9 (62, 72.3)	0.006	51.0 (44.6, 58.4)	0.64	24.1 (20.2, 28.7)	0.32
Non-US Born and YRS US 10-19	29.5 (26.3, 33.1)	0.60	60.9 (55.7, 66.7)	0.05	50.2 (43.8, 57.7)	0.58	21.7 (19.2, 24.4)	0.12
Non-US Born and YRS US ≥20	30.6 (29.1, 32.2)	0.26	60.2 (56.4, 64.3)	0.05	57.5 (53.4, 62.0)	0.60	24.1 (21.9, 26.5)	0.28
US Born	28.0 (24.2, 32.5)	ref	47.4 (37.5, 59.9)	ref	54.2 (43.7, 67.1)	ref	29.8 (20.4, 43.4)	ref

TABLE XIII (continued).
WEIGHTED AGE-ADJUSTED BIVARIATE ASSOCIATIONS OF GEOMETRIC MEAN AND 95% CONFIDENCE INTERVALS (95% CI) FOR SELECT HORMONES WITH BASELINE (VISIT 1) COVARIATES AMONG POST-MENOPAUSAL FEMALES (N=714)

	Luteinizing hormone (LH), mIU/mL		**Follicle stimulating hormone** (FSH), mIU/mL		**Sex hormone binding globulin** (SHBG), nmol/L		**Estradiol** (E2), pmol/L	
	GM (95% CI)	**p-value**	**GM (95% CI)**	**p-value**	**GM (95% CI)**	**p-value**	**GM (95% CI)**	**p-value**
Education, > High school grad	32.3 (30.5, 34.2)	0.01	64.7 (60.3, 69.5)	0.008	50.9 (46.1, 56.3)	0.22	24.1 (21.4, 27.3)	0.96
High school graduate	30.9 (28.2, 33.7)	0.22	62.7 (56.3, 69.9)	0.08	62.1 (57.6, 67.0)	0.02	23.2 (19.9, 27.1)	0.65
< High school	28.8 (26.8, 30.9)	ref	55.8 (51.5, 60.5)	ref	55.2 (50.8, 60.0)	ref	24.3 (21.9, 26.9)	ref
Income ≥$30,000	29.9 (27.6, 32.4)	0.85	60.3 (55.9, 65)	0.85	51.7 (45.1, 59.2)	0.15	26.2 (21.3, 32.1)	0.31
Less than $30,000	30.8 (29.1, 32.5)	0.85	60.6 (57, 64.4)	0.88	54.8 (51.5, 58.4)	0.25	23.5 (21.8, 25.4)	0.69
Missing/not reported	30.4 (26.4, 34.9)	ref	61.5 (50.5, 74.9)	ref	60.5 (51.5, 71.1)	ref	22.7 (18.9, 27.1)	ref
Have health insurance	30.1 (28.5, 31.7)	0.31	57.8 (53.7, 62.2)	0.02	55.7 (52.2, 59.4)	0.39	24.6 (22.3, 27.1)	0.55
No health insurance	31.3 (29.4, 33.4)	ref	64.7 (60.9, 68.8)	ref	52.7 (47.4, 58.7)	ref	23.3 (20.3, 26.7)	ref
Current cigarette use	30.9 (28, 34)	0.61	62.4 (54.3, 71.6)	0.56	58.4 (52.5, 65.0)	0.18	25.0 (20.4, 30.5)	0.53
Former	32.2 (29.5, 35.2)	0.18	61.9 (55.4, 69.2)	0.55	54.2 (48.4, 60.7)	0.87	25.9 (21.8, 30.7)	0.28
Never	30 (28.5, 31.6)	ref	59.7 (56.4, 63.2)	ref	53.6 (49.5, 58.0)	ref	23.3 (21.5, 25.3)	ref
High alcohol use	28.2 (24.3, 32.6)	0.26	56.2 (45.3, 69.7)	0.48	64.1 (60.6, 67.7)	<0.0001	17.6 (14.9, 20.8)	0.005
Low	30.2 (28.1, 32.5)	0.67	60.1 (55.3, 65.3)	0.78	57.2 (52.9, 61.8)	0.15	26.1 (22.7, 30.0)	0.15
Never	30.8 (29.3, 32.4)	ref	60.9 (57.5, 64.5)	ref	53.0 (49.2, 57.1)	ref	23.2 (21.3, 25.2)	ref
Cardiovascular disease	27.9 (24.8, 31.5)	0.13	51.7 (46.2, 58)	0.005	57.6 (47.0, 70.7)	0.57	23.3 (19.3, 28.1)	0.75
No	30.8 (29.5, 32.2)	ref	61.5 (58.3, 64.7)	ref	54.2 (51.0, 57.6)	ref	24.1 (22.4, 26.0)	ref
Hypertension (BP>=140/90/Meds)**,** Yes	30.2 (28.4, 32.1)	0.60	61.9 (57.4, 66.9)	0.37	56.1 (51.0, 61.8)	0.37	26.9 (23.7, 30.5)	0.006
No	30.9 (29.1, 32.7)	ref	59.5 (56.3, 62.9)	ref	53.2 (49.6, 57.0)	ref	22.0 (20.7, 23.5)	ref
Body mass index (BMI), kg/m^2								
Obese	26.3 (24.7, 28)	<0.0001	50.5 (47.5, 53.8)	<0.0001	45.1 (41.0, 49.6)	<0.0001	27.6 (24.1, 31.5)	0.002
Overweight	33.3 (31.3, 35.4)	0.39	66.6 (61.7, 71.9)	0.27	57.5 (53.4, 61.9)	0.01	22.8 (20.5, 25.5)	0.14
Normal/Underweight	34.6 (32.3, 37.2)	ref	71.8 (64.5, 79.9)	ref	71.8 (61.6, 83.6)	ref	20.1 (17.7, 22.9)	ref

TABLE XIII (continued).
WEIGHTED AGE-ADJUSTED BIVARIATE ASSOCIATIONS OF GEOMETRIC MEAN AND 95% CONFIDENCE INTERVALS (95% CI) FOR SELECT HORMONES WITH BASELINE (VISIT 1) COVARIATES AMONG POST-MENOPAUSAL FEMALES (N=714)

	Luteinizing hormone (LH), mIU/mL		**Follicle stimulating hormone** (FSH), mIU/mL		**Sex hormone binding globulin** (SHBG), nmol/L		**Estradiol** (E2), pmol/L	
	GM (95% CI)	**p-value**	**GM (95% CI)**	**p-value**	**GM (95% CI)**	**p-value**	**GM (95% CI)**	**p-value**
Prediabetes	29.5 (27.7, 31.4)	0.09	58.2 (54.7, 61.8)	0.04	48.2 (44.7, 52.1)	<0.0001	24.9 (22.5, 27.6)	0.28
Normal glucose	32.0 (30.1, 34.0)	ref	63.8 (59.3, 68.6)	ref	63.7 (59.0, 68.8)	ref	23.0 (20.9, 25.3)	ref
Physical activity level, Low	29.8 (28, 31.8)	0.88	59.1 (55, 63.6)	0.58	53.6 (49.4, 58.2)	0.38	24.7 (22.3, 27.4)	0.26
Moderate	31.8 (29.8, 33.8)	0.62	62.4 (58.6, 66.4)	0.85	55.1 (51.4, 59.1)	0.49	23.3 (20.9, 26.1)	0.47
High	29.1 (20.6, 41)	ref	64.1 (48.7, 84.3)	ref	61.3 (45.7, 82.1)	ref	21.2 (16.7, 27.0)	ref
High LDL ≥160 mg/dl	31.4 (29.6, 33.2)	0.30	65.1 (60.8, 69.8)	0.02	52.8 (46.8, 59.6)	0.55	23.5 (20.4, 27.1)	0.68
No	30.1 (28.6, 31.8)	ref	58.5 (55, 62.2)	ref	55.1 (51.6, 58.8)	ref	24.3 (22.5, 26.3)	ref
Low HDL <40 mg/dl	26.5 (23.2, 30.3)	0.02	51.9 (42.6, 63.2)	0.09	43.4 (37.1, 50.8)	0.003	27.3 (20.4, 36.6)	0.35
No	31.1 (29.8, 32.4)	ref	61.6 (58.6, 64.8)	ref	55.9 (52.5, 59.4)	ref	23.7 (22.1, 25.4)	ref
High triglycerides ≥200 mg/dl	30.6 (27.3, 34.2)	0.99	58.8 (52.6, 65.8)	0.61	42.5 (36.3, 49.7)	0.002	21.0 (18.7, 23.6)	0.03
No	30.6 (29.3, 31.9)	ref	60.8 (57.5, 64.2)	ref	56.1 (52.7, 59.8)	ref	24.4 (22.6, 26.4)	ref
C-reactive protein ≥2 mg/L	29.2 (27.6, 31)	0.02	56.4 (52.9, 60.1)	0.0002	48.5 (45.0, 52.2)	<0.0001	25.7 (23.1, 28.6)	0.04
No	32.5 (30.5, 34.6)	ref	66.8 (62.3, 71.7)	ref	63.8 (59.0, 69.0)	ref	22.0 (20.1, 24.1)	ref
Low eGFR < 60, Yes	43.2 (33.3, 56.1)	0.008	78.1 (59.2, 102.9)	0.07	71.9 (55.0, 93.9)	0.04	33.0 (22.2, 49.0)	0.11
No	30.3 (29.1, 31.5)	ref	60.1 (57.2, 63.3)	ref	54.0 (51.0, 57.3)	ref	23.8 (22.2, 25.6)	ref
Albuminuria, Yes	31.2 (24.4, 39.7)	0.87	72 (61, 84.9)	0.03	57.7 (48.0, 69.3)	0.52	25.4 (19.5, 33.0)	0.68
No	30.5 (29.3, 31.7)	ref	59.6 (56.5, 62.8)	ref	54.2 (51.0, 57.5)	ref	23.9 (22.2, 25.7)	ref
CKD, Yes	32.3 (26, 40)	0.58	71.4 (61.8, 82.4)	0.02	61.8 (51.6, 73.9)	0.14	27.0 (21.4, 34.1)	0.30
No	30.4 (29.2, 31.6)	ref	59.4 (56.3, 62.6)	ref	53.6 (50.5, 57.0)	ref	23.7 (22.0, 25.5)	ref

TABLE XIV.
WEIGHTED AGE-ADJUSTED BIVARIATE ASSOCIATIONS OF GEOMETRIC MEAN AND 95% CONFIDENCE INTERVALS (95% CI) FOR PITUITARY HORMONES WITH BASELINE (VISIT 1) COVARIATES AMONG MALES

	Luteinizing hormone (LH), mIU/mL		**Follicle stimulating hormone** (FSH), mIU/mL	
	GM (95% CI)	**p-value**	**GM (95% CI)**	**p-value**
Overall	5.7 (5.4, 6.0)		5.9 (5.6, 6.3)	
Age in years, 65+	6.5 (5.2, 8.0)	0.12	7.7 (6.2, 9.5)	0.0005
55-64	5.7 (5.3, 6.1)	0.31	6.0 (5.5, 6.6)	0.008
45-54 (ref)	5.4 (5.2, 5.7)	ref	5.2 (4.9, 5.5)	ref
Hispanic/Latino background				
Central American	6.8 (5.8, 8.0)	0.006	7.2 (6.2, 8.3)	0.003
Cuban	5.5 (4.9, 6.1)	0.65	6.0 (5.4, 6.6)	0.19
Dominican	6.3 (5.6, 7.0)	0.008	5.4 (4.3, 6.7)	0.93
More than one/other	5.7 (4.5, 7.2)	0.57	6.0 (4.4, 8.2)	0.55
Puerto Rican	6.6 (5.7, 7.7)	0.008	6.5 (5.2, 8.0)	0.14
South American	5.2 (4.4, 6.1)	0.87	5.5 (4.9, 6.3)	0.86
Mexican	5.3 (5.0, 5.6)	ref	5.5 (5.0, 6.0)	ref
Born in United States	6.4 (5.6, 7.3)	0.04	6.4 (5.4, 7.6)	0.31
Non-US Born	5.6 (5.3, 5.9)	ref	5.8 (5.4, 6.2)	ref
<10 years living in US	6.0 (5.4, 6.7)	0.63	6.3 (5.7, 7.0)	0.62
Non-US Born and YRS US 10-19	5.9 (5.3, 6.5)	0.84	5.9 (5.2, 6.7)	0.88
Non-US Born and YRS US ≥20	5.5 (5.0, 6.0)	0.39	5.7 (5.1, 6.3)	0.54
US Born	5.8 (5.2, 6.5)	ref	6.0 (5.2, 7.0)	ref
Education				
> High school grad	5.7 (5.3, 6.2)	0.75	5.7 (5.2, 6.3)	0.51
High school graduate	5.9 (5.3, 6.5)	0.49	6.1 (5.5, 6.7)	0.93
< High school	5.6 (5.1, 6.2)	ref	6.0 (5.4, 6.7)	ref
Income ≥$30,000	5.6 (5.2, 6.1)	0.75	5.6 (5.0, 6.2)	0.06
Less than $30,000	5.7 (5.3, 6.2)	0.82	6.0 (5.6, 6.4)	0.12
Missing/not reported	6.0 (4.2, 8.6)	ref	8.2 (5.6, 12.1)	ref
Have health insurance	5.7 (5.3, 6.2)	0.89	5.8 (5.4, 6.3)	0.64
No health insurance	5.7 (5.4, 6.1)	ref	6.0 (5.6, 6.4)	ref
Current cigarette use	6.1 (5.6, 6.6)	0.57	5.8 (5.2, 6.5)	0.58
Former	5.3 (4.8, 5.8)	0.10	5.8 (5.3, 6.3)	0.46
Never	5.9 (5.4, 6.3)	ref	6.1 (5.5, 6.8)	ref
High alcohol use	5.5 (4.6, 6.5)	0.90	6.7 (5.4, 8.2)	0.29
Low	5.9 (5.6, 6.2)	0.26	5.8 (5.4, 6.3)	0.79
Never	5.6 (5.1, 6.1)	ref	5.9 (5.4, 6.5)	ref
Cardiovascular disease	5.8 (4.8, 7.0)	0.91	6.5 (5.3, 8.0)	0.35
No	5.7 (5.4, 6.0)	ref	5.8 (5.5, 6.2)	ref

TABLE XIV (continued).
WEIGHTED AGE-ADJUSTED BIVARIATE ASSOCIATIONS OF GEOMETRIC MEAN AND 95% CONFIDENCE INTERVALS (95% CI) FOR PITUITARY HORMONES WITH BASELINE (VISIT 1) COVARIATES AMONG MALES

	Luteinizing hormone (LH), mIU/mL		**Follicle stimulating hormone** (FSH), mIU/mL	
	GM (95% CI)	**p-value**	**GM (95% CI)**	**p-value**
Hypertension (BP>=140/90 and Med Use), Yes	5.7 (5.2, 6.2)	0.78	6.1 (5.6, 6.7)	0.29
No	5.7 (5.4, 6.1)	ref	5.8 (5.3, 6.2)	ref
Body mass index (BMI), kg/m^2				
Obese	5.5 (5.1, 5.9)	0.0007	5.9 (5.4, 6.5)	0.54
Overweight	5.4 (5.0, 5.8)	0.001	5.7 (5.3, 6.1)	0.30
Normal/Underweight	6.9 (6.1, 7.7)	ref	6.3 (5.3, 7.4)	ref
Prediabetes	5.8 (5.4, 6.2)	0.54	6.0 (5.5, 6.5)	0.40
Normal glucose (no diabetes)	5.6 (5.3, 5.9)	ref	5.7 (5.3, 6.2)	ref
Physical activity level, Low	5.5 (5.1, 5.9)	0.18	5.7 (5.2, 6.1)	0.08
Moderate	5.8 (5.3, 6.4)	0.67	5.9 (5.4, 6.5)	0.22
High	6.0 (5.3, 6.7)	ref	6.5 (5.7, 7.5)	ref
High LDL ≥160 mg/dl	5.6 (5.2, 6.1)	0.78	5.7 (5.0, 6.4)	0.47
No	5.7 (5.4, 6.1)	ref	5.9 (5.5, 6.4)	ref
Low HDL <40 mg/dl	5.5 (5.1, 6.0)	0.38	5.9 (5.2, 6.5)	0.87
No	5.8 (5.4, 6.2)	ref	5.9 (5.5, 6.3)	ref
High triglycerides ≥200 mg/dl	5.6 (5.1, 6.1)	0.44	5.5 (4.9, 6.2)	0.20
No	5.8 (5.4, 6.1)	ref	6.0 (5.6, 6.4)	ref
C-reactive protein ≥2 mg/L	5.6 (5.1, 6.1)	0.43	5.6 (5.2, 6.1)	0.18
No	5.8 (5.4, 6.2)	ref	6.1 (5.6, 6.6)	ref
Low eGFR < 60, Yes	4.9 (2.4, 10.3)	0.69	7.1 (4.6, 10.9)	0.40
No	5.7 (5.5, 6.0)	ref	5.9 (5.5, 6.2)	ref
Albuminuria, Yes	6.5 (5.1, 8.4)	0.24	8.4 (6.7, 10.6)	0.0005
No	5.6 (5.3, 5.9)	ref	5.6 (5.3, 5.9)	ref
CKD, Yes	6.5 (5.2, 8.1)	0.19	7.8 (6.3, 9.8)	0.004
No	5.6 (5.3, 5.8)	ref	5.6 (5.3, 5.9)	ref

TABLE XV.
WEIGHTED AGE-ADJUSTED BIVARIATE ASSOCIATIONS OF GEOMETRIC MEAN AND 95% CONFIDENCE INTERVALS (95% CI) FOR SEX STEROID HORMONES WITH BASELINE (VISIT 1) COVARIATES AMONG MALES

	Sex hormone binding globulin (SHBG), nmol/L		**Estradiol** (E2), pmol/L		**Free Estradiol** (E2), pmol/L		**Total testosterone**, ng/dL		**Free testosterone**, ng/dL	
	GM (95% CI)	**p-value**	**GM (95% CI)**	**p-value**	**GM (95% CI)**	**p-value**	**GM (95% CI)**	**p-value**	**Mean (95% CI)**	**p-value**
Overall	45.5 (43.5, 47.5)		82.9 (79.0, 87.0)		1.36 (1.29, 1.43)		390 (370, 410)		6.3 (6.0, 6.6)	
Age in years, 65+	59.4 (53.0, 66.7)	<0.0001	79.1 (68.5, 91.3)	0.37	1.17 (0.99, 1.37)	0.009	390 (329, 462)	0.91	5.3 (4.4, 6.3)	0.004
55-64	47.7 (44.6, 51.0)	<0.0001	82.4 (75.0, 90.6)	0.61	1.33 (1.21, 1.47)	0.09	384 (352, 419)	0.63	6.0 (5.5, 6.5)	0.002
45-54 (ref)	39.4 (37.0, 41.9)	ref	84.8 (80.5, 89.4)	ref	1.47 (1.39, 1.56)	ref	394 (372, 417)	ref	7.0 (6.6, 7.4)	ref
Hispanic/Latino background										
Central American	44.7 (36.9, 54.0)	0.47	85.5 (71.7, 102.0)	0.30	1.43 (1.21, 1.68)	0.38	406 (341, 483)	0.60	6.7 (5.9, 7.6)	0.89
Cuban	45.1 (42.2, 48.1)	0.08	81.3 (73.6, 89.8)	0.40	1.33 (1.19, 1.49)	0.87	375 (339, 415)	0.57	6.1 (5.4, 6.7)	0.08
Dominican	42.8 (39.2, 46.6)	0.57	89.6 (76.9, 104.4)	0.08	1.52 (1.30, 1.77)	0.09	399 (369, 433)	0.51	6.8 (6.3, 7.2)	0.64
More than one/other	52.7 (43.6, 63.8)	0.02	98.4 (78.6, 123.1)	0.04	1.54 (1.18, 2.02)	0.26	374 (242, 578)	0.88	5.5 (3.4, 8.9)	0.45
Puerto Rican	58.6 (52.4, 65.5)	<0.0001	84.7 (71.9, 99.9)	0.31	1.25 (1.06, 1.47)	0.53	431 (363, 511)	0.23	5.9 (5.0, 6.9)	0.14
South American	38.7 (35.0, 42.9)	0.31	93.5 (78.8, 111.1)	0.04	1.64 (1.37, 1.96)	0.02	357 (314, 406)	0.26	6.4 (5.7, 7.2)	0.54
Mexican	41.4 (38.5, 44.5)	ref	77.5 (73.4, 81.9)	ref	1.32 (1.24, 1.40)	ref	387 (369, 406)	ref	6.6 (6.4, 6.9)	ref
Born in United States	56.1 (50.6, 62.1)	<0.0001	85.5 (74.9, 97.5)	0.59	1.29 (1.12, 1.47)	0.34	404 (345, 473)	0.59	5.7 (4.8, 6.7)	0.12
Non-US Born	43.2 (41.3, 45.2)	ref	82.3 (78.2, 86.6)	ref	1.38 (1.31, 1.46)	ref	386 (368, 406)	ref	6.5 (6.2, 6.8)	ref
<10 years living in US	43.6 (40.5, 46.9)	0.009	79.8 (74.0, 86.1)	0.34	1.33 (1.22, 1.46)	0.85	395 (372, 421)	0.69	6.6 (6.1, 7.1)	0.14
Non-US Born and YRS US 10-19	41.1 (36.1, 46.8)	0.007	83.8 (74.3, 94.6)	0.84	1.43 (1.26, 1.62)	0.39	387 (345, 434)	0.87	6.7 (6.1, 7.2)	0.12
Non-US Born and YRS US ≥20	46.8 (44.3, 49.5)	0.07	83.5 (77.6, 89.8)	0.76	1.36 (1.26, 1.46)	0.71	390 (360, 423)	0.78	6.2 (5.7, 6.7)	0.34
US Born	53.1 (46.8, 60.3)	ref	85.2 (75.8, 95.8)	ref	1.31 (1.13, 1.53)	ref	380 (317, 456)	ref	5.5 (4.5, 6.9)	ref

TABLE XV (continued).
WEIGHTED AGE-ADJUSTED BIVARIATE ASSOCIATIONS OF GEOMETRIC MEAN AND 95% CONFIDENCE INTERVALS (95% CI) FOR SEX STEROID HORMONES WITH BASELINE (VISIT 1) COVARIATES AMONG MALES

	Sex hormone binding globulin (SHBG), nmol/L		**Estradiol** (E2), pmol/L		**Free Estradiol** (E2), pmol/L		**Total testosterone**, ng/dL		**Free testosterone**, ng/dL	
	GM (95% CI)	**p-value**	**GM (95% CI)**	**p-value**	**GM (95% CI)**	**p-value**	**GM (95% CI)**	**p-value**	**Mean (95% CI)**	**p-value**
Education										
> High school grad	44.7 (41.8, 47.8)	0.54	84.6 (78.3, 91.4)	0.30	1.40 (1.29, 1.53)	0.22	384 (354, 418)	0.49	6.3 (5.8, 6.8)	0.73
High school graduate	46.0 (41.8, 50.6)	0.99	84.7 (76.5, 93.9)	0.37	1.37 (1.23, 1.54)	0.48	383 (355, 414)	0.44	6.1 (5.6, 6.6)	0.36
< High school	46.0 (42.9, 49.3)	ref	80.0 (74.2, 86.2)	ref	1.31 (1.21, 1.41)	ref	400 (369, 433)	ref	6.4 (5.9, 6.9)	ref
Income ≥$30,000	44.6 (40.8, 48.9)	0.90	88.0 (82.8, 93.6)	0.75	1.46 (1.39, 1.54)	0.78	406 (377, 437)	0.70	6.7 (6.4, 6.9)	0.72
Less than $30,000	46.1 (44.0, 48.2)	0.79	79.0 (73.6, 84.8)	0.11	1.29 (1.19, 1.39)	0.12	379 (353, 407)	0.88	6.0 (5.6, 6.6)	0.77
Missing/not reported	45.1 (38.9, 52.3)	ref	90.3 (78.3, 104.3)	ref	1.50 (1.26, 1.79)	ref	386 (305, 490)	ref	6.3 (4.8, 8.3)	ref
Have health insurance	47.6 (44.5, 50.8)	0.02	85.1 (79.2, 91.4)	0.21	1.37 (1.27, 1.47)	0.78	398 (369, 429)	0.32	6.2 (5.8, 6.7)	0.56
No health insurance	42.9 (40.8, 45.1)	ref	80.2 (75.5, 85.2)	ref	1.35 (1.26, 1.44)	ref	380 (359, 402)	ref	6.4 (6.0, 6.8)	ref
Current cigarette use	52.7 (49.0, 56.6)	0.0006	79.3 (70.1, 89.7)	0.26	1.23 (1.07, 1.40)	0.03	402 (360, 450)	0.79	5.9 (5.2, 6.7)	0.03
Former	42.5 (39.4, 46.0)	0.59	82.5 (76.4, 89.1)	0.43	1.38 (1.27, 1.51)	0.43	360 (330, 393)	0.02	6.0 (5.5, 6.6)	0.01
Never	43.8 (40.7, 47.2)	ref	85.8 (80.4, 91.6)	ref	1.44 (1.36, 1.53)	ref	409 (385, 435)	ref	6.8 (6.6, 7.1)	ref
High alcohol use	44.3 (39.8, 49.4)	0.26	92.4 (78.9, 108.2)	0.15	1.55 (1.31, 1.83)	0.07	392 (359, 427)	0.59	6.5 (6.0, 7.0)	0.19
Low	43.6 (41.5, 45.8)	0.06	82.9 (78.4, 87.7)	0.74	1.39 (1.32, 1.47)	0.24	397 (379, 417)	0.46	6.6 (6.4, 6.9)	0.04
Never	47.7 (44.2, 51.6)	ref	81.5 (74.9, 88.6)	ref	1.30 (1.19, 1.43)	ref	381 (345, 422)	ref	5.9 (5.3, 6.6)	ref
Cardiovascular disease	43.2 (38.8, 48.1)	0.37	79.0 (64.5, 96.9)	0.63	1.32 (1.07, 1.63)	0.76	371 (329, 419)	0.46	6.2 (5.4, 7.0)	0.76
No	45.7 (43.6, 47.9)	ref	83.3 (79.1, 87.6)	ref	1.36 (1.29, 1.44)	ref	392 (370, 414)	ref	6.3 (6.0, 6.7)	ref
Hypertension (BP>=140/90 and Med Use), Yes	41.8 (39.5, 44.3)	0.001	84.4 (77.7, 91.8)	0.59	1.43 (1.31, 1.56)	0.19	360 (333, 390)	0.007	6.1 (5.6, 6.6)	0.33
No	47.8 (45.1, 50.7)	ref	81.9 (76.9, 87.3)	ref	1.32 (1.23, 1.42)	ref	409 (385, 434)	ref	6.4 (6.0, 6.8)	ref

TABLE XV (continued).
WEIGHTED AGE-ADJUSTED BIVARIATE ASSOCIATIONS OF GEOMETRIC MEAN AND 95% CONFIDENCE INTERVALS (95% CI) FOR SEX STEROID HORMONES WITH BASELINE (VISIT 1) COVARIATES AMONG MALES

	Sex hormone binding globulin (SHBG), nmol/L		**Estradiol** (E2), pmol/L		**Free Estradiol** (E2), pmol/L		**Total testosterone**, ng/dL		**Free testosterone**, ng/dL	
	GM (95% CI)	**p-value**	**GM (95% CI)**	**p-value**	**GM (95% CI)**	**p-value**	**GM (95% CI)**	**p-value**	**Mean (95% CI)**	**p-value**
BMI, Obese	38.9 (36.6, 41.3)	<0.0001	86.5 (78.3, 95.5)	0.29	1.50 (1.35, 1.66)	0.004	313 (288, 340)	<0.0001	5.5 (5.0, 6.0)	0.007
Overweight	44.7 (42.0, 47.6)	<0.0001	82.4 (77.4, 87.7)	0.61	1.37 (1.28, 1.47)	0.05	404 (377, 433)	0.008	6.6 (6.2, 7.1)	0.85
Normal/Underweight	58.2 (52.9, 64.0)	ref	79.7 (71.0, 89.4)	ref	1.19 (1.06, 1.34)	ref	484 (433, 539)	ref	6.7 (6.0, 7.5)	ref
Prediabetes	42.6 (40.2, 45.2)	<0.0001	81.8 (76.5, 87.5)	0.40	1.37 (1.28, 1.47)	0.64	368 (345, 394)	0.0004	6.2 (5.8, 6.6)	0.17
Normal glucose (no diabetes)	51.5 (48.8, 54.4)	ref	85.0 (80.2, 90.1)	ref	1.34 (1.26, 1.42)	ref	435 (406, 465)	ref	6.6 (6.1, 7.1)	ref
Physical activity level, Low	45.4 (42.1, 49.0)	0.73	82.6 (76.0, 89.9)	0.68	1.35 (1.24, 1.48)	0.76	382 (354, 412)	0.50	6.1 (5.7, 6.6)	0.65
Moderate	45.9 (43.4, 48.6)	0.57	84.0 (78.4, 90.0)	0.49	1.38 (1.29, 1.48)	0.52	406 (375, 439)	0.10	6.6 (6.1, 7.1)	0.18
High	44.3 (39.5, 49.7)	ref	80.2 (72.0, 89.4)	ref	1.32 (1.17, 1.48)	ref	363 (319, 412)	ref	5.9 (5.1, 6.9)	ref
High LDL ≥160 mg/dl	42.6 (38.5, 47.3)	0.13	80.8 (73.3, 89.1)	0.57	1.36 (1.24, 1.50)	0.99	390 (357, 426)	0.97	6.6 (6.2, 6.9)	0.16
No	46.5 (44.4, 48.8)	ref	83.5 (78.9, 88.4)	ref	1.36 (1.28, 1.44)	ref	391 (368, 415)	ref	6.2 (5.8, 6.6)	ref
Low HDL <40 mg/dl	38.3 (35.7, 41.1)	<0.0001	81.8 (75.2, 89.0)	0.73	1.42 (1.30, 1.55)	0.27	345 (326, 365)	<0.0001	6.1 (5.8, 6.5)	0.37
No	48.6 (46.2, 51.2)	ref	83.3 (78.7, 88.2)	ref	1.34 (1.26, 1.42)	ref	409 (383, 437)	ref	6.4 (6.0, 6.8)	ref
High triglycerides ≥200 mg/dl	36.8 (33.1, 40.9)	<0.0001	76.8 (68.7, 85.9)	0.13	1.35 (1.19, 1.52)	0.85	330 (296, 368)	0.0004	6.0 (5.4, 6.6)	0.25
No	48.3 (46.4, 50.4)	ref	84.7 (80.2, 89.5)	ref	1.36 (1.29, 1.44)	ref	409 (387, 432)	ref	6.4 (6.0, 6.8)	ref
C-reactive protein ≥2 mg/L	43.2 (41.1, 45.4)	0.04	86.2 (80.2, 92.7)	0.18	1.45 (1.34, 1.56)	0.06	366 (337, 398)	0.05	6.1 (5.6, 6.6)	0.34
No	47.0 (44.1, 50.1)	ref	80.7 (75.6, 86.1)	ref	1.31 (1.22, 1.40)	ref	406 (381, 433)	ref	6.4 (6.0, 6.8)	ref
Low eGFR < 60, Yes	43.4 (37.4, 50.3)	0.54	74.2 (51.5, 106.8)	0.54	1.23 (0.81, 1.87)	0.63	270 (139, 526)	0.26	4.5 (2.1, 9.5)	0.35
No	45.5 (43.5, 47.6)	ref	83.2 (79.2, 87.5)	ref	1.37 (1.30, 1.44)	ref	395 (378, 414)	ref	6.4 (6.1, 6.7)	ref
Albuminuria, Yes	48.5 (42.3, 55.6)	0.31	85.7 (73.3, 100.1)	0.64	1.35 (1.16, 1.58)	0.95	365 (291, 458)	0.52	5.6 (4.5, 6.9)	0.21
No	45.0 (43.1, 47.1)	ref	82.5 (78.5, 86.7)	ref	1.36 (1.29, 1.44)	ref	394 (376, 412)	ref	6.4 (6.1, 6.7)	ref
CKD, Yes	47.4 (41.8, 53.7)	0.48	84.6 (73.3, 97.6)	0.76	1.35 (1.18, 1.55)	0.92	368 (302, 448)	0.50	5.7 (4.7, 6.9)	0.25
No	45.1 (43.1, 47.2)	ref	82.6 (78.5, 86.9)	ref	1.36 (1.29, 1.44)	ref	394 (376, 413)	ref	6.4 (6.1, 6.7)	ref

TABLE XVI.
MULTIVARIABLE ADJUSTED ASSOCIATIONS BETWEEN SERUM LEVELS OF PITUITARY AND SEX STEROID HORMONE CONCENTRATIONS AND EGFR, ALBUMINURIA, UACR, AND CKD AT BASELINE AMONG POST-MENOPAUSAL FEMALES

	Continuous eGFR (mL/minute/1.73m²)	**Continuous UACR (mg/g)**	**Albuminuria**		**CKD**	
	GM (95% CI)[a]	**GM (95% CI)[a]**	**% (95% CI)**	**OR (95% CI)[b]**	**% (95% CI)**	**OR (95% CI)[b]**
Luteinizing hormone (LH), mIU/mL						
LH T1 (3.6-26.1) (ref)	90.4 (86.6, 94.1)	13.3 (7.9, 22.4)	9.6 (0.1, 19.1)	1.0 (ref)	9.9 (0.4, 19.5)	1.0 (ref)
LH T2 (26.2-37.4)	87.6 (83.9, 91.3)	11.2 (8.4, 14.9)	6.8 (2.3, 11.3)	0.68 (0.19, 2.4)	9.8 (4.3, 15.2)	1.0 (0.32, 3.4)
LH T3 (37.5-97.3)	83.0 (78.4, 87.6)[c]	12.6 (8.5, 18.7)	10.3 (4.8, 15.9)	1.0 (0.31, 3.5)	12.5 (6.5, 18.6)	1.6 (0.52, 5.0)
p-value	<0.0001 (trend)	0.71 (trend)	0.74	0.77 (trend)	0.83	0.41 (trend)
Follicle stimulating hormone (FSH), mIU/mL						
FSH T1 (4.0-50.3) (ref)	90.5 (86.8, 94.2)	13.9 (8.5, 22.4)	9.8 (0.0, 20.2)	1.0 (ref)	10.7 (0.4, 21.1)	1.0 (ref)
FSH T2 (50.6-70.7)	88.4 (84.3, 92.4)	10.3 (7.7, 13.7)	5.9 (2.1, 9.7)	0.66 (0.19, 2.3)	7.4 (3.0, 11.8)	0.84 (0.27, 2.6)
FSH T3 (70.8-191.9)	83.8 (79.4, 88.1)[c]	12.6 (8.6, 18.6)	10.5 (4.7, 16.4)	1.2 (0.36, 3.7)	13.5 (7.0, 19.9)	1.8 (0.67, 4.8)
p-value	<0.0001 (trend)	0.61 (trend)	0.62	0.41 (trend)	0.50	0.22 (trend)
Sex hormone binding globulin (SHBG), nmol/L						
SHBG T1 (14-43) (ref)	86.7 (82.0, 91.5)	11.3 (6.5, 19.7)	9.1 (0.0, 19.3)	1.0 (ref)	9.3 (0.0, 19.6)	1.0 (ref)
SHBG T2 (44-66)	87.7 (82.9, 92.4)	12.1 (8.6, 17.1)	6.5 (2.5, 10.5)	0.89 (0.28, 2.8)	7.9 (3.3, 12.5)	1.1 (0.37, 3.2)
SHBG T3 (67-278)	86.9 (83.3, 90.5)	13.5 (9.6, 19)	11.2 (5.5, 16.9)	1.7 (0.47, 6.2)	15.0 (8.7, 21.4)	2.7 (0.88, 8.1)
p-value	0.98 (trend)	0.31 (trend)	0.63	0.22 (trend)	0.34	0.07 (trend)

[a] Adjusted for age (continuous, years), systolic blood pressure (continuous), body mass index (continuous), fasting blood glucose (continuous), self-reported ethnicity/background, hypertension medication use (yes/no), and statin medication use (yes/no)
[b] Adjusted for age (continuous, years), self-reported ethnicity/background, hypertension medication use (yes/no), and diabetes status (prediabetes/normal)
[c] $p<0.05$

TABLE XVI (continued).
MULTIVARIABLE ADJUSTED ASSOCIATIONS BETWEEN SERUM LEVELS OF PITUITARY AND SEX STEROID HORMONE CONCENTRATIONS AND EGFR, ALBUMINURIA, UACR, AND CKD AT BASELINE AMONG POST-MENOPAUSAL FEMALES

	Continuous eGFR (mL/minute/1.73m²)	**Continuous UACR (mg/g)**	**Albuminuria**		**CKD**	
	GM (95% CI)[a]	**GM (95% CI)[a]**	**% (95% CI)**	**OR (95% CI)[b]**	**% (95% CI)**	**OR (95% CI)[b]**
Estradiol (E2), pmol/L						
E2 T1 (<LOD) (ref)	86.5 (82.5, 90.5)	11.8 (8.5, 16.2)	7.0 (4.1, 10.0)	1.0 (ref)	8.3 (5.0, 11.5)	1.0 (ref)
E2 T2 (19-68)	88.3 (83.7, 93.0)	14.9 (7.9, 18.2)	14.3 (0.0, 28.9)	1.9 (0.58, 6.2)	18.3 (3.4, 33.1)	2.2 (0.86, 5.7)
E2 T3 (69-1883)	90.1 (84.8, 95.4)	9.6 (7.0, 13.1)	11.0 (0.3, 21.8)	1.0 (0.28, 3.9)	13.5 (2.3, 24.6)	1.3 (0.41, 4.3)
p-value	0.13 (trend)	0.97 (trend)	0.49	0.57 (trend)	0.27	0.15 (trend)
Using reference limits						
E2 Low (< 18.4 pmol/L)	86.5 (82.4, 90.5)	11.9 (8.5, 16.6)	7.0 (4.1, 10.0)	0.62 (0.24, 1.6)	8.3 (5.0, 11.5)	0.51 (0.23, 1.1)
E2 Normal/High (18.4+ pmol/L)	88.8 (84.6, 92.9)	13.4 (8.0, 22.4)	13.4 (2.5, 24.2)	1.0 (ref)	16.9 (5.9, 28.0)	1.0 (ref)
p-value	0.23	0.46	0.27	0.35	0.14	0.09
Free Estradiol, pmol/L						
Free E2 T1 (0.08-0.23) (ref)	86.2 (82.6, 89.9)	12.8 (9.0, 18.1)	9.8 (4.6, 15.0)	1.0 (ref)	12.1 (6.4, 17.8)	1.0 (ref)
Free E2 T2 (0.24-0.32)	86.9 (82.1, 91.8)	11.4 (8.0, 16.3)	4.3 (1.3, 7.2)	0.37 (0.14, 1.0)	4.6 (1.6, 7.6)	0.30 (0.12, 0.75)[c]
Free E2 T3 (0.32-34.8)	88.4 (83.9, 92.9)	12.9 (7.7, 21.6)	13.4 (2.8, 24.0)	1.0 (0.35, 2.9)	16.8 (6.0, 27.6)	1.1 (0.45, 2.5)
p-value	0.33 (trend)	0.96 (trend)	0.19	0.89 (trend)	0.06	0.89 (trend)
Dehydroepiandrosterone sulfate (DHEAS), umol/L						
DHEAS T1 (0.05-1.62) (ref)	86.3 (82.8, 89.9)	13.3 (7.8, 22.8)	10.2 (1.9, 18.4)	1.0 (ref)	13.1 (4.6, 21.7)	1.0 (ref)
DHEAS T2 (1.63-2.81)	88.3 (84.0, 92.6)	11.3 (8.4, 15.3)	9.5 (3.1, 15.8)	0.80 (0.23, 2.8)	9.7 (3.3, 16.0)	0.71 (0.24, 2.1)
DHEAS T3 (2.82-10.02)	87.1 (82.2, 92.0)	11.9 (8.7, 16.1)	6.4 (2.5, 10.4)	0.40 (0.09, 1.7)	8.8 (4.0, 13.6)	0.60 (0.17, 2.1)
p-value	0.62 (trend)	0.55 (trend)	0.71	0.24 (trend)	0.63	0.43 (trend)

[a] Adjusted for age (continuous, years), systolic blood pressure (continuous), body mass index (continuous), fasting blood glucose (continuous), self-reported ethnicity/background, hypertension medication use (yes/no), and statin medication use (yes/no)
[b] Adjusted for age (continuous, years), self-reported ethnicity/background, hypertension medication use (yes/no), and diabetes status (prediabetes/normal); [c] $p<0.05$

TABLE XVII.
MULTIVARIABLE ADJUSTED ASSOCIATIONS BETWEEN SERUM LEVELS OF PITUITARY AND SEX STEROID HORMONE CONCENTRATIONS AND EGFR, ALBUMINURIA, UACR, AND CKD AT BASELINE AMONG MALES

	Continuous eGFR (mL/minute/1.73m2)	**Continuous UACR (mg/g)**	**Albuminuria n=132 13.2% (10.1, 16.3%)**		**CKD n=146 15.0% (11.7, 18.2%)**	
	GM (95% CI)[a]	**GM (95% CI)[a]**	**% (95% CI)**	**OR (95% CI)[b]**	**% (95% CI)**	**OR (95% CI)[b]**
Luteinizing hormone (LH), mIU/mL						
LH T1 (0.1-4.5) (ref)	94.1 (91.1, 97.1)	6.8 (5.5, 8.4)	10.4 (6.0, 14.8)	1.0 (ref)	10.9 (6.4, 15.3)	1.0 (ref)
LH T2 (4.6-6.7)	92.8 (89.4, 96.3)	6.6 (5.4, 8.0)	8.7 (4.6, 12.9)	0.83 (0.40, 1.7)	11.8 (6.3, 17.3)	1.1 (0.54, 2.2)
LH T3 (6.8-45.4)	89.6 (85.3, 93.8)[c]	8.8 (6.7, 11.5)[c]	20.3 (13.8, 26.9)	2.1 (1.1, 4.0)[c]	22.1 (15.4, 28.7)	2.1 (1.1, 3.9)[c]
p-value	0.01 (trend)	0.003 (trend)	0.004	0.03	0.01	0.02
Follicle stimulating hormone (FSH), mIU/mL						
FSH T1 (0.9-4.3) (ref)	92.4 (89.2, 95.7)	6.7 (5.4, 8.3)	8.0 (4.4, 11.6)	1.0 (ref)	10.4 (5.4, 15.4)	1.0 (ref)
FSH T2 (4.4-6.8)	91.7 (88.5, 94.9)	6.9 (5.6, 8.5)	9.4 (5.4, 13.4)	1.1 (0.55, 2.1)	11.3 (6.9, 15.7)	0.92 (0.46, 1.8)
FSH T3 (6.9-65.0)	92.0 (87.8, 96.3)	8.5 (6.6, 10.9)[c]	21.0 (14.2, 27.7)	2.5 (1.3, 4.8)[c]	22.1 (15.2, 29.0)	1.9 (0.94, 3.8)
p-value	0.86 (trend)	0.006 (trend)	0.0004	0.004	0.005	0.06
Sex hormone binding globulin (SHBG), nmol/L						
SHBG T1 (11-36) (ref)	93.7 (90.5, 96.9)	7.7 (6.3, 9.3)	13.2 (8.3, 18.2)	1.0 (ref)	14.4 (9.3, 19.5)	1.0 (ref)
SHBG T2 (37-53)	90.7 (87.3, 94.2)	6.9 (5.6, 8.6)	8.0 (4.8, 11.1)	0.50 (0.24, 1.0)	11.5 (6.7, 16.4)	0.64 (0.32, 1.3)
SHBG T3 (54-317)	92.1 (87.9, 96.4)	7.7 (5.8, 10.3)	17.5 (10.9, 24.2)	1.4 (0.74, 2.6)	18.3 (11.6, 25.0)	1.2 (0.61, 2.2)
p-value	0.41 (trend)	0.92 (trend)	0.03	0.25	0.24	0.56
Estradiol (E2), pmol/L						
E2 T1 (<LOD-75) (ref)	92.5 (88.3, 96.6)	7.1 (5.6, 9.0)	10.8 (6.1, 15.5)	1.0 (ref)	13.3 (7.6, 19.0)	1.0 (ref)
E2 T2 (76-105)	93.2 (90.0, 96.4)	7.1 (5.7, 8.8)	10.7 (6.0, 15.4)	0.99 (0.47, 2.1)	11.8 (7.0, 16.7)	0.87 (0.43, 1.8)
E2 T3 (106-305)	90.4 (87.0, 93.7)	8.1 (6.3, 10.4)	18.4 (11.6, 25.2)	2.0 (0.95, 4.2)	20.1 (13.2, 27.1)	1.8 (0.85, 3.8)
p-value	0.32 (trend)	0.19 (trend)	0.10	0.07	0.14	0.13

[a] Adjusted for age (continuous, years), systolic blood pressure (continuous), body mass index (continuous), fasting blood glucose (continuous), self-reported ethnicity/background, hypertension medication use (yes/no), and statin medication use (yes/no)
[b] Adjusted for age (continuous, years), self-reported ethnicity/background, hypertension medication use (yes/no), and diabetes status (prediabetes/normal)
[c] $p<0.05$

TABLE XVII (continued).
MULTIVARIABLE ADJUSTED ASSOCIATIONS BETWEEN SERUM LEVELS OF PITUITARY AND SEX STEROID HORMONE CONCENTRATIONS AND EGFR, ALBUMINURIA, UACR, AND CKD AT BASELINE AMONG MALES

	Continuous eGFR (mL/minute/1.73m2)	**Continuous UACR (mg/g)**	**Albuminuria n=132 13.2% (10.1, 16.3%)**		**CKD n=146 15.0% (11.7, 18.2%)**	
	GM (95% CI)[a]	**GM (95% CI)[a]**	**% (95% CI)**	**OR (95% CI)[b]**	**% (95% CI)**	**OR (95% CI)[b]**
Free Estradiol, pmol/L						
Free E2 T1 (0.1-1.3) (ref)	92.9 (88.7, 97.2)	7.3 (5.7, 9.2)	11.8 (7.3, 16.3)	1.0 (ref)	14.2 (8.7, 19.6)	1.0 (ref)
Free E2 T2 (1.3-1.8)	92.8 (89.5, 96.1)	7.5 (5.9, 9.7)	13.6 (7.2, 19.9)	1.2 (0.55, 2.5)	14.2 (7.8, 20.6)	1.0 (0.47, 2.1)
Free E2 T3 (1.8-5.5)	90.3 (87.2, 93.5)	7.4 (5.9, 9.2)	14.5 (9.5, 19.4)	1.2 (0.64, 2.5)	16.8 (11.6, 22.0)	1.2 (0.64, 2.4)
p-value	0.21 (trend)	0.85 (trend)	0.78	0.49	0.78	0.54
Dehydroepiandrosterone sulfate (DHEAS), umol/L						
DHEAS T1 (0.19-3.36) (ref)	91.6 (87.7, 95.5)	7.9 (6.1, 10.2)	17.6 (11.1, 24.2)	1.0 (ref)	20.4 (13.2, 27.5)	1.0 (ref)
DHEAS T2 (3.37-5.13)	93.7 (90.9, 96.5)	6.7 (5.5, 8.3)	8.5 (5.0, 12.0)	0.52 (0.24, 1.1)	9.8 (6.1, 13.5)	0.55 (0.27, 1.1)
DHEAS T3 (5.14-14.9)	90.4 (86.7, 94.1)	7.7 (6.1, 9.7)	12.5 (7.7, 17.3)	0.93 (1.8)	13.5 (8.5, 18.5)	0.95 (0.50, 1.8)
p-value	0.52 (trend)	0.79 (trend)	0.05	0.74	0.03	0.76
Testosterone, ng/dL						
T T1 (3-350)	91.4 (88.2, 94.5)	7.3 (6.1, 8.9)	15.2 (9.7, 20.7)	1.0 (ref)	18.2 (12.0, 24.4)	1.0 (ref)
T T2 (351-473	92.9 (88.9, 96.9)	7.3 (5.6, 9.6)	10.9 (6.9, 14.9)	0.69 (0.36, 1.3)	12.1 (7.9, 16.3)	0.60 (0.31, 1.1)
T T3 (474-1106)	91.8 (88.3, 95.4)	7.5 (6.0, 9.4)	13.5 (7.0, 20.0)	1.1 (0.59, 2.2)	14.6 (8.0, 21.2)	1.0 (0.51, 2.0)
p-value	0.77 (trend)	0.82 (trend)	0.54	0.77	0.33	0.90
Free Testosterone, ng/dL						
Free T T1 (0.02-6.18)	90.3 (86.5, 94.2)	8.3 (6.4, 10.8)	17.6 (11.7, 23.4)	1.0 (ref)	19.9 (13.4, 26.3)	1.0 (ref)
Free T T2 (6.18-7.84)	94.0 (90.7, 97.4)	6.8 (5.4, 8.4)	12.1 (6.2, 17.9)	0.75 (0.36, 1.6)	13.5 (7.5, 19.5)	0.78 (0.38, 1.6)
Free T T3 (7.85-14.56)	92.2 (88.8, 95.5)	6.9 (5.6, 8.5)[c]	9.0 (5.3, 12.7)	0.65 (0.34, 1.2)	10.5 (6.4, 14.6)	0.75 (0.39, 1.5)
p-value	0.27 (trend)	0.02 (trend)	0.08	0.15	0.06	0.38

[a] Adjusted for age (continuous, years), systolic blood pressure (continuous), body mass index (continuous), fasting blood glucose (continuous), self-reported ethnicity/background, hypertension medication use (yes/no), and statin medication use (yes/no)
[b] Adjusted for age (continuous, years), self-reported ethnicity/background, hypertension medication use (yes/no), and diabetes status (prediabetes/normal)
[c] $p<0.05$

TABLE XVIII.
CHANGE IN CHARACTERISTICS FROM VISIT 1 TO VISIT 2 AMONG ANCILLARY STUDY PARTICIPANTS

	Visit 1	Visit 2
	N (weighted %)	N (weighted %)
Income <$40,000 (annually), %	1314 (81.6%)	1202 (75.7%)
Have health insurance, %	939 (57.1%)	1404 (84.4%)
Current cigarette use, %	388 (21.5%)	309 (17.2%)
Hypertension (BP>=140/90 and Med Use)**, %**	620 (40.7%)	922 (58.7%)
Average systolic BP (mmHg)[a]	130 (128, 131)	131 (130, 133)
Average diastolic BP (mmHg)[a]	76 (75, 77)	74 (73, 75)
Body mass index (BMI), Norm/Underweight	326 (20.7%)	309 (20.7%)
Overweight (25 ≤ BMI < 30)**, %**	763 (42.1%)	731 (41.6%)
Obese (BMI ≥ 30)**, %**	665 (34.2%)	678 (37.7%)
Diabetes, %	0	472 (18.3%)
Prediabetes, %	921 (61.6%)	837 (56.1%)
Normal glucose (no diabetes), %	836 (38.4%)	448 (25.6%)
Glucose, fasting (mg/dL)[a]	96.5 (95.8, 97.1)	102.2 (100.8, 103.6)
Total cholesterol, mg/dl[a]	214 (210, 218)	199 (196, 201)
LDL cholesterol, mg/dl[a]	135 (131, 138)	121 (119, 124)
HDL cholesterol, mg/dl (geometric mean)	48.4 (47.5, 49.4)	49.4 (47.9, 50.4)
Triglycerides, mg/dl (geometric mean)	126 (121, 131)	113 (108, 117)
eGFR, mL/minute/1.73m² (pooled)[a]	92.1 (90.9, 93.4)	87.1 (85.8, 88.4)
Male	93.7 (92.0, 95.3)	88.6 (86.8, 90.4)
Female	90.4 (88.5, 92.2)	85.3 (83.4, 87.2)
Low eGFR (pooled) , %	47 (3.2%)	81 (5.3%)
Male, %	28 (3.7%)	46 (4.5%)
Female, %	19 (2.7%)	35 (6.1%)
UACR, mg/g (pooled geometric mean)	8.3 (7.6, 9.1)	5.7 (5.2, 6.3)
Male	7.3 (6.6, 7.9)	5.3 (4.7, 5.9)
Female	9.7 (8.1, 11.5)	6.3 (5.3, 7.5)
Albuminuria (pooled) , %	198 (11.2%)	235 (12.7%)
Male, %	132 (13.2%)	152 (13.7%)
Female, %	66 (8.8%)	83 (11.5%)
CKD (pooled)	225 (13.0%)	283 (16.2%)
Male, %	146 (15.0%)	176 (16.2%)
Female, %	79 (10.7%)	107 (16.1%)

[a]Continuous characteristics presented as mean (95% CI)

TABLE XIX.
ADJUSTED WEIGHTED PROSPECTIVE ASSOCIATIONS OF CONTINUOUS AND RANKED TERTILES OF SERUM HORMONE LEVELS AT BASELINE (VISIT 1) WITH CHANGES IN EGFR FROM VISIT 1 TO VISIT 2 (OVER SIX YEAR FOLLOW-UP) AMONG POST-MENOPAUSAL FEMALES (N=714)

	Continuous eGFR (mL/minute/1.73m²) at Visit 2			
Pituitary hormones:	**Crude β (95% CI)[a]**	**p-value**	**Adjusted β (95% CI)[c]**	**p-value**
Luteinizing hormone (LH), mIU/mL	-0.02 (-0.12, 0.07)	0.66	-0.08 (-0.19, 0.03)	0.14
LH T1 (3.6-26.1) (ref)	ref		ref	
LH T2 (26.2-37.4)	3.5 (0.66, 6.3)	0.01	2.3 (-0.62, 5.2)	0.12
LH T3 (37.5-97.3)	-1.5 (-5.3, 2.2)	0.41	-3.6 (-7.5, 0.35)	0.07
p for trend	0.41		0.09	
Follicle stimulating hormone (FSH), mIU/mL	-1.5 (-4.7, 1.8)[b]	0.37	-1.1 (-4.3, 2.1)[b]	0.50
FSH T1 (4.0-50.3) (ref)	ref		ref	
FSH T2 (50.6-70.7)	2.6 (-0.62, 5.9)	0.11	3.2 (0.38, 6.1)	0.02
FSH T3 (70.8-191.9)	-2.2 (-5.7, 1.3)	0.22	-2.0 (-4.8, 0.84)	0.16
p for trend	0.18		0.12	
Sex steroid hormones:				
Sex hormone binding globulin (SHBG), nmol/L	-0.02 (-0.06, 0.01)	0.23	-0.01 (-0.05, 0.03)	0.55
SHBG T1 (14-43) (ref)	ref		ref	
SHBG T2 (44-66)	-1.7 (-5.7, 2.3)	0.41	-0.91 (-4.4, 2.6)	0.61
SHBG T3 (67-278)	-2.2 (-5.4, 1.0)	0.18	-1.9 (-5.1, 1.4)	0.26
p for trend	0.19		0.42	
Estradiol (E2), pmol/L	-0.004 (-0.01, 0.01)	0.43	-0.005 (-0.01, 0.005)	0.34
E2 T1 (<LOD) (ref)	ref		ref	
E2 T2 (19-68)	-0.16 (-3.3, 3.0)	0.92	-0.29 (-3.6, 2.9)	0.86
E2 T3 (69-1883)	0.59 (-3.7, 4.9)	0.79	-0.74 (-4.8, 3.3)	0.72
p for trend	0.89		0.73	
Free Estradiol, pmol/L	-0.14 (-0.63, 0.34)	0.56	-0.19 (-0.69, 0.29)	0.43
Free E2 T1 (0.08-0.23) (ref)	ref		ref	
Free E2 T2 (0.24-0.32)	1.4 (-2.7, 5.6)	0.49	1.8 (-2.0, 5.7)	0.35
Free E2 T3 (0.32-34.8)	0.27 (-2.6, 3.1)	0.85	-0.01 (-2.9, 2.9)	0.99
p for trend	0.81		0.91	
Dehydroepiandrosterone sulfate (DHEAS), umol/L	1.1 (0.26, 1.9)	0.01	0.66 (-0.06, 1.4)	0.07
DHEAS T1 (0.05-1.62) (ref)	ref		ref	
DHEAS T2 (1.63-2.81)	4.8 (0.88, 8.7)	0.02	4.2 (0.60, 7.8)	0.02
DHEAS T3 (2.82-10.02)	4.4 (0.74, 8.0)	0.02	3.0 (-0.04, 6.1)	0.05
p for trend	0.02		0.06	

[a] Adjusted for eGFR at visit 1 and time from Visit 1 to Visit 2
[b] FSH was log transformed when modeled

[c] Adjusted for eGFR at visit 1 and time from Visit 1 to Visit 2, age (continuous, years), self-reported ethnicity/background, systolic blood pressure (at visit 1), fasting blood glucose (at visit 1), body mass index (at visit 1), triglyceride level (at visit 1) and difference in level from visit 1 to visit 2, and antihypertensive medication use (at visit 1)

TABLE XX.
Adjusted weighted prospective associations of continuous and ranked tertiles of serum hormone levels at baseline (Visit 1) with changes in UACR from Visit 1 to Visit 2 (over six year follow-up) among post-menopausal females (n=714)

	Continuous log UACR (mg/g) at Visit 2			
Pituitary hormones:	**Crude β (95% CI)[a]**	**p-value**	**Adjusted β (95% CI)[c]**	**p-value**
Luteinizing hormone (LH)	0.003 (-0.004, 0.01)	0.36	0.005 (-0.001, 0.01)	0.12
LH T2 vs. T1 (ref)	0.02 (-0.21, 0.24)	0.88	0.04 (-0.15, 0.24)	0.65
LH T3 vs. T1 (ref)	-0.02 (-0.26, 0.23)	0.89	0.05 (-0.18, 0.29)	0.64
p for trend	0.89		0.87	
Follicle stimulating hormone (FSH)	0.002 (-0.001, 0.005)	0.19	0.002 (-0.001, 0.005)	0.24
FSH T2 vs. T1 (ref)	0.17 (-0.07, 0.42)	0.17	0.11 (-0.12, 0.34)	0.36
FSH T3 vs. T1 (ref)	0.07 (-0.12, 0.28)	0.47	0.07 (-0.13, 0.27)	0.49
p for trend	0.57		0.66	
Sex steroid hormones:				
Sex hormone binding globulin (SHBG)	-0.001 (-0.003, 0.001)	0.32	-0.002 (-0.003, 0.0001)	0.07
SHBG T2 vs. T1 (ref)	-0.06 (-0.32, 0.19)	0.64	-0.15 (-0.37, 0.07)	0.18
SHBG T3 vs. T1 (ref)	-0.11 (-0.30, 0.09)	0.29	-0.19 (-0.40, 0.02)	0.07
p for trend	0.28		0.02	
Estradiol (E2)	-0.0002 (-0.0005, 0.0001)	0.30	-0.0001 (-0.0004, 0.0002)	0.48
E2 T2 vs. T1 (ref)	0.07 (-0.19, 0.34)	0.59	0.11 (-0.14, 0.37)	0.38
E2 T3 vs. T1 (ref)	-0.14 (-0.36, 0.07)	0.18	-0.12 (-0.31, 0.07)	0.23
p for trend	0.67		0.84	
Free Estradiol	-0.008 (-0.03, 0.01)	0.43	-0.005 (-0.02, 0.02)	0.66
Free E2 T2 vs. T1 (ref)	-0.01 (-0.20, 0.17)	0.89	0.05 (-0.11, 0.21)	0.54
Free E2 T3 vs. T1 (ref)	0.04 (-0.17, 0.26)	0.69	0.11 (-0.10, 0.33)	0.29
p for trend	0.70		0.22	
Dehydroepiandrosterone sulfate (DHEAS)	-0.01 (-0.14, 0.11)[b]	0.83	-0.01 (-0.13, 0.11)[b]	0.89
DHEAS T2 vs. T1 (ref)	0.10 (-0.14, 0.34)	0.42	0.10 (-0.12, 0.32)	0.36
DHEAS T3 vs. T1 (ref)	0.05 (-0.17, 0.27)	0.63	0.09 (-0.11, 0.28)	0.37
p for trend	0.61		0.25	

[a] Adjusted for UACR at visit 1 and time from Visit 1 to Visit 2; [b] DHEAS was log transformed when modeled as a continuous variable; [c] Adjusted for UACR at visit 1, time from Visit 1 to Visit 2, age (continuous, years), self-reported ethnicity/background, systolic blood pressure (at visit 1) and difference in level from visit 1 to visit 2, fasting blood glucose (at visit 1), nativity (US vs. foreign born), and antihypertensive medication use (at visit 1)

TABLE XXI.
ADJUSTED WEIGHTED PROSPECTIVE ASSOCIATIONS OF CONTINUOUS AND RANKED TERTILES OF SERUM HORMONE LEVELS AT BASELINE (VISIT 1) WITH CHANGES IN EGFR FROM VISIT 1 TO VISIT 2 (OVER SIX YEAR FOLLOW-UP) AMONG MALES (N=1,043)

	Continuous eGFR (mL/minute/1.73m²) at Visit 2			
Pituitary hormones:	**Crude β (95% CI)**[a]	**p-value**	**Adjusted β (95% CI)**[b]	**p-value**
Luteinizing hormone (LH)	-0.10 (-0.36, 0.16)	0.47	-0.01 (-0.27, 0.26)	0.95
LH T2 vs. T1 (ref)	-2.0 (-4.1, 0.03)	0.05	-1.5 (-3.4, 0.41)	0.12
LH T3 vs. T1 (ref)	0.62 (-2.8, 1.6)	0.58	0.39 (-1.8, 2.6)	0.73
p for trend	0.59		0.74	
Follicle stimulating hormone (FSH)	-0.03 (-0.18, 0.11)	0.65	0.04 (-0.12, 0.20)	0.64
FSH T2 vs. T1 (ref)	-0.28 (-2.4, 1.8)	0.79	-0.16 (-2.1, 1.8)	0.87
FSH T3 vs. T1 (ref)	-0.68 (-3.1, 1.7)	0.57	0.06 (-2.2, 2.4)	0.96
p for trend	0.57		0.95	
Sex steroid hormones:				
Sex hormone binding globulin (SHBG)	-0.04 (-0.08, -0.005)	0.02	-0.03 (-0.06, 0.01)	0.16
SHBG T2 vs. T1 (ref)	-3.3 (-5.4, -1.1)	0.003	-2.6 (-4.7, -0.54)	0.01
SHBG T3 vs. T1 (ref)	-3.0 (-5.1, -0.83)	0.007	-2.1 (-4.5, 0.32)	0.09
p for trend	0.01		0.11	
Estradiol (E2)	-0.005 (-0.03, 0.02)	0.68	-0.005 (-0.02, 0.02)	0.65
E2 T2 vs. T1 (ref)	0.22 (-1.9, 2.3)	0.83	-0.13 (-2.1, 1.8)	0.89
E2 T3 vs. T1 (ref)	-1.3 (-3.6, 1.1)	0.28	-1.4 (-3.5, 0.62)	0.17
p for trend	0.29		0.17	
Dehydroepiandrosterone sulfate (DHEAS)	0.35 (0.01, 0.68)	0.04	0.04 (-0.29, 0.38)	0.81
DHEAS T2 vs. T1 (ref)	0.72 (-1.5, 2.9)	0.52	-0.67 (-2.9, 1.5)	0.55
DHEAS T3 vs. T1 (ref)	1.7 (-0.43, 3.8)	0.12	-0.18 (-2.3, 1.9)	0.87
p for trend	0.12		0.87	
Testosterone	-0.003 (-0.009, 0.003)	0.32	-0.003 (-0.009, 0.003)	0.39
T T2 vs. T1 (ref)	-2.4 (-4.8, -0.05)	0.04	-2.2 (-4.5, 0.04)	0.05
T T3 vs. T1 (ref)	-2.2 (-4.4, 0.08)	0.06	-2.6 (-4.8, -0.32)	0.02
p for trend	0.06		0.02	
Free Testosterone	0.10 (-0.33, 0.53)	0.65	-0.13 (-0.55, 0.29)	0.53
Free T T2 vs. T1 (ref)	0.34 (-1.8, 2.4)	0.75	0.18 (-1.8, 2.2)	0.86
Free T T3 vs. T1 (ref)	-0.09 (-2.2, 2.0)	0.93	-1.3 (-3.4, 0.71)	0.19
p for trend	0.95		0.23	

[a] Adjusted for eGFR at visit 1 and time from Visit 1 to Visit 2

[b] Adjusted for eGFR at visit 1 and time from Visit 1 to Visit 2, age (continuous, years), self-reported ethnicity/background, systolic blood pressure (at visit 1), fasting blood glucose (at visit 1), body mass index (at visit 1), triglyceride level (at visit 1) and difference in level from visit 1 to visit 2, and antihypertensive medication use (at visit 1)

TABLE XXII.
ADJUSTED WEIGHTED PROSPECTIVE ASSOCIATIONS OF RANKED TERTILES OF SERUM HORMONE LEVELS AT BASELINE (VISIT 1) WITH CHANGES IN UACR FROM VISIT 1 TO VISIT 2 (OVER SIX YEAR FOLLOW-UP) AMONG MALES (N=1,043)

	Continuous log UACR (mg/g) at Visit 2			
Pituitary hormones:	**Crude β (95% CI)**[a]	**p-value**	**Adjusted β (95% CI)**[c]	**p-value**
Luteinizing hormone (LH)	0.006 (-0.01, 0.03)	0.59	0.002 (-0.02, 0.02)	0.85
LH T2 vs. T1 (ref)	0.03 (-0.18, 0.25)	0.76	0.03 (-0.18, 0.24)	0.76
LH T3 vs. T1 (ref)	0.07 (-0.13, 0.28)	0.49	0.02 (-0.19, 0.24)	0.81
p for trend	0.49		0.81	
Follicle stimulating hormone (FSH)	0.01 (-0.01, 0.02)	0.35	0.004 (-0.01, 0.02)	0.53
FSH T2 vs. T1 (ref)	-0.13 (-0.31, 0.05)	0.15	-0.13 (-0.30, 0.04)	0.14
FSH T3 vs. T1 (ref)	0.07 (-0.13, 0.28)	0.47	0.05 (-0.13, 0.24)	0.57
p for trend	0.42		0.51	
Sex steroid hormones:				
Sex hormone binding globulin (SHBG)	0.13 (-0.05, 0.31)[b]	0.16	0.13 (-0.05, 0.32)[b]	0.15
SHBG T2 vs. T1 (ref)	-0.09 (-0.29, 0.11)	0.39	-0.12 (-0.32, 0.08)	0.23
SHBG T3 vs. T1 (ref)	0.08 (-0.13, 0.29)	0.46	0.07 (-0.15, 0.30)	0.53
p for trend	0.42		0.49	
Estradiol (E2)	-0.0001 (-0.002, 0.002)	0.92	-0.0003 (-0.002, 0.002)	0.74
E2 T2 vs. T1 (ref)	0.10 (-0.10, 0.31)	0.33	0.10 (-0.19, 0.23)	0.31
E2 T3 vs. T1 (ref)	0.03 (-0.19, 0.25)	0.80	0.02 (-0.19, 0.23)	0.87
p for trend	0.79		0.85	
Dehydroepiandrosterone sulfate (DHEAS)	-0.01 (-0.04, 0.02)	0.89	-0.002 (-0.04, 0.04)	0.91
DHEAS T2 vs. T1 (ref)	-0.11 (-0.32, 0.09)	0.28	-0.10 (-0.25, 0.21)	0.37
DHEAS T3 vs. T1 (ref)	-0.06 (-0.26, 0.14)	0.54	-0.02 (-0.25, 0.21)	0.84
p for trend	0.52		0.86	
Testosterone	-0.0001 (-0.001, 0.0005)	0.75	-0.0001 (-0.001, 0.0005)	0.83
T T2 vs. T1 (ref)	-0.10 (-0.33, 0.12)	0.36	-0.12 (-0.35, 0.12)	0.33
T T3 vs. T1 (ref)	-0.01 (-0.22, 0.20)	0.93	0.006 (-0.20, 0.21)	0.96
p for trend	0.92		0.99	
Free Testosterone	-0.02 (-0.07, 0.03)	0.35	-0.02 (-0.06, 0.03)	0.47
Free T T2 vs. T1 (ref)	-0.24 (-0.43, -0.05)	0.01	-0.23 (-0.42, -0.03)	0.02
Free T T3 vs. T1 (ref)	-0.12 (-0.32, 0.08)	0.24	-0.08 (-0.27, 0.10)	0.39
p for trend	0.20		0.31	

[a] Adjusted for UACR at visit 1 and time from Visit 1 to Visit 2; [b] SHBG was log transformed when modeled as a continuous variable; [c] Adjusted for UACR at visit 1, time from Visit 1 to Visit 2, age (continuous, years), self-reported ethnicity/background, systolic blood pressure (at visit 1) and difference in level from visit 1 to visit 2, fasting blood glucose (at visit 1), nativity (US vs. foreign born), and antihypertensive medication use (at visit 1)

TABLE XXIII.
WEIGHTED PREVALENCE AND ODDS OF INCIDENT LOW EGFR, ALBUMINURIA, AND CKD COMPOSITE BY BASELINE CONTINUOUS AND RANKED TERTILE SERUM HORMONE CONCENTRATIONS AMONG POST-MENOPAUSAL FEMALES (N=635)

	Albuminuria			CKD		
	% (95% CI)	OR (95% CI)[a]	p-value	% (95% CI)	OR (95% CI)[a]	p-value
Luteinizing hormone (LH), mIU/mL		0.94 (0.88, 0.99)	0.04		0.99 (0.94, 1.1)	0.72
LH T1 (3.6-26.1) (ref)	9.6 (1.5, 17.8)	ref		14.6 (5.7, 23.4)	ref	
LH T2 (26.2-37.4)	5.8 (1.6, 10.0)	0.60 (0.17, 2.1)	0.42	7.2 (2.4, 112.0)	0.56 (0.19, 1.6)	0.29
LH T3 (37.5-97.3)	1.5 (0.3, 2.8)	0.18 (0.05, 0.66)	0.01	9.2 (2.5, 15.9)	1.2 (0.34, 4.4)	0.75
p-value	0.12	0.04		0.32	0.87	
Follicle stimulating hormone (FSH), mIU/mL		0.98 (0.96, 1.01)	0.14		1.0 (0.99, 1.0)	0.22
FSH T1 (4.0-50.3) (ref)	11.1 (2.2, 20.1)	ref		13.4 (4.4, 22.3)	ref	
FSH T2 (50.6-70.7)	3.9 (0.4, 7.5)	0.25 (0.07, 0.90)	0.03	8.6 (3.0, 14.1)	0.56 (0.19, 1.6)	0.28
FSH T3 (70.8-191.9)	3.1 (0.6, 5.7)	0.22 (0.05, 0.94)	0.04	9.2 (3.1, 15.3)	0.79 (0.21, 3.0)	0.73
p-value	0.11	0.04		0.61	0.74	
Sex hormone binding globulin (SHBG), nmol/L		0.99 (0.97, 1.01)	0.52		0.99 (0.98, 1.0)	0.94
SHBG T1 (14-43) (ref)	6.5 (2.3, 10.6)	ref		8.6 (3.9, 13.3)	ref	
SHBG T2 (44-66)	6.5 (0.0, 13.4)	0.57 (0.24, 1.4)	0.21	10.9 (3.0, 18.8)	0.87 (0.37, 2.0)	0.74
SHBG T3 (67-278)	3.9 (0.8, 7.0)	0.25 (0.05, 1.2)	0.08	10.8 (4.2, 17.4)	0.91 (0.23, 3.6)	0.89
p-value	0.71	0.07		0.87	0.92	
Estradiol (E2), pmol/L		0.99 (0.98, 1.01)	0.34		0.99 (0.98, 1.0)	0.34
E2 T1 (<LOD) (ref)	6.1 (2.1, 10.0)	ref		10.8 (5.8, 15.8)	ref	
E2 T2 (19-68)	4.7 (0.0, 10.4)	0.79 (0.17, 3.8)	0.77	8.2 (1.3, 15.2)	0.84 (0.23, 3.1)	0.80
E2 T3 (69-1883)	4.3 (0.1, 8.6)	0.72 (0.19, 2.7)	0.63	8.9 (1.3, 16.5)	1.4 (0.41, 4.9)	0.58
p-value	0.84	0.61		0.77	0.86	

[a] Adjusted for age (continuous, years), systolic blood pressure (continuous), body mass index (continuous), fasting blood glucose (continuous), self-reported ethnicity/background, HDL cholesterol level (continuous), and anti-hypertension medication use (yes/no)

TABLE XXIII (continued).
WEIGHTED PREVALENCE AND ODDS OF INCIDENT LOW EGFR, ALBUMINURIA, AND CKD COMPOSITE BY BASELINE CONTINUOUS AND RANKED TERTILE SERUM HORMONE CONCENTRATIONS AMONG POST-MENOPAUSAL FEMALES (N=635)

	Albuminuria			CKD		
	% (95% CI)	OR (95% CI)[a]	p-value	% (95% CI)	OR (95% CI)[a]	p-value
Free Estradiol, pmol/L		0.53 (0.19, 1.5)	0.22		0.58 (0.21, 1.6)	0.30
Free E2 T1 (0.08-0.23) (ref)	7.4 (0.0, 14.9)	ref		12.5 (3.8, 21.3)	ref	
Free E2 T2 (0.24-0.32)	4.4 (1.0, 7.7)	0.79 (0.23, 2.7)	0.71	8.9 (3.5, 14.3)	0.73 (0.23, 2.3)	0.59
Free E2 T3 (0.32-34.8)	5.4 (1.2, 9.6)	0.91 (0.24, 3.5)	0.89	9.1 (3.6, 14.7)	0.87 (0.23, 3.2)	0.84
p-value	0.70	0.85		0.71	0.80	
Dehydroepiandrosterone sulfate (DHEAS), umol/L		1.1 (0.82, 1.5)	0.46		1.2 (0.90, 1.7)	0.19
DHEAS T1 (0.05-1.62) (ref)	5.5 (1.4, 9.7)	ref		13.0 (5.6, 20.4)	ref	
DHEAS T2 (1.63-2.81)	3.6 (1.3, 5.9)	0.62 (0.18, 2.1)	0.43	5.0 (2.3, 7.7)	0.47 (0.16, 1.4)	0.17
DHEAS T3 (2.82-10.02)	8.1 (0.0, 16.4)	2.1 (0.56, 8.1)	0.26	12.4 (3.4, 21.4)	1.9 (0.65, 5.5)	0.24
p-value	0.55	0.32		0.21	0.37	

[a] Adjusted for age (continuous, years), systolic blood pressure (continuous), body mass index (continuous), fasting blood glucose (continuous), self-reported ethnicity/background, HDL cholesterol level (continuous), and anti-hypertension medication use (yes/no)

TABLE XXIV.
WEIGHTED PREVALENCE AND ODDS OF INCIDENT LOW EGFR, ALBUMINURIA, AND CKD COMPOSITE BY BASELINE CONTINUOUS AND RANKED TERTILE SERUM HORMONE CONCENTRATIONS AMONG MALES (N=897)

	Albuminuria			CKD		
	% (95% CI)	OR (95% CI)[a]	p-value	% (95% CI)	OR (95% CI)[b]	p-value
Luteinizing hormone (LH), mIU/mL		1.0 (0.98, 1.1)	0.21		1.0 (0.98, 1.1)	0.15
LH T1 (0.1-4.5) (ref)	5.0 (2.3, 7.7)	ref		6.6 (3.3, 9.9)	ref	
LH T2 (4.6-6.7)	6.3 (2.4, 10.2)	1.4 (0.57, 3.3)	0.48	8.7 (4.4, 13.1)	1.5 (0.72, 3.3)	0.27
LH T3 (6.8-45.4)	5.9 (2.4, 9.4)	1.1 (0.55, 2.4)	0.73	7.1 (3.4, 10.7)	1.0 (0.53, 2.1)	0.88
p-value	0.85	0.72		0.70	0.85	
Follicle stimulating hormone (FSH), mIU/mL		1.0 (0.96, 1.1)	0.59		1.0 (0.96, 1.1)	0.79
FSH T1 (0.9-4.3) (ref)	5.5 (2.1, 8.8)	ref		7.4 (3.5, 11.2)	ref	
FSH T2 (4.4-6.8)	3.8 (1.1, 6.5)	0.57 (0.26, 1.3)	0.18	5.7 (2.3, 9.1)	0.63 (0.29, 1.4)	0.24
FSH T3 (6.9-65.0)	7.9 (3.7, 12.1)	1.3 (0.56, 3.1)	0.52	9.5 (5.0, 14.0)	1.2 (0.55, 2.6)	0.66
p-value	0.23	0.48		0.38	0.63	
Sex hormone binding globulin (SHBG), nmol/L		1.0 (0.99, 1.0)	0.09		1.01 (1.00, 1.02)	0.05
SHBG T1 (11-36) (ref)	7.4 (3.3, 11.4)	ref		7.8 (3.7, 11.9)	ref	
SHBG T2 (37-53)	2.6 (0.90, 4.2)	0.31 (0.11, 0.88)	0.03	6.2 (2.6, 9.7)	0.72 (0.29, 1.8)	0.47
SHBG T3 (54-317)	7.2 (3.4, 11.0)	1.1 (0.42, 3.1)	0.79	8.5 (4.6, 12.4)	1.2 (0.51, 3.0)	0.63
p-value	0.07	0.83		0.67	0.64	
Estradiol (E2), pmol/L		1.0 (0.99, 1.0)	0.87		0.99 (0.99, 1.0)	0.51
E2 T1 (<LOD-75) (ref)	5.1 (1.8, 8.5)	ref		7.0 (3.3, 10.6)	ref	
E2 T2 (76-105)	6.9 (3.0, 10.8)	1.3 (0.49, 3.5)	0.59	9.5 (5.0, 14.0)	1.3 (0.58, 3.1)	0.49
E2 T3 (106-305)	5.1 (2.0, 8.1)	0.96 (0.35, 2.7)	0.94	6.0 (2.7, 9.2)	0.78 (0.31, 1.9)	0.59
p-value	0.68	0.96		0.42	0.63	

[a] Adjusted for age (continuous, years), systolic blood pressure (continuous), body mass index (continuous), fasting blood glucose (continuous), HDL cholesterol level (continuous), and anti-hypertension medication use (yes/no)
[b] Adjusted for age (continuous, years), systolic blood pressure (continuous), body mass index (continuous), fasting blood glucose (continuous), HDL cholesterol level (continuous), anti-hypertension medication use (yes/no), and self-reported Hispanic/Latino background group

TABLE XXIV (continued).
WEIGHTED PREVALENCE AND ODDS OF INCIDENT LOW EGFR, ALBUMINURIA, AND CKD COMPOSITE BY BASELINE CONTINUOUS AND RANKED TERTILE SERUM HORMONE CONCENTRATIONS AMONG MALES (N=897)

	Albuminuria			CKD		
	% (95% CI)	OR (95% CI)[a]	p-value	% (95% CI)	OR (95% CI)[b]	p-value
Free Estradiol, pmol/L		0.88 (0.55, 1.4)	0.59		0.73 (0.44, 1.2)	0.22
Free E2 T1 (0.1-1.3) (ref)	4.8 (2.0, 7.7)	ref		6.6 (3.3, 9.8)	ref	
Free E2 T2 (1.3-1.8)	7.3 (3.0, 11.7)	1.7 (0.68, 4.2)	0.26	10.0 (5.2, 14.9)	1.6 (0.72, 3.6)	0.25
Free E2 T3 (1.8-5.5)	4.9 (1.9, 7.9)	1.0 (0.40, 2.6)	0.95	5.7 (2.5, 8.9)	0.77 (0.31, 1.9)	0.58
p-value	0.50	0.86		0.25	0.67	
Dehydroepiandrosterone sulfate (DHEAS), umol/L		0.94 (0.79, 1.1)	0.50		0.90 (0.77, 1.0)	0.14
DHEAS T1 (0.19-3.36) (ref)	7.7 (3.3, 12.1)	ref		10.9 (6.0, 15.8)	ref	
DHEAS T2 (3.37-5.13)	4.1 (1.7, 6.6)	0.47 (0.18, 1.2)	0.11	5.4 (2.7, 8.1)	0.46 (0.21, 1.0)	0.05
DHEAS T3 (5.14-14.9)	5.1 (2.2, 8.0)	0.63 (0.27, 1.5)	0.30	6.0 (2.7, 9.3)	0.57 (0.27, 1.2)	0.15
p-value	0.28	0.29		0.07	0.13	
Testosterone, ng/dL		1.0 (0.99, 1.0)	0.70		1.0 (0.99, 1.0)	0.34
T T1 (3-350)	6.2 (3.5, 10.0)	ref		8.8 (4.4, 13.1)	ref	
T T2 (351-473	4.7 (1.7, 7.6)	0.90 (0.32, 2.5)	0.84	6.0 (2.7, 9.3)	0.76 (0.33, 1.7)	0.52
T T3 (474-1106)	6.4 (2.8, 10.0)	1.3 (0.53, 3.2)	0.55	8.0 (4.1, 11.8)	1.2 (0.57, 2.5)	0.62
p-value	0.72	0.56		0.56	0.65	
Free Testosterone, ng/dL		0.94 (0.77, 1.1)	0.51		0.99 (0.83, 1.2)	0.87
Free T T1 (0.02-6.18)	8.7 (4.0, 13.4)	ref		10.3 (5.3, 15.3)	ref	
Free T T2 (6.18-7.84)	3.7 (1.4, 5.9)	0.47 (0.20, 1.1)	0.09	6.5 (3.1, 9.8)	0.75 (0.33, 1.7)	0.48
Free T T3 (7.85-14.56)	4.7 (1.8, 7.5)	0.64 (0.27, 1.5)	0.31	5.5 (2.5, 8.6)	0.73 (0.33, 1.6)	0.46
p-value	0.08	0.26		0.18	0.43	

[a] Adjusted for age (continuous, years), systolic blood pressure (continuous), body mass index (continuous), fasting blood glucose (continuous), HDL cholesterol level (continuous), and anti-hypertension medication use (yes/no)
[b] Adjusted for age (continuous, years), systolic blood pressure (continuous), body mass index (continuous), fasting blood glucose (continuous), HDL cholesterol level (continuous), anti-hypertension medication use (yes/no), and self-reported Hispanic/Latino background group

D. Discussion

In this study, our aim was to evaluate the associations between endogenous levels of pituitary and sex steroid hormones and multiple measures of kidney function in a cohort of Hispanic/Latino study participants. Overall at baseline, 3.2% of our sample had low eGFR, 11.2% had albuminuria, and 13.0% had the composite of either or both conditions. When we stratified the sample by sex and examined baseline associations, our major findings were that LH and FSH concentrations appeared to be inversely associated with eGFR cross-sectionally. However, when we looked at the odds of incident albuminuria and CKD at visit 2 among those who were not categorized as having albuminuria or CKD at visit 1, we again saw associations with the pituitary hormones among females specifically. Among females, we observed an inverse association between LH and odds of incident albuminuria when modeling LH both as a continuous variable and as tertiles, which remained after mutual adjustment for FSH, but we did not observe a similar association when we modeled the odds of incident CKD composite. It is possible that LH may be positively associated with urinary albumin excretion over time, but not with eGFR over time, hence the discordance with the two outcomes.

Among the male participants, LH was inversely associated with eGFR at baseline and positively associated with UACR and odds of albuminuria. However, there was no association with LH and any outcome at Visit 2. Also among males, FSH concentration appeared to be positively associated with UACR and odds of albuminuria at baseline. However, the associations with eGFR and UACR among males observed at baseline using cross-sectional data were not observed when we examined hormone

associations with levels of eGFR and UACR at visit 2 after the six year follow-up. When we evaluated the associations with free and bound testosterone, we observed an inverse association with free testosterone and UACR cross-sectionally, and an inverse association between testosterone and visit 2 eGFR. There was no association with testosterone concentrations and any dichotomous outcome, but it is unclear if this finding is indicative of no association or simply due to the small number of male participants who developed albuminuria or low eGFR by the second study visit. Our findings were minimal for other hormones and kidney parameters.

Numerous reviews exist that suggest there are sex-differences in the mechanisms and epidemiology of CKD (Neugarten, Acharya, and Silbiger 2000, Neugarten and Golestaneh 2013, Silbiger and Neugarten 2008, Silbiger and Neugarten 1995, Bairey Merz et al. 2019, Neugarten and Golestaneh 2019), yet few studies have objectively measured endogenous hormones and used such measures to assess associations with kidney function parameters. In a secondary analysis of the Diabetes Prevention Program (DPP) Outcome Study, investigators assessed the associations between SHBG, DHEAS, testosterone, estrone, and estradiol with kidney function parameters in 889 glucose-intolerant males and 1281 pre- and postmenopausal females who had healthy kidney function at randomization (UACR < 30 mg/g and eGFR ≥60 mL/min/1.73 m^2) (Kim et al. 2019). At baseline, they found an inverse association between concentrations of estradiol and eGFR, and a positive association between concentrations of DHEAS with log transformed UACR in the analyses of the male participants. Among the female participants, estrone was positively associated with eGFR. We did not observe any of these associations in our baseline analyses, though it

should be noted that our cohort had a healthier profile at baseline relative to those at risk for diabetes that were enrolled in the DPP. Additionally, the participants in our study were all postmenopausal, and menopause is generally associated with low endogenous estradiol concentrations. In the same secondary analysis of the DPP Outcome Study, investigators examined the association between sex hormone levels and incidence of low eGFR and/or UACR ≥30 mg/g among participants after 11 years of follow-up and found SHBG levels to be associated with a reduction in risk of low eGFR among male participants after multivariable adjustment. There were no other significant associations with incident disease. We observed a suggestive inverse association between baseline SHBG concentrations with eGFR at visit 2 among males in our study, but it did not reach statistical significance and the magnitude of the association was small.

A limited number of additional studies have investigated the association between sex hormone levels and eGFR or albuminuria in males, but very few of them have included the pituitary hormones. In a study of 101 men without diabetes aged 18 to 50 years old, investigators compared hormone levels by CKD stage, and found that luteinizing hormone levels were higher in the more advanced CKD stages relative to the less severe and healthy stages (Hylander and Lehtihet 2015). In the Hylander sample, only 23 of the participants had eGFR levels that are representative of those in our study, but the results are consistent with the inverse association between LH and eGFR and the positive association between LH and UACR that we observed in our cross-sectional analyses of the male participants in our study. Other studies in males (Yi et al. 2009) primarily focused on low eGFR as the endpoint or outcome of interest, and we were unable to investigate that endpoint in our study due to the low number of participants

who were determine to have low eGFR. To our knowledge, no studies other than the aforementioned study by Kim et al. 2019 have investigated the associations of hormone levels and kidney function in healthy females.

In humans, the mechanisms for sex differences in CKD have been theorized to include the influence of estradiol and or testosterone on renal function, but this is not well understood and few have investigated the mechanisms of action through which hormones could be contributing to kidney function. In our study of healthy participants, associations were most consistent with the pituitary hormones. The mechanism through which these hormones act to influence kidney function is largely unknown. Some work in pediatric populations has been conducted in this area. One prior study of 36 children (18 males and 18 females) with chronic renal failure found that the plasma half life of bio-available LH was inversely associated with eGFR, and they then postulated that chronic renal failure is associated with a reduction in the bioactivity of circulating LH (Schaefer et al. 1991). In a small study of boys with chronic renal failure, serum samples were used to investigate the binding of the LH receptor and found that those with chronic renal failure had their LH receptor binding inhibited (Dunkel et al. 1997). Further collaboration between the fields of nephrology, endocrinology, and epidemiology is necessary to understand the mechanisms operating behind the associations observed in our study, and it is imperative that future studies include females.

The strengths of this study include that our study used data from a well-characterized cohort of Hispanics/Latinos with detailed information on health conditions, medication usage, and objective laboratory measures of kidney function parameters.

We used objective measures of pituitary and sex steroid hormones from stored samples, and we were able to evaluate associations with kidney function parameters prospectively. There are limitations to our study that should be taken into consideration. The participants in our study were relatively healthy, and this study sample had very few cases of low eGFR at both baseline and follow-up. We were unable to assess associations with low eGFR, and the nature of estimating GFR using equations may introduce bias at high eGFR levels, which is representative of most of our study sample. The definitions used for our outcomes were based on single measurements of serum or urine. Although most of the hormones were objectively measured, we used previously published equations to calculate free concentrations of estradiol and testosterone for each participant. We restricted our analyses among females to those who were post-menopausal, excluding pre- and peri-menopausal women. Future analyses evaluating these associations in pre- and peri-menopausal women should be considered. Due to the design of the cohort study, we do not have information on when incident albuminuria or low eGFR occurred over the six year average follow up time. We also do not know the order of events in regard to changes in confounders over time. For example, we do not know the timing of changes in metrics such as blood pressure, body composition, glucose tolerance, or lipids in relation to changes in GFR or urine albumin excretion. We examined multiple hormones with multiple outcomes resulting in many comparisons, and as such, some of the observed associations may have been due to chance. Associations presented in this study will need to be replicated in other studies to determine if there is consistency in the associations.

E. Conclusions

This is the first study to assess associations between circulating pituitary and sex steroid hormones and kidney function parameters in a diverse cohort of Hispanic/Latino adults that includes both males and females. We conclude that pituitary hormones, specifically LH, may be associated with markers of kidney function in healthy adults. Other studies should examine if our observed associations can be replicated in other cohorts.

V. RELATIONSHIPS BETWEEN PERSISTENT ORGANIC POLLUTANTS AND KIDNEY FUNCTION: FINDINGS FROM THE HISPANIC COMMUNITY HEALTH STUDY/STUDY OF LATINOS (HCHS/SOL)

A. Rationale

Understanding the environmental factors that influence kidney disease development and progression provides potential opportunities for intervention to prevent and control disease. Investigations into environmental factors that impact kidney health have previously focused on heavy metals, agricultural chemicals, and occupational exposures. Few have evaluated associations between multiple persistent organic pollutants such as PCBs and organochlorine pesticides with kidney function, and, among those that have, studies have not included representative groups of Hispanics/Latinos.

The overall goal of this study was to describe the relationships of persistent organic pollutants measured at baseline with CKD in an ethnically diverse Hispanic/Latino population who were enrolled in a community-based cohort study and who did not have diabetes at baseline. Our specific aims were to 1) describe the relationships of persistent organic pollutants measured at baseline, with baseline prevalence of CKD and measures of eGFR and UACR; 2) determine if levels of persistent organic pollutants were associated with changes in eGFR and UACR from Visit 1 to Visit 2; and 3) examine the relationships of baseline levels of persistent organic pollutants with the subsequent development of CKD at Visit 2.

B. Methods

1. Study population

This study used baseline and prospective data from HCHS/SOL. In brief, HCHS/SOL is a multisite prospective cohort study designed to identify risk and protective factors for chronic disease among persons from diverse Hispanic/Latino background groups living across the United States. The cohort included 16,415 men and women between 18 to 74 years of age at the time of recruitment. Participants were recruited from 2008 until 2011 from randomly selected households in San Diego, CA; Bronx, NY; Chicago, IL; and Miami, FL. The HCHS/SOL included first through third generation participants of Mexican, Cuban, Puerto Rican, Dominican Republic, Central and South-American background. Details of the study design and sampling methods were previously published (Lavange et al. 2010, Sorlie et al. 2010). The Persistent Organic Pollutants, Endogenous Hormones and Diabetes in Latinos Ancillary Study oversampled from middle-aged and older participants ages 45-74 in the HCHS/SOL study using a case-cohort study design. To select the random sample, participants were stratified by baseline glucose measurements (1,176 with prediabetes at baseline and 1,174 with normal baseline glucose measurements) and approximately equally divided between men and women ages 45 -74 years (1,148 men and 1,202 women), and with only one participant per household within each sex and blood glucose subgroup. Participants who transitioned from pre-diabetes to diabetes during the follow up period were oversampled to ensure that approximately half of those in this category had transitioned to diabetes. The final ancillary study sample consisted of 2,350 HCHS/SOL males and females who either had prediabetes or normal glucose parameters at Visit 1.

Of the 1,344 HCHS/SOL ancillary study participants with pollutant measurements available, 1,072 (80%) were included in the cross-sectional and longitudinal analyses comparing eGFR and UACR at visits 1 and 2. Participants missing information (values are not mutually exclusive) on serum cystatin C (n=9) or urine albumin/creatinine ratio (n=76) at baseline were excluded. A total of 162 participants were excluded because of missing data on one or more serum pollutants. An additional 30 participants were excluded due to missing serum cystatin C (n=2) or urine albumin/creatinine ratio (n=28) data at Visit 2. For analyses of incident albuminuria and/or CKD composite, participants with low eGFR or albuminuria at visit 1 were excluded.

2. Variable definitions

a. Measures of kidney function

Urine albumin was measured on the ProSpec nephelometric analyzer (Dade Behring GMBH, Marburg, Germany) using an immunoturbidometric method. Urine creatinine was measured in both serum and urine on a Roche Modular P Chemistry Analyzer (Roche Diagnostics, Indianapolis, IN) using a creatinase enzymatic method. We defined albuminuria using sex-specific cutoffs (urine albumin/creatinine ratio ≥17 mg/g in males and ≥25 mg/g in females) (Mattix et al. 2002). Glomerular filtration rate was estimated using the CKD-EPI creatinine-cystatin C equation (eGFRcreat-cyst) (Inker et al. 2012). Serum creatinine measurements were traced by isotope dilution mass spectrometry. Serum cystatin C was measured using a turbidimetric method on the Roche Modular P Chemistry Analyzer (Gentian AS, Moss, Norway). Low eGFR was defined as eGFRcreat-cyst <60 ml/min per 1.73 m2. At

baseline, CKD was defined by either a low eGFR or the presence of albuminuria using sex-specific cutoffs. We defined incident low eGFR as eGFR <60 ml/min per 1.73 m2 with eGFR decline ≥1 ml/min per 1.73 m2 per year of follow –up. We defined incident CKD as low eGFR <60 ml/min per 1.73 m2 with eGFR decline ≥1 ml/min per 1.73 m2 per year of follow -up or presence of new onset albuminuria (sex-specific) at Visit 2 among those who did not have low eGFR or albuminuria at Visit 1.

b. <u>Environmental pollutant measurements</u>

Serum samples for pollutant measurements were collected at the baseline HCHS/SOL examination visit. Measurements of PBDEs, BB-153, PCBs, and persistent pesticides were conducted at the National Center for Environmental Health at the Centers for Diseases Control and Prevention. The methodology used to process the samples included automatic fortification of the samples with internal standards using a Gilson 215 liquid handler (Gilson lnc.; Middleton, Wl). This was followed by automated liquid liquid extraction of the samples using a liquid handler. Removal of co-extracted lipids were performed on a silica: silica/sulfuric acid column using the Rapid Trace (Biotage; Uppsala, Sweden) equipment for automation. Gas chromatography isotope dilution high resolution mass spectrometry employing a DFS (Thermo DFS, Bremen, Germany) instrument was performed to determine the final analytical value for each of the target analytes in each sample. The total methodology used has been published previously (Sjodin et al. 2004, Jones R 2012).

Concentrations of measured analytes are available as ng/g lipid weight (weight of serum lipids). Total cholesterol was measured in serum on a Roche Modular

P Chemistry Analyzer (Roche Diagnostics Corporation) using a cholesterol oxidase enzymatic method (Roche Diagnostics, Indianapolis, IN 46250) at the HCHS/SOL central laboratory. Triglycerides were measured in serum on a Roche Modular P chemistry analyzer, (Roche Diagnostics, Indianapolis, IN 46250) using a glycerol blanking enzymatic method (Roche Diagnostics, Indianapolis, IN 46250) at the HCHS/SOL central laboratory.

In total, 43 analytes were measured and reported in ng/g lipid. The analytes are listed in Table XXV, and included 10 PBDEs, 1 PBB, 24 PCBs, and 8 pesticides. For any sample below the limit of detection, we substituted the value of the limit of detection divided by the square root of two. For analysis, we created summary measures of 1) total PCBs; 2) total PBDEs; 3) estrogenic PCBs (Wolff et al. 1997); 4) anti-estrogenic PCBs (Wolff et al. 1997); 5) Wolff Group 3 Cytochrome P450, family 1, subfamily A (CYP1A)/ Cytochrome P450, family 2, subfamily B (CYP2B) inducing PCBs (Wolff et al. 1997); 6) CYP1A inducer/substrate PCBs (Warner et al., 2012); 7) CYP2B inducer PCBs (Warner et al., 2012); 8) mixed CYP1A/CYP2B inducing PCBs (Warner et al., 2012); and 9) total DDT and metabolites. We analyzed data from one PBB and six individual pesticides as individual analytes: BB-153, β-hexachlorocyclohexane, HCB, mirex, oxychlordane, p,p'-DDE, and trans-nonachlor.

c. <u>Covariates</u>

Study participants reported their age, sex, years of education (less than high school, high school, more than high school), Hispanic/Latino heritage, household income (<10k, 10k-20k, 20k-40k, 40k-75k, 75k+), health insurance status (yes/no),

nativity (born in U.S. (yes/no)), heritage group (Central American, Cuban, Dominican, Mexican, Puerto Rican, and South American), language (Spanish/English), and current smoking status. Anthropometric measurements of weight (kilograms), height (centimeters), and waist circumference (centimeters) were performed by trained study staff following a standard protocol. Body mass index was calculated as weight in kilograms divided by height in squared meters. Questionnaire, examination, and laboratory data was used to classify diabetes status (normal or prediabetes at baseline) and hypertension status (yes/no). Systolic and diastolic blood pressure measurements (mmHg; continuous) were taken using a standardized study protocol. Triglycerides (continuous, mg/dL) and LDL and HDL cholesterol (continuous, mg/dL) were measured at the HCHS/SOL central laboratory. Medication use was reported for: antihypertensives, ACE Inhibitors, Angiotensin II Receptor Antagonists, NSAIDs, and statin medications.

Among females, menopause status was derived by a series of steps that included evaluation of the participant's age (≥62 years old determined to be post-menopausal) and menstruation status (among those who reported absence of menses, if FSH was >25.8 mIU/mL or LH >7.7 mIU/mL, the participant was determined to be post-menopausal; among with FSH < 25.8 mIU/mL and LH < 7.7 mIU/mL, the participant was determined to be peri-menopausal). If the participant reported current menses or did not answer the question regarding menstruation status, if FSH was >25.8 mIU/mL or LH >7.7 mIU/mL, the participant was determined to be peri-menopausal and for those with FSH < 25.8 mIU/mL and LH < 7.7 mIU/mL, the participant was determined to be pre-menopausal.

3. Statistical analysis

All analyses used SAS Version 9.4 (Cary, NC) and Stata Statistical Software, Release 13 (StataCorp LP, College Station, TX) and followed methodology for complex survey data, taking the appropriate ancillary study sampling weights into account. The analyses were conducted in a series of four steps. Distributions of all continuous outcomes and covariates were examined, and the natural log transformation was applied to those that were skewed. Then descriptive statistics using baseline data from the HCHS/SOL ancillary study were produced to show the proportions of study participants with low eGFR, albuminuria, and the composite CKD overall and by demographic characteristics such as age, sex, education, income, language preference, and specific Hispanic/Latino background. The Rao-Scottt Chi-square test was used to compare weighted proportions, and the t-test was used to compare weighted means. Geometric means for each summary measure of PBDEs, PCBs, and total DDT and metabolites as well as individual concentrations of PBB-153 and persistent pesticides with 95% CIs were produced overall and by covariates. For descriptive purposes, continuous covariates were categorized or dichotomized using clinically relevant cut points.

Cross-sectional associations between each continuous summary measure of PBDEs, PCBs, and total DDT and metabolites and individual concentrations of PBB-153 and persistent pesticides and measures of eGFR and log UACR were estimated using linear regression models. Logistic regression models were estimated for the dichotomous outcomes albuminuria and the CKD composite. Due to the small number of cases, odds of low eGFR was not evaluated. Multivariable linear and logistic models

were built for each individual analyte or summary concentration with a forward approach. Models were initially adjusted for age and total lipids. Evaluation of the presence of effect modification was conducted by adding an interaction term between the hormone and the covariate to the model. Effect modification was assessed for sex (male vs. female) and prediabetes status (prediabetes vs. normal). For effect modification, a p-value < 0.05 was considered statistically significant. The forward approach was used to assess confounding by adding potential confounding variables identified during bivariate analyses to the model one at a time and evaluating a > 10% change in the estimate. The natural log transformation was applied to each continuous analyte for modeling to reduce the influence of extreme values. Analytes were also modeled as quartiles to evaluate non-linear relationships. Quartiles were modeled as an ordinal variable to evaluate linear trend.

To prospectively assess changes in eGFR and log UACR from visit 1 to visit 2 we used linear regression models to model each outcome at visit 2. The relationships of both continuous (log transformed) and ranked quartile values of each analyte was evaluated after controlling for baseline eGFR and UACR values, time elapsed between study visits, and relevant confounders. In addition to examining baseline characteristics as potential confounders, differences in covariates comparing visit 2 to baseline levels were considered as confounders. We assessed potential confounding by time varying diabetes status (normal, pre, or diabetes at Visit 2), systolic and diastolic blood pressure measurements (mmHg; continuous), body mass index (continuous, kg/m^2), total, LDL & HDL cholesterol (continuous, mg/dL), and triglycerides (continuous, mg/dL) in our prospective analyses by adding the visit 2 variable to the model for categorical

characteristics or by adding the difference between visit 1 and visit 2 values to the model for continuous characteristics.

Logistic regression models were used to explore risk for incident CKD, as previously defined, and new onset albuminuria at Visit 2 among those who did not have low eGFR or albuminuria at Visit 1. In these models, associations were evaluated between both continuous (log transformed) and ranked quartile analyte values. Due to the small number of incident cases, these models were initially minimally adjusted for age and lipids.

C. Results

Among the 1,072 participants in the study sample, the median age was 54 years old (IQR 48 to 60) and 54.0% were female. The average eGFR was 94.1 (95% CI 92.5, 95.6), and the median UACR was 6.3 mg/g (IQR 4.5 to 11.7). Few (19.8%) reported being born in the United States, and 22% reported living in the United States for ten or fewer years. A total of 22 participants (3.4% (95% CI 1.6, 5.3%) had low eGFR, 103 (8.2% (95% CI 8.2, 15.1%) had albuminuria, and 114 (13.5% (95% CI 9.9, 17.1%) had CKD. As shown in Tables XXVI and XXVII, the proportion of participants with albuminuria was similar among males and females and across various demographic characteristics. The proportion of participants with albuminuria among those that reported being born in the United States (15.3%) was larger compared to those born outside the United States (10.8%), but the difference was not statistically significant. As expected, the proportion of participants with albuminuria was larger among those with existing hypertension (17.5%) compared to those without (8.4%) and

among those with prediabetes (14.1%) compared to without (8.7%). A larger proportion of participants had albuminuria among those in the low physical activity group relative to higher levels of self-reported physical activity, but the absolute numbers in the other groups were very small. Neither levels of fasting blood glucose nor lipid levels differed among those with and without albuminuria. Many proportions of those with the CKD composite were similar to what we observed with albuminuria. The proportion of participants with the CKD composite among those that reported being born in the United States (19.8%) was larger compared to those born outside the United States (11.9%), but the difference was not statistically significant (p=0.06). A larger proportion of participants had the CKD composite among those in the low income group relative to higher levels of self-reported income or missing income information, but the absolute numbers in the other groups were very small. A larger proportion of participants had the CKD composite among those with health insurance (16.9%) relative to those without (10.0%).

The average exposure concentrations for the indices of exposures across various demographic characteristics of the study sample are shown in Tables XXVIII and XXIX. As expected, most exposure concentrations varied by age, sex, Hispanic/Latino background group, nativity, and acculturation level.

When modeled as continuous variables, none of the analyte concentrations were associated with eGFR. There was some evidence of an inverse association between oxychlordane and eGFR and of a positive association between DDE and the sum of DDT and its metabolites in models minimally adjusted for age and lipids, but this was no longer observed after multivariable adjustment for other factors that predicted

eGFR. Similarly, there weren't any associations between ranked quartile analyte concentrations and eGFR after adjustment. There was no evidence of effect modification by sex or prediabetes status, as none of the interaction terms were statistically significant.

When the associations between continuous analyte concentrations and UACR were assessed, none of the analyte concentrations were associated with UACR. There was some evidence of a positive association between total PCBs, total estrogenic PCBs, and the Warner classification of CYP2B PCBs with UACR, but these associations did not reach statistical significance. Similarly, there weren't any associations between ranked quartile analyte concentrations and UACR. None of the interaction terms were statistically significant, indicating that there was no evidence of effect modification by sex or prediabetes status.

A total of 22 participants (3.4% weighted (95% CI 1.6 to 5.3%)) had low eGFR, 103 had albuminuria (11.7% weighted (95% CI 8.2 to 15.1%)), and 114 had the composite of low eGFR and/or albuminuria (13.5% weighted (95% CI 9.9 to 17.1%)). The proportion of participants with albuminuria and the CKD composite as well as the cross-sectional associations between continuous concentrations and ranked quartiles of PCB analyte concentrations and baseline odds of albuminuria and the CKD composite are presented in Table XXX. Although it appeared that a smaller proportion of participants had albuminuria in the lowest analyte quartile relative to the higher quartiles for most of the PCB analyte measure, there was no statistical difference in the proportion of participants with albuminuria within the different strata of PCB analyte concentrations. Some of these differences were statistically significant when the

proportions were estimated for the CKD composite. It is unknown if this is driven by the slightly larger number of cases using the CKD outcome, or by an association with eGFR that we cannot assess individually due to the small number of cases of low eGFR within our sample. When we evaluated the associations between the analyte concentrations, some of the PCB indices appeared to be positively associated with odds of albuminuria and CKD composite when modeling the continuous and the ranked quartile concentrations. This was the case for total PCBs, total estrogenic PCBs, CYP1A, and CYP2B inducing PCBs. It is not known if the associations were stronger for the CKD composite due to the larger number of cases using the CKD outcome, or by an association with low eGFR that we cannot assess using this sample.

When we examined the proportion of cases of albuminuria and the CKD composite within the strata of total PBDEs and the individual pesticides, there were smaller proportions with each outcome as concentrations of total DDT and metabolites and individual measures of DDE increased (Table XXXI). Among all the pesticides evaluated, we observed reduced odds of each outcome with increasing DDE concentration. A similar observation was seen when we modeled the sum of DDT and its metabolites. Results were consistent when modeling continuous and ranked quartiles of the DDT and DDE measures. There were no other associations between any outcome with total PBDEs or any of the other persistent pesticides.

Next, we evaluated the associations between measured analytes and eGFR and UACR at visit 2. At visit 2, a larger proportion of participants (82%) reported having health insurance compared to only 48% at visit 1 (Table XXXII). The proportion with hypertension was slightly higher at visit 2, and the proportion without prediabetes or

diabetes at visit 2 decreased to 28% from 45% at visit 1. Average eGFR at both visits was similar, and the average geometric mean UACR level at visit 2 was slightly lower (5.4 mg/g) compared to visit 1 (8.5 mg/g).

There were no associations between any of the PCB classifications and eGFR at visit 2 (Table XXXIII). When we modeled the associations between total PBDEs and eGFR at visit 2, we observed an inverse association (Table XXXIV). The association held even after multivariable adjustment for eGFR at visit 1, time from visit 1 to visit 2, age (continuous, years), self-reported ethnicity/background, sex (male/female), systolic blood pressure (at visit 1), fasting blood glucose (at visit 1), and difference in triglycerides from visit 1 to visit 2. The association was also consistent when total PBDEs were modeled as ranked quartiles (B Q4 vs. Q1 -2.3 (95% CI -5.0, 0.32), p=0.08, p for trend=0.06). There were no other associations with visit 2 eGFR.

When we assessed the associations between the PCB classifications and UACR at visit 2 (Table XXXIVI), we observed positive associations between total PCBs, total estrogenic PCBs, and the Wolf group 3 CYP1A/2B, and Warner CYP2B PCBs. When we modeled the associations between total PBDEs and the persistent pesticides with UACR at visit 2, we observed an inverse association (Table XXXVII) between total DDT and metabolites and DDE with UACR. The association held even after multivariable adjustment for UACR at visit 1, time from visit 1 to visit 2, age (continuous, years), self-reported ethnicity/background, sex (male/female), systolic blood pressure (at visit 1), fasting blood glucose (at visit 1), and difference in triglycerides from visit 1 to visit 2. There were no other associations with visit 2 UACR.

After restricting to the 958 participants (503 female and 455 male) who had information on eGFR and UACR at visit 2 and who did not have low eGFR or albuminuria at visit 1, a total of 28 participants (3.5% (95% CI 1.9 to 5.1%%)) low eGFR, 50 (4.8% (95% CI 3.1 to 6.6%) had incident albuminuria and 70 participants (7.6% (95% CI 5.4 to 9.9%)) had incident CKD. Associations between baseline analyte levels and incident albuminuria and CKD among participants are presented in in Table XXXVII. None of the analyte concentrations appeared to be associated with incident albuminuria or CKD among participants.

TABLE XXV.
ANALYTES MEASURED IN THE HCHS/SOL ANCILLARY STUDY OF PERSISTENT ORGANIC POLLUTANTS

Analyte	Full name	Number not reportable	Number <LOD (%)
PBDE17	2,2´,4- Tribromodiphenyl ether	1	1286 (95.7)
PBDE28	2,4,4´-Tribromodiphenyl ether	1	297 (22.1)
PBDE47	2,2´,4,4´-Tetrabromodiphenyl ether	1	8 (0.6)
PBDE85	2,2´,3,4,4´-Tentabromodiphenyl ether	0	817 (60.8)
PBDE99	2,2´,4,4´,5-Pentabromodiphenyl ether	0	107 (8.0)
PBDE100	2,2´,4,4´,6-Pentabromodiphenyl ether	0	32 (2.4)
PBDE153	2,2´,4,4´,5,5´-Hexabromodiphenyl ether	1	5 (0.4)
PBDE154	2,2´,4,4´,5,6´-Hexabromodiphenyl ether	1	904 (67.3)
PBDE183	2,2´,3,4,4´,5´,6-Heptabromodiphenyl ether	2	993 (73.9)
PBDE209	Decabromodiphenyl ether	26	491 (36.5)
PBB153	2,2´,4,4´,5,5´-Hexabromobiphenyl	1	176 (13.1)
PCB28	2,4,4'-Trichlorobiphenyl	12	205 (15.2)
PCB66	2,3',4,4'-Tetrachlorobiphenyl	3	453 (33.7)
PCB74	2,4,4',5-Tetrachlorobiphenyl	3	3 (0.2)
PCB99	2,2',4,4',5-Pentachlorobiphenyl	9	7 (0.5)
PCB105	2,3,3',4,4'-Pentachlorobiphenyl	17	105 (7.8)
PCB114	2,3,4,4´,5-Pentachlorobiphenyl	3	572 (42.6)
PCB118	2,3',4,4',5-Pentachlorobiphenyl	8	1 (0.1)
PCB138-158	2,2',3,4,4',5'- and 2,3,3',4,4',6-Hexachlorobiphenyl	7	1 (0.1)
PCB146	2,2',3,4',5,5'-Hexachlorobiphenyl	8	10 (0.7)
PCB153	2,2',4,4',5,5'-Hexachlorobiphenyl	3	0
PCB156	2,3,3',4,4',5-Hexachlorobiphenyl	7	8 (0.6)
PCB157	2,3,3',4,4',5'-Hexachlorobiphenyl	3	277 (20.6)
PCB167	2,3',4,4',5,5'-Hexachlorobiphenyl	13	190 (14.1)
PCB170	2,2',3,3',4,4',5-Heptachlorobiphenyl	7	2 (0.1)
PCB178	2,2',3,3',5,5',6-Heptachlorobiphenyl	38	97 (7.2)
PCB180	2,2',3,4,4',5,5'-Heptachlorobiphenyl	4	0
PCB183	2,2',3,4,4',5',6-Heptachlorobiphenyl	29	44 (3.3)
PCB187	2,2',3,4',5,5',6-Heptachlorobiphenyl	19	5 (0.4)
PCB189	2,3,3',4,4',5,5'-Heptachlorobiphenyl	8	700 (52.1)
PCB194	2,2',3,3',4,4',5,5'-Octachlorobiphenyl	9	8 (0.6)
PCB196-203	2,2',3,3',4,4',5',6- and 2,2',3,4,4',5,5',6-Octachlorobiphenyl	13	5 (0.4)
PCB199	2,2',3,3',4,5,6,6'-Octachlorobiphenyl	7	6 (0.5)
PCB206	2,2',3,3',4,4',5,5',6-Nonachlorobiphenyl	8	18 (1.3)
PCB209	Decachlorobiphenyl	6	85 (6.3)
HCB	Hexachlorobenzene	20	0
β-HCCH	β-Hexachlorocyclohexane	17	162 (12.0)

TABLE XXV (continued).
ANALYTES MEASURED IN THE HCHS/SOL ANCILLARY STUDY OF PERSISTENT ORGANIC POLLUTANTS

Analyte	**Full name**	**Number not reportable**	**Number <LOD (%)**
OXYCHLOR	Oxychlordane	8	33 (2.5)
T-NONA	Trans-Nonachlor	3	6 (0.4)
PP-DDE	2,2-Bis(4-chlorophenyl)-1,1-dichloroethene	9	0
OP-DDT	2-(4-chlorophenyl)-2-(2-chlorophenyl)- 1,1,1-trichloroethan	2	1277 (95.0)
PP-DDT	2,2-Bis(4-chlorophenyl-1,1,1-trichloroethan	3	1167 (86.8)
MIREX	Mirex	3	665 (49.5)

TABLE XXVI.
WEIGHTED BASELINE DEMOGRAPHIC AND CLINICAL UNIVARIATE (OVERALL) AND BIVARIATE (BY ALBUMINURIA AND CKD STATUS) CATEGORICAL CHARACTERISTICS OF PARTICIPANTS (N=1,072)

	Overall	**Albuminuria**	**p-value**	**CKD**	**p-value**
	N (weighted %)	**% (95% CI)**		**% (95% CI)**	
Male, %	522 (46.0)	12.2 (8.4, 15.9)	0.80	14.5 (10.1, 18.8)	0.62
Female, %	550 (54.0)	11.3 (5.7, 16.9)		12.7 (7.0, 18.4)	
Menopause Status					
Pre	65 (9.4)	13.2 (0.4, 26.1)	0.34	13.2 (0.4, 26.1)	0.20
Peri	116 (16.5)	5.0 (0.6, 9.4)		5.0 (0.6, 9.4)	
Post	369 (74.1)	12.4 (5.1, 19.7)		14.3 (7.0, 21.7)	
Hispanic/Latino background					
Central American	101 (8.0)	9.0 (2.3, 15.6)	0.28	9.0 (2.3, 15.6)	0.11
Cuban	183 (25.1)	13.6 (7.6, 19.5)		15.9 (8.8, 22.9)	
Dominican	108 (9.8)	6.9 (0.5, 13.3)		8.4 (1.7, 15.1)	
More than one/Other heritage	21 (2.8)	5.4 (0.0, 15.9)		5.4 (0.0, 15.9)	
Puerto Rican	160 (15.6)	15.9 (8.7, 23.1)		19.6 (11.4, 27.9)	
South American	99 (6.1)	2.5 (0.0, 6.5)		2.6 (0.0, 6.5)	
Mexican (ref)	400 (32.6)	12.5 (4.4, 20.7)		14.1 (6.0, 22.3)	
Born in United States, %	222 (19.8)	15.3 (9.4, 21.3)	0.21	19.8 (13.0, 26.7)	0.06
<10 years living in US, %	212 (22.0)	10.5 (5.5, 15.5)	0.41	10.5 (5.5, 15.5)	0.35
< High school education, %	433 (40.5)	11.8 (5.0, 18.5)	0.21	13.6 (6.7, 20.5)	0.47
Income <$30,000 (annually), %	688 (64.6)	13.8 (8.9, 18.7)	0.12	15.9 (10.7, 21.1)	0.09
Have health insurance, %	546 (52.0)	13.4 (9.4, 17.3)	0.83	16.9 (12.3, 21.5)	0.07
Current cigarette use, %	218 (20.1)	11.2 (5.7, 16.7)	0.99	12.0 (6.5, 17.6)	0.90
Never drink alcohol, %	539 (53.4)	12.4 (6.7, 18.0)	0.80	13.5 (7.8, 19.2)	0.98
Hypertension (BP>=140/90 and Med Use)**, %**	316 (35.9)	17.5 (11.9, 23.0)	0.01	22.0 (15.8, 28.3)	0.001
Body mass index (BMI), Norm/Underweight, %	207 (21.2)	10.2 (4.0, 16.3)	0.64	12.3 (5.7, 18.9)	0.83
Overweight (25 ≤BMI<30), %	469 (42.7)	10.5 (6.5, 14.5)		12.8 (8.0, 17.6)	
Obese (BMI ≥ 30), %	395 (36.1)	13.8 (6.4, 21.2)		14.9 (7.4, 22.4)	
Prediabetes, %	427 (54.9)	14.1 (8.3, 20.0)	0.09	15.7 (9.7, 21.6)	0.17
Normal glucose, %	645 (45.1)	8.7 (6.1, 11.3)		10.9 (7.2, 14.5)	
Medication use, %					
ACEi/ARB	151 (17.2)	16.4 (8.9, 23.9)	0.19	18.1 (10.4, 25.8)	0.22
NSAIDs	216 (20.1)	10.9 (5.6, 16.3)	0.79	12.3 (6.6, 18.0)	0.68
Statins	102 (11.1)	21.4 (1.5, 41.3)	0.32	26.7 (7.2, 46.2)	0.18
Low Physical activity, %	486 (48.0)	15.6 (9.4, 21.8)	0.03	16.8 (10.6, 23.1)	0.07

TABLE XXVII.
WEIGHTED BASELINE DEMOGRAPHIC AND CLINICAL UNIVARIATE (OVERALL) AND BIVARIATE (BY ALBUMINURIA AND CKD STATUS) CONTINUOUS CHARACTERISTICS OF PARTICIPANTS (N=1,072)

	Overall	Albuminuria	p-value	CKD	p-value
	Mean (95% CI)	Mean (95% CI)		Mean (95% CI)	
Age, yr[a]	54 (48, 60)	54 (49, 64)	0.30	57 (49, 66)	0.03
Glucose, fasting (mg/dL)	94.9 (94.1, 95.6)	95.8 (93.7, 98.0)	0.33	95.6 (93.5, 97.6)	0.46
Total cholesterol, mg/dl	210 (207, 214)	215 (206, 225)	0.32	214 (204, 224)	0.43
LDL cholesterol, mg/dl	131 (128, 134)	134 (128, 141)	0.39	134 (127, 140)	0.51
HDL cholesterol, mg/dl	52 (50, 53)	54 (47, 61)	0.41	54 (48, 61)	0.40
Triglycerides, mg/dl[a]	112 (107, 118)	113 (91, 157)	0.83	111 (86, 156)	0.73
C-reactive protein, mg/L[a]	1.9 (1.0, 3.8)	2.1 (1.0, 4.2)	0.15	2.1 (1.0, 4.2)	0.22

[a]: Weighted median (25th-75th percentile)

TABLE XXVIII.
WEIGHTED BIVARIATE ASSOCIATIONS OF GEOMETRIC MEAN (GM) AND 95% CONFIDENCE INTERVALS (95% CI) FOR SUMMARY MEASURES OF LIPID-ADJUSTED TOTAL PBDES, TOTAL PCBS, TOTAL DDT AND METABOLITES, AND OXYCHLORDANE WITH BASELINE (VISIT 1) COVARIATES AMONG STUDY PARTICIPANTS

	Total PBDEs (ng/g lipid)		**Total PCBs (ng/g lipid)**		**Total DDT/DDE (ng/g lipid)**		**Oxychlordane (ng/g lipid)**	
	GM (95% CI)	**p-value**	**GM (95% CI)**	**p-value**	**GM (95% CI)**	**p-value**	**GM (95% CI)**	**p-value**
Overall	35.5 (33.5, 37.7)		119 (112, 126)		648 (598, 703)		8.3 (7.8, 8.8)	
Age in years								
65+	39.4 (31.7, 48.9)	0.35	198 (168, 232)	<0.0001	791 (613, 1021)	0.006	14.1 (12.3, 16.2)	<0.0001
55-64	33.5 (30.9, 36.2)	0.30	129 (118, 141)	<0.0001	749 (653, 859)	0.0004	9.2 (8.5, 10.0)	<0.0001
45-54 (ref)	35.8 (33.2, 38.6)	ref	94 (88, 100)	ref	546 (496, 602)	ref	6.4 (6.0, 6.9)	ref
Sex, Male	39.4 (35.8, 43.5)	0.0008	121 (111, 131)	0.57	519 (458, 590)	<0.0001	7.5 (6.9, 8.1)	0.003
Female	32.5 (30.3, 34.9)		117 (108, 127)		782 (702, 871)		9.0 (8.3, 9.9)	
Menopause Status								
Pre	30.9 (26.9, 35.4)	0.67	87 (73, 102)	<0.0001	572 (437, 749)	0.01	5.7 (4.9, 6.7)	<0.0001
Peri	36.7 (31.1, 43.3)	0.18	88 (77, 99)	<0.0001	715 (582, 879)	0.21	7.3 (6.4, 8.3)	0.0003
Post (ref)	31.9 (29.3, 34.6)	ref	130 (117, 143)	ref	830 (732, 942)	ref	10.0 (9.0, 11.2)	ref
Hispanic/Latino background								
Central American	30.8 (26.8, 35.4)	0.001	68 (60, 78)	<0.0001	1494 (1233, 1811)	<0.0001	7.5 (6.5, 8.7)	0.12
Cuban	33.9 (29.2, 39.4)	0.03	139 (125, 154)	<0.0001	585 (498, 688)	0.0001	8.4 (7.5, 9.5)	0.80
Dominican	34.3 (29.1, 40.5)	0.05	118 (108, 129)	0.04	500 (410, 610)	<0.0001	5.5 (5.0, 6.0)	<0.0001
More than one/other	34.7 (27.6, 43.6)	0.20	104 (79, 136)	0.95	439 (270, 713)	0.007	6.2 (4.4, 8.6)	0.06
Puerto Rican	31.3 (27.6, 35.6)	0.003	178 (157, 202)	<0.0001	302 (256, 357)	<0.0001	11.8 (10.2, 13.6)	0.001
South American	37.1 (29.6, 46.5)	0.40	105 (87, 126)	0.88	847 (617, 1163)	0.85	6.7 (5.8, 7.7)	0.007
Mexican (ref)	40.7 (36.6, 45.2)	ref	103 (94, 113)	ref	874 (774, 987)	ref	8.6 (7.7, 9.6)	ref
Study Center, Bronx	31.2 (28.1, 34.6)	<0.0001	143 (129, 158)	0.007	390 (341, 446)	<0.0001	7.4 (6.4, 8.6)	0.02
Chicago	31.7 (29.0, 34.6)	<0.0001	90 (80, 101)	0.001	634 (543, 741)	0.001	8.2 (7.4, 9.1)	0.14
Miami	33.5 (29.8, 37.6)	<0.0001	116 (104, 129)	0.94	755 (656, 869)	0.07	8.5 (7.6, 9.4)	0.29
San Diego (ref)	47.6 (42.5, 53.2)	ref	117 (105, 130)	ref	897 (795, 1012)	ref	9.1 (8.4, 9.9)	ref
Born in United States	35.0 (31.2, 39.3)	0.99	173 (156, 191)	<0.0001	331 (289, 380)	<0.0001	11.5 (10.2, 12.9)	<0.0001
Non-US Born	35.7 (33.3, 38.2)		108 (101, 115)		765 (701, 834)		7.6 (7.2, 8.1)	

TABLE XXVIII (continued).
WEIGHTED BIVARIATE ASSOCIATIONS OF GEOMETRIC MEAN (GM) AND 95% CONFIDENCE INTERVALS (95% CI) FOR SUMMARY MEASURES OF LIPID-ADJUSTED TOTAL PBDES, TOTAL PCBS, TOTAL DDT AND METABOLITES, AND OXYCHLORDANE WITH BASELINE (VISIT 1) COVARIATES AMONG STUDY PARTICIPANTS

	Total PBDEs (ng/g lipid)		**Total PCBs (ng/g lipid)**		**Total DDT/DDE (ng/g lipid)**		**Oxychlordane (ng/g lipid)**	
	GM (95% CI)	**p-value**	**GM (95% CI)**	**p-value**	**GM (95% CI)**	**p-value**	**GM (95% CI)**	**p-value**
<10 years living in US	30.4 (27.8, 33.2)	0.002	110 (95, 128)	0.002	802 (687, 937)	<0.0001	7.0 (6.1, 8.0)	<0.0001
Non-US Born and YRS US 10-19	32.0 (28.1, 36.4)	0.04	89 (81, 98)	<0.0001	771 (622, 957)	<0.0001	6.7 (5.8, 7.9)	<0.0001
Non-US Born and YRS US ≥20	39.4 (35.7, 43.5)	0.83	133 (123, 143)	0.10	626 (562, 697)	<0.0001	9.4 (8.7, 10.1)	0.23
US Born (ref)	38.8 (33.5, 44.9)	ref	151 (133, 171)	ref	341 (283, 412)	ref	10.4 (9.0, 11.9)	ref
Education								
> High school grad	32.6 (30.4, 35.0)	0.05	119 (110, 128)	0.62	593 (530, 664)	0.02	8.1 (7.4, 8.8)	0.43
High school graduate	39.1 (34.0, 45.0)	0.58	130 (115, 146)	0.13	604 (514, 709)	0.07	8.2 (7.3, 9.3)	0.66
< High school (ref)	37.0 (32.9, 41.6)	ref	115 (103, 128)	ref	730 (638, 836)	ref	8.6 (7.7, 9.5)	ref
Income ≥$30,000	36.7 (33.9, 39.6)	0.20	114 (106, 124)	0.13	563 (499, 635)	0.002	8.0 (7.3, 8.8)	0.02
Less than $30,000	35.3 (32.4, 38.3)	0.35	119 (110, 128)	0.19	674 (609, 745)	0.03	8.3 (7.7, 8.9)	0.03
Missing/not reported (ref)	31.8 (25.4, 39.7)	ref	154 (105, 225)	ref	986 (705, 1378)	ref	10.9 (8.6, 13.8)	ref
Reported occupational pesticide exposure, yes	36.9 (26.7, 51.1)	0.82	114 (96, 135)	0.63	990 (697, 1407)	0.02	9.1 (7.7, 10.7)	0.30
No	35.5 (33.4, 37.7)		119 (112, 126)		639 (589, 693)		8.3 (7.8, 8.8)	
Have health insurance	35.6 (32.5, 38.9)	0.85	137 (128, 147)	<0.0001	526 (473, 586)	<0.0001	8.9 (8.2, 9.6)	0.02
No health insurance	35.5 (32.9, 38.4)		101 (92, 111)		822 (740, 912)		7.7 (7.0, 8.4)	
Current cigarette use	36.4 (32.0, 41.4)	0.14	118 (105, 132)	0.58	463 (392, 547)	<0.0001	7.5 (6.7, 8.5)	0.29
Former	40.3 (35.2, 46.2)	0.008	130 (115, 148)	0.07	713 (623, 816)	0.88	9.3 (8.4, 10.2)	0.07
Never (ref)	33.0 (30.9, 35.3)	ref	114 (106, 122)	ref	704 (627, 790)	ref	8.2 (7.5, 8.9)	ref
High alcohol use	43.1 (33.3, 55.6)	0.14	123 (102, 148)	0.56	540 (429, 680)	0.02	8.5 (6.5, 11.1)	0.88
Low	35.0 (32.2, 38.0)	0.78	122 (113, 132)	0.36	581 (519, 652)	0.009	8.3 (7.6, 9.0)	0.96
Never (ref)	35.5 (32.5, 38.9)	ref	116 (106, 126)	ref	719 (642, 805)	ref	8.3 (7.6, 9.1)	ref
Cardiovascular disease	36.8 (29.4, 45.9)	0.74	149 (128, 174)	0.004	608 (468, 791)	0.62	10.1 (7.9, 13.0)	0.10
No	35.5 (33.3, 37.7)		117 (110, 124)		651 (599, 708)		8.2 (7.7, 8.7)	
Hypertension (BP>=140/90/Meds)**,** Yes	36.0 (31.9, 40.7)	0.67	140 (128, 155)	<0.0001	662 (579, 758)	0.66	9.8 (8.8, 10.9)	<0.0001
No	35.2 (33.1, 37.5)		108 (101, 116)		640 (584, 702)		7.6 (7.1, 8.1)	

TABLE XXVIII (continued).
WEIGHTED BIVARIATE ASSOCIATIONS OF GEOMETRIC MEAN (GM) AND 95% CONFIDENCE INTERVALS (95% CI) FOR SUMMARY MEASURES OF LIPID-ADJUSTED TOTAL PBDES, TOTAL PCBS, TOTAL DDT AND METABOLITES, AND OXYCHLORDANE WITH BASELINE (VISIT 1) COVARIATES AMONG STUDY PARTICIPANTS

	Total PBDEs (ng/g lipid)		**Total PCBs (ng/g lipid)**		**Total DDT/DDE (ng/g lipid)**		**Oxychlordane (ng/g lipid)**	
	GM (95% CI)	**p-value**	**GM (95% CI)**	**p-value**	**GM (95% CI)**	**p-value**	**GM (95% CI)**	**p-value**
Body mass index (BMI)								
Obese	36.0 (32.8, 39.4)	0.89	114 (105, 123)	0.06	744 (656, 843)	0.01	8.4 (7.5, 9.3)	0.71
Overweight	35.6 (32.0, 39.6)	0.86	116 (106, 127)	0.09	622 (551, 702)	0.32	8.3 (7.7, 9.0)	0.77
Normal/Underweight (ref)	34.6 (31.0, 38.7)	ref	134 (116, 155)	ref	555 (457, 674)	ref	8.1 (7.0, 9.3)	ref
Prediabetes	36.6 (33.6, 39.9)	0.36	123 (113, 134)	0.18	684 (606, 771)	0.12	8.4 (7.7, 9.2)	0.55
Normal glucose	34.3 (31.9, 36.9)		114 (106, 122)		607 (550, 670)		8.1 (7.6, 8.7)	
Medication use								
ACEi/ARB, Yes	37.9 (30.9, 46.6)	0.43	147 (128, 170)	0.001	768 (628, 938)	0.06	10.8 (9.3, 12.5)	0.0001
No	35.0 (33.2, 37.0)		114 (107, 121)		626 (574, 682)		7.8 (7.4, 8.4)	
NSAIDs, Yes	40.3 (34.0, 47.8)	0.09	108 (96, 121)	0.06	690 (586, 813)	0.40	8.7 (7.8, 9.6)	0.35
No	34.4 (32.4, 36.5)		122 (114, 129)		638 (582, 699)		8.2 (7.7, 8.8)	
Statins, Yes	35.1 (29.1, 42.3)	0.83	120 (102, 142)	0.88	682 (514, 904)	0.69	8.2 (6.4, 10.6)	0.95
No	35.6 (33.4, 37.9)		119 (112, 126)		644 (593, 699)		8.3 (7.8, 8.8)	
Antidepressants, Yes	36.0 (29.0, 44.7)	0.90	132 (101, 173)	0.42	561 (420, 751)	0.30	10.3 (7.7, 13.8)	0.12
No	35.5 (33.4, 37.8)		118 (111, 125)		656 (604, 713)		8.1 (7.7, 8.6)	
Antianxiety, Yes	34.0 (28.2, 41.0)	0.68	149 (112, 199)	0.11	655 (469, 913)	0.95	10.7 (7.5, 15.4)	0.15
No	35.6 (33.5, 37.9)		117 (110, 124)		648 (595, 705)		8.2 (7.7, 8.7)	
Antipsychotics, Yes	41.8 (34.2, 51.1)	0.15	147 (89, 243)	0.39	521 (207, 1313)	0.63	9.1 (5.9, 14.1)	0.66
No	35.3 (33.3, 37.6)		118 (112, 125)		653 (602, 708)		8.3 (7.8, 8.8)	
Physical activity level, Low	34.3 (31.7, 37.1)	0.24	120 (110, 131)	0.02	659 (588, 739)	0.63	8.4 (7.6, 9.2)	0.07
Moderate	36.3 (32.7, 40.2)	0.62	122 (113, 132)	0.007	648 (581, 723)	0.68	8.5 (7.8, 9.1)	0.04
High (ref)	38.2 (32.5, 44.9)	ref	98 (85, 113)	ref	604 (431, 846)	ref	7.1 (6.0, 8.3)	ref
High LDL ≥160 mg/dl	32.1 (28.6, 36.0)	0.08	114 (102, 127)	0.43	601 (505, 717)	0.33	8.4 (7.4, 9.6)	0.78
No	36.3 (33.9, 38.9)		120 (112, 128)		662 (605, 725)		8.2 (7.7, 8.8)	
Low HDL <40 mg/dl	38.7 (33.5, 44.6)	0.18	113 (100, 128)	0.41	619 (534, 717)	0.53	8.7 (7.7, 9.8)	0.45
No	34.9 (32.7, 37.2)		120 (112, 128)		654 (596, 718)		8.2 (7.7, 8.8)	

TABLE XXVIII (continued).
WEIGHTED BIVARIATE ASSOCIATIONS OF GEOMETRIC MEAN (GM) AND 95% CONFIDENCE INTERVALS (95% CI) FOR SUMMARY MEASURES OF LIPID-ADJUSTED TOTAL PBDES, TOTAL PCBS, TOTAL DDT AND METABOLITES, AND OXYCHLORDANE WITH BASELINE (VISIT 1) COVARIATES AMONG STUDY PARTICIPANTS

	Total PBDEs (ng/g lipid)		**Total PCBs (ng/g lipid)**		**Total DDT/DDE (ng/g lipid)**		**Oxychlordane (ng/g lipid)**	
	GM (95% CI)	**p-value**	**GM (95% CI)**	**p-value**	**GM (95% CI)**	**p-value**	**GM (95% CI)**	**p-value**
High triglycerides ≥200 mg/dl	32.9 (29.3, 37.0)	0.29	114 (102, 127)	0.42	613 (526, 715)	0.48	8.9 (7.9, 10.1)	0.24
No	36.0 (33.6, 38.5)		120 (112, 128)		654 (597, 716)		8.2 (7.7, 8.8)	
C-reactive protein ≥2 mg/L	36.5 (33.3, 40.0)	0.54	114 (106, 124)	0.21	660 (585, 743)	0.67	8.2 (7.5, 9.0)	0.77
No	34.6 (32.1, 37.3)		123 (113, 134)		637 (572, 709)		8.4 (7.7, 9.0)	
Low eGFR < 60, Yes	54.3 (23.3, 126.6)	0.29	219 (163, 292)	<0.0001	541 (363, 806)	0.36	13.4 (10.1, 17.8)	0.001
No	35.0 (33.2, 36.9)		116 (110, 123)		652 (601, 708)		8.1 (7.7, 8.6)	
Albuminuria, Yes	37.8 (28.2, 50.6)	0.69	138 (114, 168)	0.11	466 (381, 569)	0.001	8.2 (6.4, 10.6)	0.94
No	35.2 (33.3, 37.3)		116 (109, 124)		677 (622, 736)		8.3 (7.8, 8.8)	
CKD, Yes	37.4 (28.7, 48.7)	0.68	150 (124, 182)	0.01	464 (383, 561)	0.0003	9.1 (7.1, 11.7)	0.42
No	35.2 (33.3, 37.3)		114 (108, 122)		683 (628, 742)		8.2 (7.7, 8.7)	

TABLE XXIX.
WEIGHTED BIVARIATE ASSOCIATIONS OF GEOMETRIC MEAN (GM) AND 95% CONFIDENCE INTERVALS (95% CI) FOR LIPID-ADJUSTED SUMMARY MEASURES OF PERSISTENT PESTICIDES WITH BASELINE (VISIT 1) COVARIATES AMONG STUDY PARTICIPANTS

	β-Hexachlorocyclohexane (ng/g lipid)		**Hexachlorobenzene (ng/g lipid)**		**Mirex (ng/g lipid)**		**Trans-Nonachlor (ng/g lipid)**	
	GM (95% CI)	**p-value**	**GM (95% CI)**	**p-value**	**GM (95% CI)**	**p-value**	**GM (95% CI)**	**p-value**
Overall	9.8 (8.9, 10.8)		13.3 (12.4, 14.3)		4.5 (4.3, 4.8)		12.5 (11.8, 13.3)	
Age in years								
65+	12.6 (9.1, 17.5)	0.03	14.9 (12.1, 18.4)	0.13	4.4 (3.6, 5.3)	0.37	22.3 (19.6, 25.4)	<0.0001
55-64	10.7 (9.2, 12.4)	0.02	13.8 (12.1, 15.7)	0.22	4.2 (3.9, 4.6)	0.01	14.5 (13.3, 15.8)	<0.0001
45-54 (ref)	8.5 (7.5, 9.6)	ref	12.5 (11.6, 13.5)	ref	4.8 (4.5, 5.1)	ref	9.3 (8.6, 10.0)	ref
Sex, Male	8.2 (6.9, 9.8)	0.002	11.6 (10.5, 12.8)	0.0002	4.4 (4.1, 4.8)	0.57	12.2 (11.2, 13.2)	0.37
Female	11.4 (10.2, 12.7)		15.0 (13.6, 16.5)		4.6 (4.3, 4.9)		12.9 (11.7, 14.1)	
Menopause Status								
Pre	6.8 (5.3, 8.9)	<0.0001	10.9 (9.1, 13.0)	0.001	5.3 (4.6, 6.1)	0.02	8.1 (6.9, 9.6)	<0.0001
Peri	11.3 (8.6, 14.7)	0.61	15.3 (12.8, 18.3)	0.89	5.2 (4.4, 6.1)	0.09	9.7 (8.4, 11.2)	<0.0001
Post (ref)	12.2 (10.8, 13.8)	ref	15.5 (13.7, 17.5)	ref	4.4 (4.0, 4.8)	ref	14.5 (13.0, 16.3)	ref
Hispanic/Latino background								
Central American	8.8 (7.0, 11.1)	0.29	8.4 (7.7, 9.1)	<0.0001	5.2 (4.2, 6.4)	0.46	10.3 (8.5, 12.4)	0.01
Cuban	18.2 (14.7, 22.7)	<0.0001	10.0 (9.2, 10.9)	<0.0001	4.5 (4.0, 5.0)	0.40	13.2 (11.5, 15.1)	0.91
Dominican	4.3 (3.8, 4.8)	<0.0001	7.9 (7.4, 8.4)	<0.0001	5.1 (4.5, 5.8)	0.34	9.1 (8.2, 10.1)	<0.0001
More than one/other	7.9 (3.9, 16.0)	0.48	19.9 (9.4, 42.1)	0.53	5.3 (4.0, 7.0)	0.47	8.6 (7.0, 10.7)	0.003
Puerto Rican	5.4 (4.5, 6.5)	<0.0001	10.2 (9.4, 11.0)	<0.0001	3.4 (3.0, 4.0)	<0.0001	16.7 (14.3, 19.4)	0.02
South American	13.9 (9.6, 20.1)	0.12	10.1 (8.8, 11.5)	<0.0001	4.7 (4.0, 5.6)	0.92	9.2 (7.6, 11.2)	0.001
Mexican (ref)	10.2 (9.0, 11.6)	ref	25.2 (22.0, 29.0)	ref	4.7 (4.4, 5.2)	ref	13.3 (12.0, 14.8)	ref
Study Center, Bronx	5.6 (4.7, 6.7)	<0.0001	8.9 (8.4, 9.5)	<0.0001	4.1 (3.7, 4.6)	0.04	11.6 (10.2, 13.1)	0.007
Chicago	9.4 (7.8, 11.4)	0.51	11.6 (10.9, 12.3)	<0.0001	4.6 (4.2, 5.0)	0.55	11.2 (9.9, 12.5)	0.001
Miami	15.9 (13.4, 18.8)	<0.0001	9.9 (9.2, 10.7)	<0.0001	4.7 (4.3, 5.1)	0.80	12.7 (11.2, 14.3)	0.11
San Diego (ref)	8.8 (7.9, 9.8)	ref	34.7 (29.7, 40.4)	ref	4.8 (4.3, 5.2)	ref	14.3 (13.1, 15.8)	ref
Born in United States	5.3 (4.6, 6.1)	<0.0001	10.9 (10.2, 11.7)	<0.0001	3.5 (3.1, 3.9)	<0.0001	16.4 (14.5, 18.6)	<0.0001
Non-US Born	11.4 (10.2, 12.7)		14.0 (12.9, 15.2)		4.8 (4.6, 5.1)		11.7 (11.0, 12.5)	

TABLE XXIX (continued).
WEIGHTED BIVARIATE ASSOCIATIONS OF GEOMETRIC MEAN (GM) AND 95% CONFIDENCE INTERVALS (95% CI) FOR LIPID-ADJUSTED SUMMARY MEASURES OF PERSISTENT PESTICIDES WITH BASELINE (VISIT 1) COVARIATES AMONG STUDY PARTICIPANTS

	β-Hexachlorocyclohexane (ng/g lipid)		**Hexachlorobenzene (ng/g lipid)**		**Mirex (ng/g lipid)**		**Trans-Nonachlor (ng/g lipid)**	
	GM (95% CI)	**p-value**	**GM (95% CI)**	**p-value**	**GM (95% CI)**	**p-value**	**GM (95% CI)**	**p-value**
<10 years living in US	18.4 (14.7, 23.0)	<0.0001	12.3 (10.9, 13.9)	0.64	5.3 (4.8, 5.8)	<0.0001	10.1 (8.6, 11.8)	0.004
Non-US Born and YRS US 10-19	11.9 (9.8, 14.4)	<0.0001	15.0 (12.3, 18.3)	0.03	5.2 (4.7, 5.7)	<0.0001	10.3 (8.9, 11.8)	0.003
Non-US Born and YRS US ≥20	7.8 (7.1, 8.5)	0.003	13.5 (12.4, 14.8)	0.07	4.2 (4.0, 4.5)	0.004	14.9 (13.7, 16.1)	0.45
US Born (ref)	5.3 (4.2, 6.6)	ref	11.8 (10.6, 13.2)	ref	3.3 (2.8, 3.9)	ref	13.9 (12.0, 16.1)	ref
Education								
> High school grad	9.8 (8.7, 11.0)	0.98	13.4 (12.0, 14.9)	0.81	4.4 (4.0, 4.8)	0.21	11.9 (10.9, 13.0)	0.06
High school graduate	10.0 (8.1, 12.4)	0.85	12.5 (10.8, 14.4)	0.32	4.3 (3.9, 4.8)	0.14	12.0 (10.5, 13.7)	0.16
< High school (ref)	9.8 (8.2, 11.7)	ref	13.6 (12.3, 15.1)	ref	4.7 (4.4, 5.2)	ref	13.6 (12.2, 15.0)	ref
Income ≥$30,000	9.0 (7.7, 10.5)	0.001	15.6 (13.6, 18.0)	0.21	4.3 (3.9, 4.7)	0.01	11.8 (10.8, 12.9)	0.02
Less than $30,000	9.5 (8.6, 10.6)	0.002	12.3 (11.5, 13.3)	0.65	4.5 (4.3, 4.8)	0.02	12.6 (11.7, 13.7)	0.07
Missing/not reported (ref)	27.7 (14.2, 53.9)	ref	13.1 (10.3, 16.6)	ref	6.3 (4.8, 8.1)	ref	17.3 (12.4, 24.2)	ref
Reported occupational pesticide exposure, yes	7.0 (5.2, 9.6)	0.03	15.2 (11.6, 20.0)	0.35	4.9 (3.8, 6.4)	0.53	15.4 (12.8, 18.6)	0.03
No	9.9 (9.0, 11.0)		13.3 (12.4, 14.2)		4.5 (4.3, 4.8)		12.5 (11.7, 13.3)	
Have health insurance	7.9 (7.1, 8.9)	<0.0001	11.4 (9.9, 13.1)	0.38	4.3 (4.0, 4.6)	0.01	13.4 (12.4, 14.5)	0.02
No health insurance	12.4 (10.7, 14.3)		14.7 (12.7, 17.2)		4.9 (4.5, 5.2)		11.7 (10.6, 12.8)	
Current cigarette use	9.2 (7.7, 11.1)	0.92	13.4 (12.4, 14.6)	0.05	4.2 (3.8, 4.6)	0.24	11.3 (10.0, 12.9)	0.19
Former	11.8 (9.5, 14.7)	0.04	12.9 (9.2, 18.0)	0.30	4.8 (4.3, 5.3)	0.43	13.8 (12.2, 15.5)	0.20
Never (ref)	9.1 (8.2, 10.3)	ref	13.6 (12.1, 15.4)	ref	4.5 (4.2, 4.9)	ref	12.5 (11.5, 13.6)	ref
High alcohol use	8.0 (5.9, 10.7)	0.10	13.1 (12.1, 14.3)	0.91	4.9 (3.7, 6.5)	0.72	13.4 (10.1, 17.9)	0.75
Low	9.1 (8.1, 10.2)	0.11	15.2 (11.1, 20.9)	0.62	4.4 (4.0, 4.8)	0.34	12.3 (11.3, 13.4)	0.51
Never (ref)	10.6 (9.1, 12.3)	ref	13.2 (12.3, 14.2)	ref	4.6 (4.3, 5.0)	ref	12.8 (11.7, 14.0)	ref
Cardiovascular disease	13.4 (9.8, 18.3)	0.04	13.2 (11.6, 15.1)	0.39	4.6 (3.9, 5.4)	0.87	14.1 (11.1, 17.9)	0.33
No	9.6 (8.7, 10.7)		13.4 (12.4, 14.4)		4.5 (4.3, 4.8)		12.5 (11.7, 13.3)	

TABLE XXIX (continued).
WEIGHTED BIVARIATE ASSOCIATIONS OF GEOMETRIC MEAN (GM) AND 95% CONFIDENCE INTERVALS (95% CI) FOR LIPID-ADJUSTED SUMMARY MEASURES OF PERSISTENT PESTICIDES WITH BASELINE (VISIT 1) COVARIATES AMONG STUDY PARTICIPANTS

	β-Hexachlorocyclohexane (ng/g lipid)		**Hexachlorobenzene (ng/g lipid)**		**Mirex (ng/g lipid)**		**Trans-Nonachlor (ng/g lipid)**	
	GM (95% CI)	**p-value**	**GM (95% CI)**	**p-value**	**GM (95% CI)**	**p-value**	**GM (95% CI)**	**p-value**
Hypertension (BP>=140/90/Meds)**,** Yes	9.7 (8.3, 11.2)	0.83	11.4 (9.9, 13.1)	0.90	4.2 (3.8, 4.6)	0.06	15.2 (13.6, 16.9)	<0.0001
No	9.9 (8.7, 11.3)		14.7 (12.7, 17.2)		4.7 (4.4, 5.0)		11.3 (10.5, 12.1)	
Body mass index (BMI), kg/m^2								
Obese	11.2 (9.6, 13.1)	0.03	13.0 (11.9, 14.1)	0.56	4.5 (4.1, 4.9)	0.96	12.5 (11.4, 13.7)	0.68
Overweight	9.4 (7.9, 11.3)	0.44	13.4 (12.1, 14.8)	0.78	4.6 (4.2, 5.0)	0.71	12.8 (11.7, 14.0)	0.47
Normal/Underweight (ref)	8.5 (7.0, 10.2)	ref	13.8 (11.3, 16.8)	ref	4.5 (3.9, 5.1)	ref	12.0 (10.3, 14.1)	ref
Prediabetes	10.3 (8.8, 12.0)	0.29	13.7 (12.3, 15.3)	0.31	4.5 (4.2, 4.9)	0.89	13.1 (12.1, 14.3)	0.08
Normal glucose	9.3 (8.3, 10.4)		12.8 (11.9, 13.8)		4.5 (4.3, 4.9)		11.9 (10.9, 12.9)	
Medication use								
ACEi/ARB, Yes	10.6 (8.8, 12.6)	0.39	12.9 (10.7, 15.6)	0.71	4.6 (4.0, 5.2)	0.82	17.5 (15.2, 20.2)	<0.0001
No	9.7 (8.6, 10.8)		13.4 (12.5, 14.4)		4.5 (4.2, 4.8)		11.7 (11.0, 12.5)	
NSAIDs, Yes	9.7 (8.4, 11.2)	0.85	13.6 (11.9, 15.6)	0.71	4.4 (3.9, 5.0)	0.71	12.5 (11.1, 14.2)	0.99
No	9.8 (8.7, 11.1)		13.2 (12.2, 14.3)		4.5 (4.3, 4.8)		12.5 (11.7, 13.4)	
Statins, Yes	8.7 (6.6, 11.4)	0.37	12.4 (10.6, 14.5)	0.36	5.1 (4.3, 6.1)	0.13	12.9 (10.4, 16.2)	0.76
No	10.0 (8.9, 11.1)		13.4 (12.5, 14.5)		4.5 (4.2, 4.7)		12.5 (11.7, 13.3)	
Antidepressants, Yes	7.7 (6.0, 9.8)	0.05	12.1 (10.0, 14.8)	0.33	4.2 (3.5, 5.1)	0.45	13.6 (9.7, 18.9)	0.62
No	10.0 (9.0, 11.1)		13.4 (12.5, 14.4)		4.5 (4.3, 4.8)		12.5 (11.7, 13.3)	
Antianxiety, Yes	13.9 (10.8, 17.9)	0.01	12.7 (10.4, 15.4)	0.62	4.8 (3.7, 6.1)	0.68	15.8 (10.6, 23.4)	0.23
No	9.6 (8.7, 10.7)		13.4 (12.4, 14.4)		4.5 (4.3, 4.8)		12.4 (11.7, 13.2)	
Antipsychotics, Yes	15.7 (3.9, 62.8)	0.49	9.9 (7.6, 12.9)	0.03	5.7 (3.6, 8.9)	0.32	13.2 (6.9, 25.1)	0.88
No	9.7 (8.9, 10.5)		13.4 (12.5, 14.4)		4.5 (4.3, 4.7)		12.5 (11.8, 13.3)	
Physical activity level, Low	10.9 (9.3, 12.9)	0.003	13.8 (12.3, 15.5)	0.57	4.6 (4.2, 4.9)	0.21	12.6 (11.4, 13.9)	0.27
Moderate	9.5 (8.4, 10.6)	0.03	12.9 (12.0, 14.0)	0.95	4.3 (4.0, 4.7)	0.10	12.7 (11.7, 13.8)	0.21
High (ref)	6.6 (4.9, 8.8)	ref	13.0 (11.0, 15.3)	ref	5.2 (4.3, 6.4)	ref	11.4 (9.7, 13.3)	ref

TABLE XXIX (continued).
WEIGHTED BIVARIATE ASSOCIATIONS OF GEOMETRIC MEAN (GM) AND 95% CONFIDENCE INTERVALS (95% CI) FOR LIPID-ADJUSTED SUMMARY MEASURES OF PERSISTENT PESTICIDES WITH BASELINE (VISIT 1) COVARIATES AMONG STUDY PARTICIPANTS

	β-Hexachlorocyclohexane (ng/g lipid)		**Hexachlorobenzene (ng/g lipid)**		**Mirex (ng/g lipid)**		**Trans-Nonachlor (ng/g lipid)**	
	GM (95% CI)	**p-value**	**GM (95% CI)**	**p-value**	**GM (95% CI)**	**p-value**	**GM (95% CI)**	**p-value**
High LDL ≥160 mg/dl	10.9 (8.7, 13.7)	0.31	13.9 (11.5, 16.8)	0.63	3.6 (3.2, 4.1)	0.0001	12.7 (11.0, 14.6)	0.83
No	9.6 (8.7, 10.7)		13.3 (12.4, 14.2)		4.8 (4.5, 5.0)		12.5 (11.6, 13.4)	
Low HDL <40 mg/dl	8.7 (7.2, 10.5)	0.18	12.7 (11.0, 14.6)	0.47	4.4 (4.0, 4.8)	0.52	13.3 (11.6, 15.1)	0.37
No	10.1 (9.0, 11.2)		13.5 (12.4, 14.6)		4.6 (4.3, 4.8)		12.4 (11.6, 13.3)	
High triglycerides ≥200 mg/dl	9.7 (7.8, 12.0)	0.92	12.6 (10.2, 15.5)	0.55	3.9 (3.4, 4.4)	0.01	13.7 (12.0, 15.7)	0.18
No	9.8 (8.8, 11.0)		13.4 (12.5, 14.4)		4.6 (4.4, 4.9)		12.4 (11.5, 13.3)	
C-reactive protein ≥2 mg/L	11.0 (9.5, 12.8)	0.01	12.5 (11.4, 13.6)	0.05	4.4 (4.1, 4.8)	0.35	12.3 (11.3, 13.5)	0.57
No	8.8 (7.8, 9.8)		14.2 (12.8, 15.7)		4.6 (4.3, 5.0)		12.8 (11.7, 13.9)	
Low eGFR < 60, Yes	10.6 (7.3, 15.3)	0.68	11.9 (9.1, 15.4)	0.38	3.8 (2.9, 4.8)	0.15	21.4 (16.4, 27.9)	<0.0001
No	9.8 (8.8, 10.8)		13.4 (12.5, 14.3)		4.6 (4.3, 4.8)		12.3 (11.6, 13.1)	
Albuminuria, Yes	10.1 (7.8, 13.1)	0.81	12.1 (10.4, 14.2)	0.23	4.4 (3.9, 5.1)	0.74	12.7 (10.1, 16.0)	0.91
No	9.8 (8.8, 10.8)		13.5 (12.5, 14.5)		4.5 (4.3, 4.8)		12.5 (11.7, 13.4)	
CKD, Yes	9.6 (7.6, 12.2)	0.86	12.1 (10.6, 13.9)	0.17	4.3 (3.8, 4.9)	0.44	13.9 (11.1, 17.5)	0.32
No	9.8 (8.9, 10.9)		13.5 (12.5, 14.6)		4.6 (4.3, 4.8)		12.3 (11.6, 13.1)	

TABLE XXX.
CROSS-SECTIONAL ASSOCIATIONS BETWEEN CONTINUOUS AND RANKED QUARTILES OF PCB ANALYTE CONCENTRATIONS AND BASELINE EGFR AND UACR AMONG STUDY PARTICIPANTS

	Continuous eGFR (mL/minute/1.73m^2)		**Log UACR (mg/g)**	
	Crude β (95% CI)[b]	**Adjusted β (95% CI)[c]**	**Crude β (95% CI)[b]**	**Adjusted β (95% CI)[c]**
Total PCBs[a]	-1.8 (-4.2, 0.6)	-1.0 (-3.3, 1.3)	0.11 (-0.05, 0.27)	0.12 (-0.03, 0.27)
p-value (continuous)	0.14	0.39	0.19	0.11
Q1 (ref)	ref	ref	ref	ref
Q2	-1.2 (-3.9, 1.5)	0.07 (-2.7, 2.8)	0.36 (-0.23, 0.95)	0.28 (-0.19, 0.76)
Q3	-2.0 (-5.6, 1.5)	0.14 (-3.3, 3.6)	0.22 (0.02, 0.43)[d]	0.18 (-0.05, 0.41)
Q4	-3.1 (-7.4, 1.1)	-0.7 (-4.6, 3.1)	0.24 (0.01, 0.47)[d]	0.27 (-0.05, 0.59)
p for trend	0.14	0.69	0.16	0.10
Total Estrogenic PCBs[a]	-0.8 (-2.7, 1.2)	-0.3 (-2.0, 1.4)	0.12 (-0.02, 0.27)	0.17 (-0.03, 0.37)
p-value (continuous)	0.43	0.74	0.10	0.09
Q1 (ref)	ref	ref	ref	ref
Q2	-0.5 (-3.5, 2.6)	-0.02 (-3.3, 3.3)	0.06 (-0.12, 0.25)	0.04 (-0.17, 0.25)
Q3	-0.8 (-4.8, 3.3)	1.1 (-2.6, 4.8)	0.48 (-0.06, 1.0)	0.41 (-0.12, 0.95)
Q4	-2.5 (-6.3, 1.3)	-1.3 (-5.1, 2.5)	0.21 (-0.06, 0.48)	0.31 (-0.11, 0.73)
p for trend	0.19	0.59	0.09	0.11
Total Anti-Estrogenic PCBs[a]	-2.2 (-4.6, 0.21)	-1.2 (-3.7, 1.2)	0.11 (-0.04, 0.27)	0.07 (-0.08, 0.23)
p-value (continuous)	0.07	0.33	0.14	0.33
Q1 (ref)	ref	ref	ref	ref
Q2	1.6 (-1.4, 4.6)	2.9 (-0.03, 5.8)	0.31 (-0.29, 0.91)	0.18 (-0.24, 0.60)
Q3	-4.2 (-7.5, -0.9)[d]	-2.3 (-5.3, 0.7)	0.23 (0.03, 0.43)[d]	0.17 (-0.06, 0.39)
Q4	-1.9 (-6.0, 2.2)	0.4 (-3.5, 4.3)	0.24 (-0.01, 0.50)	0.19 (-0.09, 0.48)
p for trend	0.09	0.55	0.18	0.21
Wolff Group 3 CYP1A/2B PCBs[a]	-1.3 (-3.4, 0.98)	-0.5 (-2.4, 1.4)	0.07 (-0.08, 0.23)	0.10 (-0.03, 0.24)
p-value (continuous)	0.28	0.62	0.35	0.12
Q1 (ref)	ref	ref	ref	ref
Q2	-0.39 (-3.2, 2.4)	0.6 (-2.2, 3.5)	0.37 (-0.19, 0.94)	0.25 (-0.19, 0.69)
Q3	-1.3 (-4.9, 2.1)	1.0 (-2.5, 4.5)	0.14 (-0.04, 0.33)	0.10 (-0.12, 0.31)
Q4	-2.7 (-7.1, 1.6)	-0.5 (-4.4, 3.5)	0.22 (-0.01, 0.45)	0.26 (-0.05, 0.57)
p for trend	0.19	0.80	0.32	0.11

[a]Continuous analyte concentrations are log transformed; [b]Adjusted for age (continuous) and total lipids (continuous); [c]Model adjusts for age (continuous), total lipids (continuous), sex (male/female), Hispanic/Latino background group, systolic blood pressure (continuous), fasting blood glucose (continuous), body mass index (continuous), education (greater than high school, high school, or less than high school), and ACE/ARB medication use (yes/no); [d]Statistically significant ($p<0.05$)

TABLE XXX (continued).
CROSS-SECTIONAL ASSOCIATIONS BETWEEN CONTINUOUS AND RANKED QUARTILES OF PCB ANALYTE CONCENTRATIONS AND BASELINE EGFR AND UACR AMONG STUDY PARTICIPANTS

	Continuous eGFR (mL/minute/1.73m^2)		**Log UACR (mg/g)**	
	Crude β (95% CI)[b]	**Adjusted β (95% CI)[c]**	**Crude β (95% CI)[b]**	**Adjusted β (95% CI)[c]**
Warner CYP1A PCBs[a]	-1.9 (-4.4, 0.6)	-0.82 (-3.8, 2.1)	0.15 (-0.0005, 0.30)	0.07 (-0.09, 0.24)
p-value (continuous)	0.14	0.58	0.05	0.39
Q1 (ref)	ref	ref	ref	ref
Q2	-0.4 (-4.1, 3.3)	0.5 (-2.9, 3.9)	0.09 (-0.11, 0.28)	0.05 (-0.14, 0.24)
Q3	-2.7 (-6.0, 0.6)	-1.6 (-5.1, 1.9)	0.54 (0.004, 1.1)	0.41 (-0.05, 0.87)
Q4	-2.6 (-6.2, 1.0)	-0.5 (-4.6, 3.6)	0.23 (-0.03, 0.50)	0.16 (-0.15, 0.47)
p for trend	0.10	0.62	0.05	0.20
Warner mixed PCBs[a]	-2.6 (-4.5, 0.42)	-1.1 (-3.4, 1.1)	0.08 (-0.08, 0.25)	0.06 (-0.08, 0.21)
p-value (continuous)	0.10	0.33	0.33	0.39
Q1 (ref)	ref	ref	ref	ref
Q2	-0.2 (-6.9, 1.2)	0.8 (-2.1, 3.7)	0.35 (-0.24, 0.94)	0.27 (-0.19, 0.72)
Q3	-2.9 (-6.1, 0.3)	-0.7 (-3.6, 2.2)	0.19 (-0.02, 0.40)	0.13 (-0.10, 0.36)
Q4	-0.28 (-6.9, 1.2)	-0.7 (-4.4, 3.0)	0.24 (0.004, 0.47)[d]	0.25 (-0.05, 0.54)
p for trend	0.09	0.54	0.23	0.16
Warner CYP2B PCBs[a]	-1.2 (-3.3, 0.93)	-0.5 (-2.4, 1.4)	0.09 (-0.06, 0.23)	0.13 (-0.01, 0.26)
p-value (continuous)	0.27	0.59	0.25	0.06
Q1 (ref)	ref	ref	ref	ref
Q2	-0.6 (-3.3, 2.1)	0.4 (-2.5, 3.2)	0.38 (-0.17, 0.94)	0.25 (-0.20, 0.70)
Q3	-1.2 (-4.8, 2.5)	1.0 (-2.6, 4.7)	0.15 (-0.03, 0.35)	0.13 (-0.10, 0.37)
Q4	-3.0 (-7.4, 1.5)	-0.8 (-4.9, 3.2)	0.22 (-0.01, 0.45)	0.25 (-0.07, 0.56)
p for trend	0.18	0.71	0.31	0.13

[a]Continuous analyte concentrations are log transformed
[b]Model adjusts for age (continuous) and total lipids (continuous)
[c]Model adjusts for age (continuous), total lipids (continuous), sex (male/female), Hispanic/Latino background group, systolic blood pressure (continuous), fasting blood glucose (continuous), body mass index (continuous), education (greater than high school, high school, or less than high school), and ACE/ARB medication use (yes/no)
[d]Statistically significant ($p<0.05$);

TABLE XXXI.
CROSS-SECTIONAL ASSOCIATIONS BETWEEN CONTINUOUS CONCENTRATIONS AND RANKED QUARTILES OF PBDE, AND PERSISTENT PESTICIDE ANALYTE CONCENTRATIONS AND BASELINE EGFR AND UACR AMONG STUDY PARTICIPANTS

	Continuous eGFR (mL/minute/1.73m^2)		**Log UACR (mg/g)**	
	Crude β (95% CI)[b]	**Model 1 β (95% CI)[c]**	**Crude β (95% CI)[b]**	**Model 1 β (95% CI)[c]**
***Total PBDEs*[a]**	-0.66 (-3.3, 2.0)	-0.86 (-3.6, 1.8)	-0.02 (-0.18, 0.14)	-0.001 (-0.15, 0.15)
p-value (continuous)	0.62	0.53	0.80	0.98
Q1 (ref)	ref	ref	ref	ref
Q2	1.3 (-2.9, 5.5)	1.3 (-2.7, 5.3)	-0.01 (-0.50, 0.47)	-0.001 (-0.41, 0.41)
Q3	4.3 (0.24, 8.3)[d]	3.7 (-0.53, 7.9)	-0.30 (-0.79, 0.19)	-0.19 (-0.57, 0.18)
Q4	1.6 (-2.1, 5.4)	1.8 (-1.9, 5.5)	-0.11 (-0.59, 0.47)	-0.11 (-0.55, 0.33)
p for trend	0.17	0.20	0.39	0.45
β-hexachlorocyclohexane[a]	0.06 (-1.7, 1.9)	-0.10 (-1.8, 1.6)	0.04 (-0.10, 0.18)	-0.03 (-0.11, 0.05)
p-value (continuous)	0.94	0.91	0.56	0.39
Q1 (ref)	ref	ref	ref	ref
Q2	0.3 (-4.0, 4.6)	0.1 (-3.6, 3.9)	0.08 (-0.13, 0.29)	-0.05 (-0.25, 0.14)
Q3	0.4 (-3.6, 4.4)	-0.6 (-4.4, 3.2)	0.14 (-0.07, 0.36)	-0.04 (-0.27, 0.18)
Q4	0.5 (-3.3, 4.4)	0.03 (-3.9, 4.0)	0.25 (-0.23, 0.74)	0.05 (-0.27, 0.36)
p for trend	0.78	0.95	0.29	0.74
Hexachlorobenzene[a]	1.2 (-0.12, 2.6)	0.93 (-0.68, 2.5)	-0.02 (-0.10, 0.06)	-0.17 (-0.41, 0.06)
p-value (continuous)	0.07	0.26	0.65	0.15
Q1 (ref)	ref	ref	ref	ref
Q2	3.0 (-1.2, 7.1)	2.6 (-1.5, 6.7)	-0.06 (-0.28, 0.16)	-0.003 (-0.24, 0.23)
Q3	0.5 (-3.4, 4.4)	0.9 (-3.5, 5.4)	0.31 (-0.19, 0.81)	0.17 (-0.13, 0.48)
Q4	3.5 (-0.1, 7.1)	3.0 (-1.4, 7.4)	-0.07 (-0.23, 0.10)	-0.32 (-0.72, 0.08)
p for trend	0.17	0.36	0.57	0.25
Mirex[a]	2.2 (-0.6, 4.9)	1.6 (-0.88, 4.0)	-0.05 (-0.21, 0.10)	-0.04 (-0.16, 0.08)
p-value (continuous)	0.12	0.21	0.48	0.52
T1 (ref)	ref	ref	ref	ref
T2	-1.9 (-5.7, 1.9)	-1.9 (-6.2, 2.4)	0.03 (-0.24, 0.29)	0.15 (-0.04, 0.34)
T3	1.8 (-8.0, 11.6)	-1.9 (-9.3, 5.3)	-0.20 (-0.46, 0.06)	-0.02 (-0.27, 0.23)
p for trend	0.77	0.45	0.52	0.43

[a]Continuous analyte concentrations are log transformed
[b]Model adjusts for age (continuous) and total lipids (continuous)
[c]Model adjusts for age (continuous), total lipids (continuous), sex (male/female), Hispanic/Latino background group, systolic blood pressure (continuous), fasting blood glucose (continuous), body mass index (continuous), education (greater than high school, high school, or less than high school), ACE/ARB medication use (yes/no), and nativity subscore
[d]Statistically significant ($p<0.05$);

TABLE XXXI (continued).
CROSS-SECTIONAL ASSOCIATIONS BETWEEN CONTINUOUS CONCENTRATIONS AND RANKED QUARTILES OF PBDE, AND PERSISTENT PESTICIDE ANALYTE CONCENTRATIONS AND BASELINE EGFR AND UACR AMONG STUDY PARTICIPANTS

	Continuous eGFR (mL/minute/1.73m^2)		**Log UACR (mg/g)**	
	Crude β (95% CI)[b]	**Model 1 β (95% CI)[c]**	**Crude β (95% CI)[b]**	**Model 1 β (95% CI)[c]**
Oxychlordane[a]	-1.7 (-3.8, 0.25)	-1.1 (-3.4, 1.2)	0.002 (-0.32, 0.32)	-0.13 (-0.43, 0.18)
p-value (continuous)	0.09	0.36	0.98	0.41
Q1 (ref)	ref	ref	ref	ref
Q2	-0.03 (-3.6, 3.5)	-0.3 (-3.9, 3.3)	-0.20 (-0.73, 0.33)	-0.19 (-0.64, 0.27)
Q3	-3.9 (-7.7, -0.2)[d]	-3.3 (-6.7, 0.1)	-0.08 (-0.60, 0.44)	-0.20 (-0.65, 0.25)
Q4	-1.3 (-4.8, 2.2)	-0.5 (-4.8, 3.8)	-0.12 (-0.64, 0.39)	-0.30 (-0.80, 0.19)
p for trend	0.18	0.53	0.75	0.24
p,p'-DDE[a]	1.1 (-0.001, 2.2)	0.7 (-0.5, 2.0)	-0.03 (-0.10, 0.03)	-0.11 (-0.26, 0.04)
p-value (continuous)	0.05	0.24	0.29	0.14
Q1 (ref)	ref	ref	ref	ref
Q2	0.8 (-2.7, 4.2)	0.9 (-2.9, 4.8)	0.17 (-0.38, 0.73)	0.04 (-0.27, 0.35)
Q3	0.8 (-3.3, 4.9)	0.7 (-3.7, 5.0)	0.006 (-0.22, 0.24)	-0.09 (-0.39, 0.21)
Q4	4.6 (0.5, 8.7)[d]	3.5 (-1.3, 8.2)	-0.10 (-0.31, 0.12)	-0.29 (-0.64, 0.05)
p for trend	0.04	0.18	0.22	0.17
Total DDE and DDT[a]	1.5 (0.11, 2.9)	1.0 (-0.5, 2.5)	-0.05 (-0.15, 0.03)	-0.15 (-0.34, 0.05)
p-value (continuous)	0.04	0.18	0.23	0.14
Q1 (ref)	ref	ref	ref	ref
Q2	0.7 (-2.7, 4.2)	0.9 (-3.1, 4.8)	0.17 (-0.38, 0.73)	0.03 (-0.28, 0.33)
Q3	0.2 (-3.9, 4.4)	0.1 (-4.3, 4.5)	0.01 (-0.22, 0.24)	-0.09 (-0.38, 0.21)
Q4	5.0 (1.0, 9.0)[d]	3.8 (-0.9, 8.6)	-0.09 (-0.31, 0.13)	-0.29 (-0.64, 0.06)
p for trend	0.03	0.16	0.25	0.19
***trans*-Nonachlor[a]**	-0.96 (-2.8, 0.89)	-0.38 (-2.5, 1.7)	0.05 (-0.16, 0.26)	-0.03 (-0.24, 0.17)
p-value (continuous)	0.31	0.72	0.64	0.76
Q1 (ref)	ref	ref	ref	ref
Q2	-0.8 (-4.5, 2.8)	-0.8 (-4.3, 2.6)	-0.33 (-0.90, 0.23)	-0.42 (-0.95, 0.10)
Q3	-1.3 (-4.8, 2.2)	-0.8 (-4.2, 2.6)	-0.22 (-0.78, 0.35)	-0.29 (-0.76, 0.18)
Q4	-2.0 (-5.6, 1.6)	-1.2 (-5.5, 3.0)	-0.05 (-0.62, 0.52)	-0.18 (-0.73, 0.37)
p for trend	0.26	0.58	0.97	0.63

[a]Continuous analyte concentrations are log transformed
[b]Model adjusts for age (continuous) and total lipids (continuous)
[c]Model adjusts for age (continuous), total lipids (continuous), sex (male/female), Hispanic/Latino background group, systolic blood pressure (continuous), fasting blood glucose (continuous), body mass index (continuous), education (greater than high school, high school, or less than high school), ACE/ARB medication use (yes/no), and nativity subscore
[d]Statistically significant ($p<0.05$)

TABLE XXXII.
CROSS-SECTIONAL ASSOCIATIONS BETWEEN CONTINUOUS CONCENTRATIONS AND RANKED QUARTILES OF PCB ANALYTE CONCENTRATIONS AND BASELINE ODDS OF ALBUMINURIA AND THE CKD COMPOSITE AMONG STUDY PARTICIPANTS

	Albuminuria			CKD		
	% (95% CI)	Model 1	Model 2	% (95% CI)	Model 1	Model 2
		OR (95% CI)[b]	OR (95% CI)[c]		OR (95% CI)[b]	OR (95% CI)[c]
Total PCBs[a]		1.5 (0.85, 2.6)	1.5 (0.90, 2.6)		1.7 (1.0, 2.9)	1.8 (1.1, 3.0)
p-value (continuous)		0.16	0.11		0.05	0.02
Q1 (ref)	6.1 (2.9, 9.2)	ref	ref	6.1 (2.9, 9.2)	ref	ref
Q2	12.4 (1.0, 23.8)	2.1 (0.65, 7.1)	2.1 (0.67, 6.9)	12.6 (1.2, 24.0)	2.2 (0.66, 7.1)	2.1 (0.65, 7.1)
Q3	12.5 (7.3, 17.8)	2.1 (0.95, 4.6)	2.2 (0.96, 5.1)	13.3 (7.9, 18.7)	2.0 (0.93, 4.5)	2.1 (0.90, 5.0)
Q4	14.2 (8.3, 20.1)	2.3 (0.98, 5.3)	2.7 (1.0, 7.0)[d]	19.1 (12.1, 26.1)	2.7 (1.2, 5.9)[d]	2.9 (1.1, 7.7)[d]
p for trend	0.43	0.14	0.05	0.10	0.06	0.02
Total Estrogenic PCBs[a]		1.5 (0.93, 2.3)	1.4 (0.94, 2.3)		1.7 (1.1, 2.5)	1.7 (1.1, 2.5)
p-value (continuous)		0.10	0.09		0.02	0.01
Q1 (ref)	6.3 (2.9, 9.7)	ref	ref	6.3 (2.9, 9.7)	ref	ref
Q2	7.6 (3.5, 11.7)	1.2 (0.50. 2.8)	0.97 (0.84, 2.5)	7.8 (3.7, 11.9)	1.1 (0.48, 2.7)	0.92 (0.35, 2.5)
Q3	17.3 (8.2, 26.4)	2.9 (1.1, 8.0)[d]	2.5 (0.8, 7.3)	17.4 (8.3, 26.5)	2.6 (0.93, 7.2)	2.0 (0.66, 6.3)
Q4	12.8 (6.9, 18.8)	2.0 (0.8, 4.9)	2.1 (0.7, 5.8)	18.6 (11.4, 26.0)	2.5 (1.1, 5.9)[d]	2.4 (0.88, 6.7)
p for trend	0.07	0.06	0.07	0.02	0.01	0.03
Total Anti-Estrogenic PCBs[a]		1.3 (0.80, 2.2)	1.3 (0.80, 2.2)		1.5 (0.93, 2.4)	1.5 (0.95, 2.5)
p-value (continuous)		0.27	0.27		0.09	0.08
Q1 (ref)	6.1 (2.6, 9.7)	ref	ref	6.1 (2.6, 9.7)	ref	ref
Q2	13.2 (1.8, 24.5)	2.2 (0.67, 7.5)	2.1 (0.69, 6.7)	13.4 (2.1, 24.7)	2.2 (0.65, 7.2)	2.0 (0.62, 6.7)
Q3	13.3 (7.6, 18.9)	2.2 (1.0, 4.8)	2.4 (0.98, 5.7)	14.7 (8.7, 20.6)	2.2 (1.0, 5.0)[d]	2.4 (0.99, 6.1)
Q4	13.0 (7.4, 18.7)	2.0 (0.80, 5.1)	2.2 (0.81, 5.9)	17.5 (10.7, 24.3)	2.3 (0.97, 5.6)	2.5 (0.91, 6.7)
p for trend	0.49	0.32	0.19	0.20	0.16	0.10

[a]Continuous analyte concentrations are log transformed; [b]Model adjusts for age (continuous) and total lipids (continuous)
[c]Model adjusts for age (continuous), total lipids (continuous), sex (male/female), systolic blood pressure (continuous), fasting blood glucose (continuous), body mass index (continuous), education (greater than high school, high school, or less than high school), ACE/ARB medication use (yes/no), and nativity subscore; [d]Statistically significant ($p<0.05$);

TABLE XXXII (continued).
CROSS-SECTIONAL ASSOCIATIONS BETWEEN CONTINUOUS CONCENTRATIONS AND RANKED QUARTILES OF PCB ANALYTE CONCENTRATIONS AND BASELINE ODDS OF ALBUMINURIA AND THE CKD COMPOSITE AMONG STUDY PARTICIPANTS

	Albuminuria			CKD		
	% (95% CI)	Model 1	Model 2	% (95% CI)	Model 1	Model 2
		OR (95% CI)[b]	OR (95% CI)[c]		OR (95% CI)[b]	OR (95% CI)[c]
Wolff Group 3 CYP1A/2B PCBs[a]		1.4 (0.81, 2.4)	1.4 (0.90, 2.4)		1.6 (0.93, 2.6)	1.6 (1.0, 2.6)
p-value (continuous)		0.25	0.13		0.09	0.03
Q1 (ref)	6.4 (3.1, 9.7)	ref	ref	6.4 (3.1, 9.7)	ref	ref
Q2	13.8 (2.8, 24.9)	2.3 (0.78, 6.8)	2.1 (0.75, 6.2)	14.0 (3.0, 25.1)	2.3 (0.77, 6.9)	2.1 (0.69, 6.2)
Q3	10.2 (5.5, 15.0)	1.5 (0.70, 3.4)	1.5 (0.63, 3.5)	10.2 (5.5, 15.0)	1.4 (0.63, 3.2)	1.3 (0.55, 3.1)
Q4	14.8 (8.7, 20.9)	2.2 (0.97, 5.1)	2.6 (1.0, 6.8)	20.6 (13.3, 27.8)	2.8 (1.3, 6.1)[d]	3.0 (1.2, 7.6)[d]
p for trend	0.35	0.21	0.07	0.04	0.06	0.02
Warner CYP1A PCBs[a]		1.3 (0.77, 2.1)	1.2 (0.74, 2.1)		1.4 (0.93, 2.2)	1.5 (0.93, 2.4)
p-value (continuous)		0.34	0.39		0.10	0.10
Q1 (ref)	5.3 (2.1, 8.5)	ref	ref	5.3 (2.1, 8.5)	ref	ref
Q2	11.7 (5.6, 17.9)	2.3 (0.99. 5.2)	2.7 (1.0, 7.0)[d]	11.9 (5.8, 18.0)	2.1 (0.93, 4.9)	2.6 (0.96, 7.0)
Q3	17.9 (7.7, 28.1)	3.7 (1.3, 10.2)[d]	4.3 (1.4, 12.9)[d]	18.2 (8.0, 28.4)	3.5 (1.3, 9.7)[d]	4.4 (1.4, 14.1)[d]
Q4	10.7 (6.1, 15.3)	1.8 (0.69, 4.7)	2.2 (0.72, 6.5)	16.1 (9.9, 22.2)	2.4 (1.0, 5.9)[d]	3.2 (1.1, 9.4)[d]
p for trend	0.11	0.35	0.28	0.08	0.11	0.08
Warner mixed PCBs[a]		1.3 (0.74, 2.2)	1.3 (0.76, 2.1)		1.4 (0.86, 2.4)	1.5 (0.89, 2.4)
p-value (continuous)		0.37	0.35		0.16	0.13
Q1 (ref)	5.7 (2.5, 8.9)	ref	ref	5.7 (2.5, 8.9)	ref	ref
Q2	14.6 (3.1, 26.0)	2.7 (0.88, 8.3)	2.7 (0.89, 8.1)	14.7 (3.3, 26.2)	2.6 (0.85, 8.1)	2.5 (0.81, 8.1)
Q3	12.1 (7.3, 16.9)	2.1 (0.95, 4.8)	2.2 (0.91, 5.2)	13.1 (8.0, 18.3)	2.1 (0.94, 4.7)	2.2 (0.88, 5.4)
Q4	13.3 (7.3, 19.2)	2.2 (0.92, 5.3)	2.6 (0.97, 6.9)	18.2 (11.1, 25.3)	2.6 (1.1, 6.1)[d]	3.0 (1.1, 7.9)[d]
p for trend	0.39	0.30	0.15	0.14	0.13	0.06

[a]Continuous analyte concentrations are log transformed; [b]Model adjusts for age (continuous) and total lipids (continuous)
[c]Model adjusts for age (continuous), total lipids (continuous), sex (male/female), systolic blood pressure (continuous), fasting blood glucose (continuous), body mass index (continuous), education (greater than high school, high school, or less than high school), ACE/ARB medication use (yes/no), and nativity subscore; [d]Statistically significant ($p<0.05$);

TABLE XXXII (continued).
CROSS-SECTIONAL ASSOCIATIONS BETWEEN CONTINUOUS CONCENTRATIONS AND RANKED QUARTILES OF PCB ANALYTE CONCENTRATIONS AND BASELINE ODDS OF ALBUMINURIA AND THE CKD COMPOSITE AMONG STUDY PARTICIPANTS

	Albuminuria			**CKD**		
	% (95% CI)	**Model 1**	**Model 2**	**% (95% CI)**	**Model 1**	**Model 2**
		OR (95% CI)[b]	**OR (95% CI)[c]**		**OR (95% CI)[b]**	**OR (95% CI)[c]**
Warner CYP2B PCBs[a]		1.4 (0.85, 2.4)	1.5 (0.94, 2.4)		1.6 (0.99, 2.7)	1.7 (1.1, 2.7)
p-value (continuous)		0.17	0.09		0.05	0.01
Q1 (ref)	6.5 (3.1, 9.8)	ref	ref	6.5 (3.1, 9.8)	ref	ref
Q2	13.2 (2.3, 24.1)	2.2 (0.71, 6.5)	1.9 (0.61, 5.8)	13.4 (2.5, 34.3)	2.2 (0.71, 6.6)	1.8 (0.56, 5.7)
Q3	10.8 (5.8, 15.7)	1.6 (0.74, 3.6)	1.6 (0.71, 3.8)	10.8 (5.8, 15.7)	1.5 (0.66, 3.3)	1.4 (0.59, 3.3)
Q4	14.7 (8.6, 20.8)	2.2 (0.95, 5.0)	2.5 (0.93, 6.6)	20.6 (13.3, 27.9)	2.7 (1.2, 5.9)[d]	2.7 (1.1, 7.1)[d]
p for trend	0.42	0.19	0.06	0.05	0.06	0.02

[a]Continuous analyte concentrations are log transformed; [b]Model adjusts for age (continuous) and total lipids (continuous)
[c]Model adjusts for age (continuous), total lipids (continuous), sex (male/female), systolic blood pressure (continuous), fasting blood glucose (continuous), body mass index (continuous), education (greater than high school, high school, or less than high school), ACE/ARB medication use (yes/no), and nativity subscore; [d]Statistically significant ($p<0.05$);

TABLE XXXIII.
CROSS-SECTIONAL ASSOCIATIONS BETWEEN CONTINUOUS CONCENTRATIONS AND RANKED QUARTILES OF PBDE AND PERSISTENT PESTICIDE ANALYTE CONCENTRATIONS AND BASELINE ODDS OF ALBUMINURIA AND THE CKD COMPOSITE AMONG STUDY PARTICIPANTS

	Albuminuria			**CKD**		
	% (95% CI)	**Model 1**	**Model 2**	**% (95% CI)**	**Model 1**	**Model 2**
		OR (95% CI)[b]	**OR (95% CI)[c]**		**OR (95% CI)[b]**	**OR (95% CI)[c]**
***Total PBDEs*[a]**		1.1 (0.70, 1.8)	1.1 (0.63, 1.8)		1.1 (0.71, 1.7)	1.1 (0.64, 1.8)
p-value (continuous)		0.61	0.77		0.67	0.80
Q1 (ref)	11.7 (2.5, 21.0)	ref	ref	14.1 (4.3, 23.9)	ref	ref
Q2	13.8 (7.8, 19.7)	1.2 (0.42, 3.3)	1.0 (0.39, 2.8)	16.3 (9.8, 22.9)	1.1 (0.42, 2.9)	0.90 (0.33, 2.4)
Q3	10.0 (4.9, 15.2)	0.84 (0.29, 2.4)	0.99 (0.39, 2.5)	10.6 (5.3, 15.8)	0.71 (0.26, 2.0)	0.78 (0.30, 2.1)
Q4	11.1 (6.1, 16.2)	0.93 (0.34, 2.6)	0.82 (0.31, 2.2)	12.8 (7.5, 18.2)	0.86 (0.34, 2.2)	0.71 (0.27, 1.9)
p for trend	0.88	0.73	0.67	0.71	0.55	0.45
β-hexachlorocyclohexane[a]		1.0 (0.74, 1.3)	1.0 (0.78, 1.4)		0.91 (0.67, 1.2)	0.95 (0.72, 1.3)
p-value (continuous)		0.99	0.78		0.55	0.74
Q1 (ref)	10.4 (6.5, 14.2)	ref	ref	11.5 (7.3, 15.8)	ref	ref
Q2	13.1 (6.0, 20.1)	1.2 (0.52, 2.6)	1.1 (0.44, 2.5)	18.0 (9.4, 26.7)	1.3 (0.63, 2.9)	1.3 (0.58, 2.9)
Q3	9.6 (3.8, 15.5)	0.79 (0.38, 1.6)	0.73 (0.34, 1.6)	12.1 (5.6, 18.5)	0.77 (0.39, 1.5)	0.76 (0.36, 1.6)
Q4	13.5 (5.0, 22.1)	1.2 (0.46, 3.2)	1.3 (0.55, 3.1)	13.8 (5.2, 22.4)	0.97 (0.35, 2.6)	1.2 (0.52, 2.9)
p for trend	0.79	0.81	0.65	0.65	0.76	0.87
Hexachlorobenzene[a]		0.82 (0.61, 1.1)	0.87 (0.64, 1.2)		0.80 (0.61, 1.1)	0.85 (0.63, 1.1)
p-value (continuous)		0.21	0.37		0.12	0.26
Q1 (ref)	11.5 (6.1, 16.9)	ref	ref	11.5 (6.1, 16.9)	ref	ref
Q2	10.8 (5.4, 16.3)	0.94 (0.41, 2.1)	1.2 (0.48, 3.1)	12.8 (7.1, 18.6)	1.1 (0.51, 2.5)	1.5 (0.61, 3.7)
Q3	15.5 (5.9, 25.1)	1.4 (0.53, 3.8)	1.6 (0.60, 4.6)	19.9 (9.9, 30.0)	1.9 (0.75, 4.6)	2.2 (0.83, 6.0)
Q4	8.0 (4.6, 11.3)	0.65 (0.32, 1.3)	0.83 (0.37, 1.8)	8.3 (4.9, 11.7)	0.65 (0.32, 1.3)	0.85 (0.37, 1.9)
p for trend	0.91	0.63	0.94	0.10	0.78	0.78

[a]Continuous analyte concentrations are log transformed; [b]Model adjusts for age and total lipids; [c]Model adjusts for age, total lipids, sex, systolic blood pressure, fasting blood glucose, body mass index, education, ACE/ARB medication use, and nativity subscore.
[d]Statistically significant ($p<0.05$);

TABLE XXXIII (continued).
CROSS-SECTIONAL ASSOCIATIONS BETWEEN CONTINUOUS CONCENTRATIONS AND RANKED QUARTILES OF PBDE AND PERSISTENT PESTICIDE ANALYTE CONCENTRATIONS AND BASELINE ODDS OF ALBUMINURIA AND THE CKD COMPOSITE AMONG STUDY PARTICIPANTS

	Albuminuria			**CKD**		
	% (95% CI)	**Model 1**	**Model 2**	**% (95% CI)**	**Model 1**	**Model 2**
		OR (95% CI)[b]	**OR (95% CI)[c]**		**OR (95% CI)[b]**	**OR (95% CI)[c]**
Mirex[a]		0.99 (0.65, 1.5)	1.0 (0.65, 1.6)		0.94 (0.62, 1.4)	1.0 (0.64, 1.5)
p-value (continuous)		0.95	0.94		0.76	0.99
Oxychlordane[a]		1.0 (0.42, 1.6)	0.82 (0.40, 1.7)		0.96 (0.51, 1.8)	1.0 (0.49, 2.1)
p-value (continuous)		0.52	0.87		0.89	0.97
Q1 (ref)	14.2 (4.1, 24.2)	ref	ref	14.3 (4.3, 24.4)	ref	ref
Q2	8.3 (4.1, 12.4)	0.49 (0.18, 1.4)	0.51 (0.18, 1.4)	8.6 (4.4, 12.8)	0.48 (0.17, 1.3)	0.46 (0.16, 1.3)
Q3	12.3 (5.8, 18.9)	0.72 (0.26, 1.9)	0.74 (0.28, 1.9)	13.5 (6.8, 20.2)	0.70 (0.26, 1.9)	0.67 (0.25, 1.8)
Q4	11.6 (6.5, 16.6)	0.55 (0.20, 1.6)	0.54 (0.18, 1.6)	16.5 (10.0, 23.1)	0.66 (0.25, 1.7)	0.61 (0.21, 1.8)
p for trend	0.72	0.38	0.35	0.50	0.58	0.50
p,p'-DDE[a]		0.70 (0.57, 0.86)	0.66 (0.51, 0.86)		0.67 (0.54, 0.82)	0.62 (0.48, 0.82)
p-value (continuous)		0.001	0.002		0.0002	0.0006
Q1 (ref)	17.0 (10.5, 23.5)	ref	ref	20.8 (13.1, 28.6)	ref	ref
Q2	12.8 (2.2, 23.5)	0.69 (0.23, 2.1)	0.63 (0.25, 1.5)	13.6 (3.0, 24.2)	0.56 (0.18, 1.7)	0.55 (0.22, 1.4)
Q3	11.8 (5.9, 17.8)	0.61 (0.28, 1.3)	0.56 (0.23, 1.4)	14.0 (7.6, 20.3)	0.52 (0.25, 1.1)	0.51 (0.20, 1.3)
Q4	6.0 (3.1, 9.0)	0.27 (0.13, 0.56)[d]	0.19 (0.07, 0.53)[d]	6.8 (3.7, 10.0)	0.20 (0.09, 0.43)[d]	0.17 (0.06, 0.46)[d]
p for trend	0.20	0.001	0.01	0.09	0.0002	0.004

[a]Continuous analyte concentrations are log transformed; [b]Model adjusts for age and total lipids; [c]Model adjusts for age, total lipids, sex, systolic blood pressure, fasting blood glucose, body mass index, education, ACE/ARB medication use, and nativity subscore.
[d]Statistically significant ($p<0.05$);

TABLE XXXIII (continued).
CROSS-SECTIONAL ASSOCIATIONS BETWEEN CONTINUOUS CONCENTRATIONS AND RANKED QUARTILES OF PBDE AND PERSISTENT PESTICIDE ANALYTE CONCENTRATIONS AND BASELINE ODDS OF ALBUMINURIA AND THE CKD COMPOSITE AMONG STUDY PARTICIPANTS

	Albuminuria			CKD		
	% (95% CI)	Model 1	Model 2	% (95% CI)	Model 1	Model 2
		OR (95% CI)[b]	OR (95% CI)[c]		OR (95% CI)[b]	OR (95% CI)[c]
Total DDE and DDT[a]		0.61 (0.46, 0.81)	0.57 (0.40, 0.82)		0.57 (0.43, 0.76)	0.53 (0.37, 0.77)
p-value (continuous)		0.001	0.002		0.0001	0.0007
Q1 (ref)	17.2 (10.7, 23.7)	ref	ref	21.1 (13.2, 28.9)	ref	ref
Q2	12.7 (2.1, 23.4)	0.68 (0.22, 2.1)	0.62 (0.25, 1.5)	13.5 (2.9, 24.1)	0.54 (0.18, 1.6)	0.54 (0.22, 1.3)
Q3	11.6 (5.8, 17.5)	0.59 (0.27, 1.2)	0.56 (0.22, 1.4)	13.7 (7.4, 20.0)	0.51 (0.24, 1.1)	0.50 (0.19, 1.3)
Q4	6.1 (3.2, 9.1)	0.27 (0.13, 0.56)[d]	0.19 (0.07, 0.53)[d]	6.9 (3.7, 10.1)	0.20 (0.09, 0.43)[d]	0.17 (0.06, 0.46)[d]
p for trend	0.20	0.001	0.01	0.08	0.0002	0.004
***trans*-Nonachlor[a]**		0.86 (0.49, 1.5)	0.88 (0.50, 1.5)		0.95 (0.57, 1.6)	1.0 (0.58, 1.8)
p-value (continuous)		0.58	0.67		0.84	0.96
Q1 (ref)	15.4 (4.4, 26.3)	ref	ref	15.4 (4.4, 26.3)	ref	ref
Q2	8.0 (4.1, 11.8)	0.45 (0.16, 1.2)	0.38 (0.13, 1.1)	8.8 (4.9, 12.7)	0.46 (0.17, 1.2)	0.37 (0.13, 1.1)
Q3	8.1 (3.1, 13.2)	0.43 (0.14, 1.3)	0.44 (0.15, 1.3)	10.1 (4.5, 15.7)	0.47 (0.16, 1.4)	0.44 (0.15, 1.3)
Q4	14.4 (8.6, 20.3)	0.70 (0.25, 1.9)	0.79 (0.29, 2.1)	18.1 (11.3, 25.0)	0.67 (0.25, 1.8)	0.73 (0.27, 2.0)
p for trend	0.30	0.56	0.79	0.22	0.56	0.75

[a]Continuous analyte concentrations are log transformed; [b]Model adjusts for age and total lipids; [c]Model adjusts for age, total lipids, sex, systolic blood pressure, fasting blood glucose, body mass index, education, ACE/ARB medication use, and nativity subscore.
[d]Statistically significant ($p<0.05$);

TABLE XXXIV.
CHANGE IN CHARACTERISTICS FROM VISIT 1 TO VISIT 2 AMONG ANCILLARY STUDY PARTICIPANTS

Characteristic	**Visit 1**	**Visit 2**
	N (weighted %)	**N (weighted %)**
Income <$40,000 (annually), %	191 (17.3%)	268 (24.8%)
Have health insurance, %	519 (48.0%)	862 (82.1%)
Current cigarette use, %	218 (20.1%)	183 (17.6%)
Hypertension (BP>=140/90 and Med Use)**, %**	316 (35.9%)	484 (51.2%)
Waist to hip ratio[a]	0.92 (0.91, 0.93)	0.93 (0.92, 0.94)
Obese (BMI 30+), %	395 (36.1%)	423 (37.8%)
Diabetes, %	--	89 (5.4%)
Prediabetes, %	427 (54.9%)	650 (65.8%)
Normal glucose (no diabetes), %	645 (45.1%)	333 (28.8%)
Total cholesterol (mg/dl)[a]	210 (207, 214)	198 (195, 202)
Triglycerides (mg/dl) (geometric mean)	118 (113, 123)	106 (101, 111)
eGFR (ml/min per 1.73 m^2**)**[a]	94.1 (92.5, 95.6)	89.8 (88.2, 91.4)
UACR (mg/g) (geometric mean)	8.5 (7.3, 9.8)	5.4 (4.6, 6.2)
Low eGFR[b]	22 (3.4%)	55 (7.1%)
Albuminuria	103 (11.7%)	110 (11.5%)
CKD	114 (13.5%)	137 (15.2%)

[a]For continuous variables, weighted mean (95% confidence interval) values are presented

[b]Low eGFR was defined as <60 at visit 1 and at visit 2 <60 w/ decline ≥1 ml/min per 1.73 m^2 per year of follow –up

TABLE XXXV.
PROSPECTIVE ASSOCIATIONS BETWEEN CONTINUOUS CONCENTRATIONS AND RANKED QUARTILES OF PCB ANALYTE CONCENTRATIONS AT BASELINE AND EGFR AND UACR LEVELS AT VISIT 2 (OVER SIX YEAR FOLLOW-UP) AMONG HCHS/SOL ANCILLARY STUDY PARTICIPANTS

	Continuous eGFR (mL/minute/1.73m^2) at Visit 2			
	Model 1 β (95% CI)[b]	p-value	**Model 2 β (95% CI)[c]**	p-value
Total PCBs[a]	-0.38 (-1.7, 1.0)	0.58	0.06 (-1.4, 1.5)	0.94
Total Estrogenic PCBs[a]	-0.76 (-1.8, 0.32)	0.17	-0.41 (-1.6, 0.78)	0.50
Total Anti-Estrogenic PCBs[a]	-0.14 (-1.5, 1.2)	0.84	0.27 (-1.2, 1.8)	0.72
Wolff Group 3 CYP1A/2B PCBs[a]	-0.35 (-1.6, 0.87)	0.57	0.06 (-1.2, 1.3)	0.92
Warner CYP1A PCBs[a]	-0.03 (-1.4, 1.4)	0.96	0.28 (-1.3, 1.9)	0.73
Warner mixed PCBs[a]	-0.41 (-1.7, 0.94)	0.55	0.02 (-1.4, 1.5)	0.98
Warner CYP2B PCBs[a]	-0.50 (-1.7, 0.71)	0.42	-0.10 (-1.3, 1.1)	0.87
	Continuous log UACR (mg/g) at Visit 2			
	Model 1 β (95% CI)[d]	p-value	**Model 2 β (95% CI)[e]**	p-value
Total PCBs[a]	0.14 (-0.01, 0.30)	0.06	0.14 (-0.01, 0.29)	0.06
Total Estrogenic PCBs[a]	0.15 (0.04, 0.27)	0.009	0.14 (0.03, 0.26)	0.01
Total Anti-Estrogenic PCBs[a]	0.10 (-0.05, 0.25)	0.17	0.11 (-0.04, 0.25)	0.17
Wolff Group 3 CYP1A/2B PCBs[a]	0.13 (0.003, 0.26)	0.04	0.13 (0.001, 0.25)	0.05
Warner CYP1A PCBs[a]	0.05 (-0.11, 0.21)	0.55	0.05 (-0.11, 0.22)	0.53
Warner mixed PCBs[a]	0.11 (-0.02, 0.27)	0.10	0.12 (-0.02, 0.26)	0.10
Warner CYP2B PCBs[a]	0.14 (0.01, 0.27)	0.03	0.14 (-0.01, 0.26)	0.04

[a] Continuous concentrations modeled after log transformation
[b] Adjusted for eGFR at visit 1, time from Visit 1 to Visit 2, age, and lipids
[c] Adjusted for eGFR at visit 1, time from Visit 1 to Visit 2, age (continuous, years), self-reported ethnicity/background, sex (male/female), systolic blood pressure (at visit 1), fasting blood glucose (at visit 1), and difference in triglyerides from visit 1 to visit 2
[d] Adjusted for UACR at visit 1, time from Visit 1 to Visit 2, age, and lipids
[e] Adjusted for UACR at visit 1, time from Visit 1 to Visit 2, age (continuous, years), self-reported ethnicity/background, sex (male/female), systolic blood pressure (at visit 1), fasting blood glucose (at visit 1), and difference in triglyerides from visit 1 to visit 2

TABLE XXXVI.
PROSPECTIVE ASSOCIATIONS BETWEEN CONTINUOUS CONCENTRATIONS AND RANKED QUARTILES OF PBDE AND PERSISTENT PESTICIDE ANALYTE CONCENTRATIONS AT BASELINE AND EGFR AND UACR LEVELS AT VISIT 2 (OVER SIX YEAR FOLLOW-UP) AMONG HCHS/SOL ANCILLARY STUDY PARTICIPANTS

	Continuous eGFR (mL/minute/1.73m^2) at Visit 2			
	Model 1 β (95% CI)[b]	p-value	**Model 2 β (95% CI)[c]**	p-value
Total PBDEs[a]	-1.5 (-2.7, -0.25)	0.02	-1.5 (-2.8, -0.26)	0.02
Pesticides:				
β-hexachlorocyclohexane[a]	0.17 (-0.62, 0.96)	0.67	0.09 (-0.74, 0.92)	0.83
Hexachlorobenzene[a]	0.50 (-0.45, 1.4)	0.30	0.72 (-0.55, 2.0)	0.27
Mirex[a]	0.99 (-0.41, 2.4)	0.16	0.82 (-0.57, 2.2)	0.25
Oxychlordane[a]	-0.07 (-1.6, 1.4)	0.93	-0.48 (-2.2, 1.3)	0.59
p,p'-DDE[a]	0.47 (-0.26, 1.2)	0.21	0.31 (-0.61, 1.2)	0.51
Total DDE and DDT[a]	0.66 (-0.20, 1.5)	0.13	0.46 (-0.63, 1.5)	0.41
***trans*-Nonachlor[a]**	-0.01 (-1.3, 1.3)	0.98	-0.22 (-1.6, 1.2)	0.76
	Continuous log UACR (mg/g) at Visit 2			
	Model 1 β (95% CI)[d]	p-value	**Model 2 β (95% CI)[e]**	p-value
Total PBDEs[a]	0.04 (-0.14, 0.22)	0.63	0.05 (-0.13, 0.23)	0.59
Pesticides:				
β-hexachlorocyclohexane[a]	-0.04 (-0.11, 0.02)	0.17	-0.02 (-0.10, 0.05)	0.49
Hexachlorobenzene[a]	-0.05 (-0.12, 0.03)	0.22	-0.02 (-0.11, 0.07)	0.64
Mirex[a]	-0.001 (-0.11, 0.11)	0.99	0.03 (-0.09, 0.14)	0.65
Oxychlordane[a]	-0.08 (-0.21, 0.05)	0.22	-0.06 (-0.20, 0.07)	0.37
p,p'-DDE[a]	-0.09 (-0.15, -0.03)	0.003	-0.08 (-0.15, -0.01)	0.02
Total DDE and DDT[a]	-0.12 (-0.19, -0.04)	0.002	-0.11 (-0.20, -0.02)	0.01
***trans*-Nonachlor[a]**	-0.06 (-0.18, 0.07)	0.38	-0.04 (-0.18, 0.09)	0.52

[a] Continuous concentrations modeled after log transformation
[b] Adjusted for eGFR at visit 1, time from Visit 1 to Visit 2, age, and lipids
[c] Adjusted for eGFR at visit 1, time from Visit 1 to Visit 2, age (continuous, years), self-reported ethnicity/background, sex (male/female), systolic blood pressure (at visit 1), fasting blood glucose (at visit 1), and difference in triglycerides from visit 1 to visit 2
[d] Adjusted for UACR at visit 1, time from Visit 1 to Visit 2, age, and lipids
[e] Adjusted for UACR at visit 1, time from Visit 1 to Visit 2, age (continuous, years), self-reported ethnicity/background, sex (male/female), systolic blood pressure (at visit 1), fasting blood glucose (at visit 1), and difference in triglycerides from visit 1 to visit 2

TABLE XXXVII.
WEIGHTED PREVALENCE AND ODDS OF INCIDENT ALBUMINURIA AND CKD COMPOSITE BY BASELINE CONTINUOUS CONCENTRATIONS OF PCB, PBB, PBDE, AND PERSISTENT PESTICIDE ANALYTE CONCENTRATIONS AMONG HCHS/SOL ANCILLARY STUDY PARTICIPANTS

	Incident Albuminuria		Incident CKD	
	Model 1 OR (95% CI)[a]	**p-value**	**Model 1 OR (95% CI)[a]**	**p-value**
Total PCBs[a]	1.5 (0.86, 2.6)	0.15	1.2 (0.72, 2.1)	0.45
Total Estrogenic PCBs[a]	1.4 (0.91, 2.1)	0.12	1.1 (0.74, 1.7)	0.61
Total Anti-Estrogenic PCBs[a]	1.5 0.82, 2.9)	0.17	1.4 (0.79, 2.4)	0.26
Wolf Group 3 CYP1A/2B PCBs[a]	1.4 (0.86, 2.3)	0.17	1.1 (0.72, 1.8)	0.56
Warner CYP1A PCBs[a]	1.6 (0.87, 3.0)	0.13	1.4 (0.82, 2.5)	0.20
Warner mixed PCBs[a]	1.5 (0.78, 2.8)	0.22	1.2 (0.72, 2.2)	0.43
Warner CYP2B PCBs[a]	1.4 (0.88, 2.3)	0.15	1.1 (0.72, 1.8)	0.58
***Total PBDEs*[a]**	1.1 (0.64, 1.9)	0.72	0.99 (0.62, 1.6)	0.98
β-hexachlorocyclohexane[a]	1.0 (0.66, 1.5)	0.99	1.1 (0.83, 1.5)	0.44
Hexachlorobenzene[a]	0.91 (0.51, 1.6)	0.76	1.0 (0.71, 1.5)	0.89
Mirex[a]	0.66 (0.36, 1.2)	0.18	0.75 (0.43, 1.3)	0.31
Oxychlordane[a]	1.3 (0.83, 2.2)	0.22	1.3 (0.83, 2.1)	0.25
p,p'-DDE[a]	0.86 (0.63, 1.2)	0.34	0.92 (0.70, 1.2)	0.51
Total DDE and DDT[a]	0.82 (0.54, 1.2)	0.36	0.89 (0.63, 1.2)	0.51
***trans*-Nonachlor[a]**	1.4 (0.91, 2.2)	0.12	1.3 (0.84, 1.9)	0.25

[a] Adjusted for age (continuous, years) and total lipids (continuous)

D. Discussion

In this study, we examined the associations between multiple persistent pollutants and kidney parameters in a relatively healthy subsample of Hispanic/Latino participants from the Hispanic Community Healthy Study/Study of Latinos. Among the 43 different chemical analytes measured from serum samples provided by the participants at their initial study visit, very few participants had non-reportable levels.

In our cross-sectional analyses, we didn't observe any associations with continuous eGFR or UACR, nor did we observe effect modification by sex. Very few participants had low eGFR, a clinically relevant cut-point for eGFR, but a substantive proportion had albuminuria which is also a clinically relevant endpoint for kidney disease. When we evaluated the associations between the analyte concentrations and albuminuria at baseline, total PCBs, total estrogenic PCBs, CYP1A, and CYP2B inducing PCBs were positively associated with odds of albuminuria and CKD composite. Although we did not observe associations between PCBs in our longitudinal analyses of eGFR, we did observe positive associations between total PCBs, total estrogenic PCBs, and the Wolff group 3 CYP1A/2B, and Warner CYP2B PCBs with UACR at visit 2. There has been one small longitudinal study of 149 participants that assessed concentrations of select PCB congeners with risk of ESRD in patients with diabetes, which found levels of non-dioxin-like PCBs (PCB 28, PCB 49, PCB 44) to be associated with as much as 75% higher risk of ESRD (Grice et al. 2017). The clinical definition of ESRD uses eGFR to determine disease status and may not be the most suitable comparison to our study, but few other studies have investigated these associations. Additionally, a small study of Chinese residents who were exposed to PCBs and PBDEs

from a nearby electronic waste facility found a positive association between total PCBs and serum creatinine (Xu et al. 2015). Although serum creatinine is related to estimated GFR, this study shows that PCBs may be related to worse kidney function in humans.

The mechanisms of action by which PCBs may exert action in the kidney have not been well elucidated. Multiple mechanisms may be involved in PCB-induced renal health effects, including Ah-receptor dependent mechanisms and receptor independent mechanisms. PCBs can exert both estrogenic and anti-estrogen responses, and specific congeners may compete for binding to the estrogen receptor. PCBs have been reported to have a wide range of effects on steroid hormone function and synthesis, and PCBs can also disrupt thyroid hormone homeostasis. It has been suggested that PCBs can disrupt the production of thyroid hormones, interfere with thyroid hormone transport, and increase the rate of metabolic clearance of the thyroid hormones. More recently, a study using cells found that PCB 77 exposure resulted in renal tubular cell apoptosis, indicating that the renal toxicity of PCBs may be related to cellular apoptosis (Su et al. 2015). The model proposed for cellular uptake and transport of PCBs following oral exposure suggests that PCBs released into the bloodstream associate with HDL and plasma proteins like albumin (Borlakoglu and Walker 1989). In our study we observed positive associations with UACR at visit 2, and with albuminuria at baseline. Although speculative, it may be warranted to consider if higher levels of PCBs are associated with increased UACR and albuminuria due to the physiological response of the body trying to clear albumin-bound PCBs from the body.

When we assessed associations with the measured persistent pesticides, we observed an inverse association between both the total sum of DDT and DDT

metabolites and DDE with odds of albuminuria. A prior study using the 1999-2004 NHANES evaluated the association between pp-DDT and pp-DDE and diabetes with UACR > 30 mg/g in a subsample of Mexican American NHANES participants (Everett, Thompson, and Dismuke 2017). Using the lipid adjusted analyte concentrations, they found that p,p'-DDT levels above 14.5 ng/g lipid-adjusted compared to levels less than or equal to 14.5 ng/g lipid-adjusted were associated with increased odds of diabetes with concurrent UACR >30 mg/g (OR= 3.18, 95% CI 1.59, 6.36) (Everett, Thompson, and Dismuke 2017). In this same study, levels of p,p'-DDE in the third quartile (≥ 1195.1 ng/g lipid-adjusted) relative to the first quartile were associated with higher odds of diabetes with UACR >30 mg/g (OR= 14.69, 95% CI 2.94-73.29). This study was based on data from 52 participants with diabetes and concurrent UACR > 30 mg/g and compared odds of diabetes with UACR > 30 mg/g to those without diabetes and with UACR < 30 mg/g. Given that the main endpoint in this study was driven by diabetes status, the resulting associations from this study may not be a good comparison to our study of adults who did not have diabetes at baseline. In our study, DDT and DDE concentrations at high levels appeared to be associated with lower odds of albuminuria. In our unpublished analyses of NHANES data examining these associations in a representative sample of U.S. adults, estimated associations between DDE and albuminuria were null, but point estimates were indicative of an inverse association. There is currently no clear understanding of the pathophysiological mechanisms of renal effects associated with exposure to DDT or DDE. Very few epidemiologic studies exist that have evaluated this association. Animal studies of the effect of DDT and DDE on the kidney have been limited to studies of kidney weight and evaluation of histological

changes in the renal tissue, and have suggested that the kidney is not a sensitive target for histological changes via DDT and DDE exposure.

Exposure to DDT and DDT metabolites in vitro has been associations with increased inflammatory response and alterations in the complement system (Dutta et al. 2008). Given this, we would not expect to observe lower odds of albuminuria among those in the highest DDE quartile relative to those with the lowest concentration. Among males, DDT has been shown to have anti-androgenic effects in addition to being inversely associated with serum testosterone (Blanco-Munoz et al. 2012). High levels of testosterone have been suggested as being associated with worsening of existing CKD in males, suggesting that in early pre-disease states, DDT may interfere with the androgenic effects associated with CKD. Another explanation for the associations observed with DDT and kidney parameters in this study could be correlation between DDT level and another lifestyle factor that is protective of kidney function but not accounted for in this study.

When we modeled the associations between total PBDEs and eGFR at visit 2, we observed an inverse association when modeling both continuous total PBDEs and when total PBDEs were modeled as ranked quartiles (β Q4 vs. Q1 -2.3 (95% CI -5.0, 0.32), p=0.08, p for trend=0.06). In a small study of 40 residents living near an electronic waste facility in China and matched control residents living in a different area, the association between PBDEs and measured serum creatinine was investigated (Xu et al. 2015). Congener specific analyses of the measured PBDEs showed that PBDE 28, PBDE 47, PBDE 85, and PBDE 153 were positively correlated with urinary levels of

β2-microglobulin (a marker of kidney injury), and that PBDE 28 and PBDE 85 were positively correlated with serum creatinine levels.

This study has several strengths including a large sample of objectively measured analytes from stored serum samples of a well characterized cohort of Hispanic/Latino study participants. There was variation in the proportion below the limit of detection for each analyte, but we were able to substitute a value for each using the sample specific detection limit. This study also has several limitations. We limited our analyses to complete cases and only included participants who had analytic values for all of the 43 measured analytes. Future analyses to impute missing data on individual analytes is planned. Although the proportion of participants with albuminuria or the composite of albuminuria and/or low eGFR was similar to national averages for kidney disease, the absolute number of cases was small, which may have limited our ability to estimate associations with sufficient statistical power for these clinically relevant categorizations. At each study visit, one measurement was available to determine eGFR and UACR for each study participant. Diagnosis of kidney disease requires serial measurements over a period of a few months to determine disease status. Diabetes and hypertension status are well-known risk factors for chronic kidney disease, however, these parameters may be in the causal pathway between POPs exposure and kidney disease. In our analyses, we compared crude estimates of associations to adjusted estimates and used a forward approach to evaluate hypertension and fasting blood glucose (a diabetes related parameter) as potential confounders. We chose to present models adjusted for baseline hypertension status and fasting blood glucose.

Future analyses to investigate the mediating role of hypertension and/or diabetes in the association of POPs and kidney function may be warranted.

E. Conclusions

In conclusion, we conducted preliminary analysis to evaluate the associations between multiple persistent organic pollutants measured in serum with measures of kidney function. We demonstrated that circulating levels of PCBs concentrations may be associated with albuminuria and small increases in UACR. We also showed that concentrations of DDE may be associated with decreased odds of albuminuria and lower levels of UACR over time. Future analyses are planned to incorporate measures from a second batch of analyte measurements, which will double our sample size. After combining the data to include the full planned sample, multiple imputation methods may be useful to impute data for exposure concentrations that are missing for various analyte measures. This will allow us to have complete environmental pollutant data for all of the participants and prevent us from losing data when restricting to complete cases. This planned additional investigation into these exposures with both our cross-sectional and longitudinal endpoints is warranted to fully understand the impact, if any, of these pollutants on renal health.

VI. CONCENTRATIONS OF MULTIPLE BETWEEN PERSISTENT ORGANIC POLLUTANTS AND MEASURES OF KIDNEY HEALTH IN ADULTS: CROSS-SECTIONAL FINDINGS FROM THE 1999-2004 NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY

A. Rationale

There is well-established evidence that environmental exposures impact human health and well-being with low-level exposures possibly contributing to the development of endocrine disorders and/or impaired cardiorenal function in the general population. Persistent organic pollutants are synthetic compounds with the ability to persist in the environment and act as endocrine disruptors in the human body. This is done by mimicking, blocking, or interfering with the hormones the human body makes naturally (Diamanti-Kandarakis et al. 2009). Used heavily in the 20th century and later banned, POPs entered the environment as components of herbicides, pesticides, plastics, and electrical equipment. Common POPs include PCBs and organochlorine pesticides, many of which have long half-lives of at least 10-15 years (Tee et al. 2003, Ritter et al. 2011, Axmon and Rignell-Hydbom 2006).

Existing evidence from animal and human studies suggest POPs may be risk factors for CKD, which affects approximately 14.8% of the population (Saran et al. 2017). A study in the Artic fox found a higher prevalence of glomerular, tubular and interstitial renal lesions in animals fed a diet high in POPs relative to those on the control diet (Sonne et al. 2008). A study in rats showed that treatment with dioxins and PCBs resulted in increases in serum creatinine and injury to the kidney, with dioxins and

PCBs having a synergistic effect (Lu et al. 2009). The few studies that assessed the relationship between POPs and kidney function in humans were largely cross-sectional and focused on diabetic nephropathy with mixed results (Everett and Thompson 2016, 2015, Everett, Thompson, and Dismuke 2017). In one study using the 1999-2004 NHANES cycles, analyses restricted to Mexican American participants showed that p,p'-DDT levels above 0.086 ng/g compared to levels less than or equal to 0.086 ng/g were associated with increased odds of diabetes with concurrent UACR >30 mg/g (OR= 4.42, 95% CI 2.23-8.76) (Everett, Thompson, and Dismuke 2017). In this same study, levels of p,p'-DDE in the fourth quartile relative to the first quartile were associated with higher odds of diabetes with UACR >30 mg/g (OR= 14.95, 95% CI 2.96-75.48). This study did not examine other pesticides or associations with eGFR. Another study of the NHANES 1999-2004 cycles showed levels of heptachlor epoxide to be associated with odds of diabetes with UACR >30 mg/g (OR= 1.75, 95% CI 1.05-2.93) (Everett and Thompson 2015). This study did not examine associations with eGFR, nor use sex-specific cut points for UACR categorization.

Few studies have examined these associations among persons without diabetes. One cross-sectional study in a non-diabetic population suggested that exposure to POPs may be associated with kidney disease independent of diabetes status (Huang, Ding, et al. 2016). In a small (n=149) longitudinal study of patients with diabetes, exposure to non-dioxin-like PCBs (PCB 28, PCB 49, PCB 44) was associated with as much as 75% higher risk of end-stage renal disease (Grice et al. 2017). More recently, investigations into the origins of CKD in agricultural communities in Central and South America, and in Asia have shown inverse associations between pesticide exposures

and eGFR and positive association with urinary albumin levels among CKD patients (Siddarth et al. 2014, Siddharth et al. 2012, Ghosh et al. 2017).

Exposure to POPs as a risk factor for CKD is largely underexplored, particularly in the context of normal glucose parameters. Further study may provide evidence to support or reject the hypothesis that associations between POPs and kidney function are largely the result of reverse causation (Everett and Thompson 2014), an argument that has been made in response to associations seen among participants with diabetic nephropathy. Mechanistically, POPs and their metabolites may interfere with endocrine processes by affecting the hypothalamic-pituitary-gonadal (Diamanti-Kandarakis et al. 2009) and hypothalamo–pituitary–thyroid (Fisher et al. 2006, Khan et al. 2002) axes in the pathway to kidney disease, leading to disease development and/or progression.

To date, analyses of kidney function parameters using measures of POPs from NHANES have been limited. As such, the role of environmental PCB and pesticide exposures may be an underexplored topic for decreased kidney function among males and females living in the United States. To the best of our knowledge, no study has assessed the overall associations between different POPs and eGFR using NHANES data, nor have sex-specific analyses been conducted. Our aim was to use readily available data from the NHANES to investigate the associations between multiple PCB congeners and organochlorine pesticides and their metabolites and two measures of kidney function (eGFR and UACR) in a nationally representative sample of adults in the United States. We also evaluated sex as a potential modifier of these associations.

B. Methods

1. Study population

The NHANES is a national survey organized by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention using a complex sampling frame to attain a sample representative of the U.S. population. The NHANES study protocols are approved by the Institutional Review Board of the NCHS, and participants provided written informed consent. The NHANES utilizes interviews and physical examinations in a national sample of non-institutionalized people living in the U.S. This study combined the 1999-2004 cycles of NHANES to form the analytic data set. Multiple persistent pollutants including polychlorinated biphenyls, chlorinated pesticides and pesticide metabolites were measured in serum in male and female participants aged 12 years and older on a one-third subsample in each cycle.

2. Variable definitions

a. Exposure measurements

During the 1999-2004 cycles, different one-third subsamples of participants aged 12 years and older were selected for measurement of different classes of environmental contaminants (Table XXXVIII). In the 1999-2002 cycles, seven polychlorinated dibenzo-p-dioxins (PCDDs), 10 dibenzofurans (PCDFs), 4 non-ortho substituted or coplanar PCBs, 38 ortho-substituted PCBs, and 10 persistent chlorinated pesticides and selected pesticide metabolites were measured in the same subsample. In the 2001-2002 cycle, three persistent chlorinated pesticides were added to the panel of pesticides and selected pesticide metabolites (endrin, aldrin, and dieldrin); however

the pesticides were measured in a different subsample from the PCDDs, PCDFs, and PCBs in the 2003-2004 cycle. All contaminants were measured in serum by high-resolution gas chromatography/isotope dilution high-resolution mass spectrometry (HRGC/ID-HRMS) at the Centers for Disease Control and Prevention National Center for Environmental Health.

For analysis of the subsample with measures of PCDDs, PCDFs, and PCBs we excluded analytes that were not measured in all three cycles. For any sample below the limit of detection, we used the value of the limit of detection divided by the square root of two as substituted by NHANES. Since the number of participants with missing data varied for each analyte, we substituted zero for any analyte that was missing for a particular participant and then created summary measures of 1) total PCBs; 2) toxic equivalencies (Van den Berg et al. 2006); 3) estrogenic PCBs (Wolff et al. 1997); 4) anti-estrogenic PCBs (Wolff et al. 1997); 5) CYP1A inducer/substrate PCBs (Warner et al. 2012), 6) CypIIB inducer PCBs (Warner et al. 2012), and 7) mixed CypIA/CypIIB inducing PCBs (Warner et al. 2012).

For analysis of the subsample with measures pesticides, we used data from nine pesticides and pesticide metabolites that were detectable in ≥30% of the samples. This included lipid adjusted concentrations (ng/g lipid) of: β-hexachlorocyclohexane (ng/g), HCB (ng/g), heptachlor epoxide (ng/g), oxychlordane (ng/g), p,p'-DDE (ng/g), p,p'-DDT (ng/g), *trans*-nonachlor (ng/g), dieldrin (ng/g) and mirex (ng/g). We applied a correction factor of 0.644 to the β-hexachlorocyclohexane concentrations for the 1999-2000 cycle as advised by NHANES, and used the value of the limit of detection divided by the square root of two as substituted by NHANES for any nondetectable levels.

b. Outcome measurements

We assessed kidney function by calculating the eGFR using participant measures of serum creatinine, age, race, and sex and applying the CKD-EPI glomerular filtration rate equation (Levey et al. 2009). In the 1999-2000 cycle, serum creatinine concentration was determined using the Jaffé reaction and the 1999 Hitachi Model 917 Multichannel Analyzer. Per the recommendation in NHANES data documentation, the creatinine values for the 1999-2000 cycle were corrected using the Deming regression. In the 2001-2004 cycles, creatinine was measured using the Jaffé rate method (kinetic alkaline picrate) with the Beckman Synchron LX20. Quality control methods did not indicate a need for correction for serum creatinine concentrations measured during NHANES 2001-2004 cycles. Since this study was based on single, not serial, creatinine measurements, we defined an eGFR less than 60 mL/min per 1.73 m^2 as low eGFR, not as CKD, when using eGFR as a dichotomous outcome.

We also calculated the UACR (urine albumin concentration in mg/dL divided by urine creatinine concentration in g/dL) using random spot urine samples collected at the time of examination. Urinary creatinine was measured using the Jaffé rate reaction and urinary albumin was measured using a solid-phase fluorescent immunoassay (Chavers, Simonson, and Michael 1984). We defined albuminuria using sex-specific cutoffs (urine albumin/creatinine ratio ≥17 mg/g in males and ≥25 mg/g in females) (Mattix et al. 2002).

c. Covariates

Each participant was interviewed to collect information on age (continuous; years), sex (male/female), education level (less than high school, high school graduate, some college, or college graduate/additional education beyond college), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, or other) and smoking behaviors. Cigarette smoking status was captured as never, former, infrequent, or daily smoking. For former smokers, we dichotomized time elapsed since quitting was as less than/equal to or greater than five years. Height and weight were measured, and BMI was calculated by dividing weight in kilograms by height in meters squared. Body mass index was used as a continuous variable and categorized into normal (BMI <25), overweight (BMI 25-29), or obese (BMI ≥30) for descriptive purposes. Total cholesterol (mg/dL) and triglycerides (mg/dL) were analyzed with a Hitachi Model 704 multichannel analyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN). Total lipids were calculated using the formula: total lipid = [total cholesterol (mg/dL) × 2.27] + triglycerides (mg/dL) + 62.3 (Phillips et al. 1989). Hypertension (yes/no) was defined using self-reported diagnosis by a physician, or any antihypertensive medication use (angiotensin converting enzyme inhibitors, angiotensin II inhibitors, renin inhibitors, beta-adrenergic blocking agents, calcium channel blocking agents, diuretics, vasodilators or peripheral vasodilators), or a systolic blood pressure reading greater than or equal to 140 mmHg or a diastolic blood pressure reading greater than or equal to 90 mmHg. Diabetes status (non-diabetic or diabetic) was ascertained from self-reported questionnaire items, or any antidiabetic medication use (antidiabetic agents), or using the percentage of glycohemoglobin present in blood samples. Participants who did not self-report that they

had diabetes, but who had HbA1c values of 6.5 or greater were classified as having diabetes. HbA1c was measured using the A1c G7 HPLC Glycohemoglobin Analyzer.

3. Statistical analysis

All analyses utilized the special subsample weights, strata, and primary sampling units to account for the complex NHANES sampling design and nonresponse using SAS 9.4 (SAS Institute, Cary, NC) and STATA 13 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP.) survey procedures. Due to the chemical analytes being measured in different subsamples, we conducted analysis using two subsamples: 1) PCDDs, PCDFs, and PCBs in the 1999-2004 cycles and 2) organochlorine pesticides in the in the 1999-2004 cycles. For both sets of subsample analyses, we used the same analytic methodology. We excluded participants under 20 years old (n=2,719), using immunosuppression medications (n=3), pregnant women (n=365), and participants with missing data for the outcomes and select covariates (serum creatinine (n=313), urine albumin or creatinine (n=141), education level (n=7), country of birth (n=1), lipids (n=318)). Values for exclusions are not mutually exclusive, and the final analytic sample consisted of 3,851 observations of PCDDs, PCDFs, and PCBs. The final sample for pesticides was 3,134 observations after excluding participants under 20 years old (n=2,765), using immunosuppression medications (n=3), pregnant women (n=378), and participants with missing data for the outcomes and select covariates (serum creatinine (n=306), urine albumin or creatinine (n=132), education level (n=6), country of birth (n=2), lipids (n=310)).

We categorized each lipid-adjusted summary measure (PCDDs, PCDFs, and PCBs) or individual contaminant (pesticides) into quartiles based on the distribution in the sample. For all categorical analyses, the first exposure quartile was considered the referent group. The lipid adjusted analyte and UACR distributions were skewed, and the natural log transformation was applied. For descriptive purposes, we calculated weighted arithmetic means and 95% confidence intervals (95% CIs) for eGFR, and weighted geometric means and 95% CIs for the continuous skewed UACR and analyte concentrations, overall and by covariates. For dichotomous outcomes of low eGFR and albuminuria we calculated weighted proportions and 95% CIs overall and by covariates. Chi-Square and T-tests were used to evaluate if levels of each outcome or analyte differed by levels of covariate categories.

Linear regression models were built for continuous eGFR and log transformed UACR (dependent variables) and logistic regression models were built for the dichotomous outcomes of low eGFR and albuminuria. All models were constructed using a forward approach beginning with individual models of each lipid adjusted analyte concentration. We modeled each analyte concentration using quartiles to allow for non-linear dose responses, and as an ordinal variable to test for linear trend. We also explored models with continuous analyte concentration and tested the assumption of linearity by adding a quadratic term for each analyte to the model. When the quadratic term was statistically significant ($p<0.05$), the analyte was entered into the model after applying the natural log transformation. This was done to assess consistency between categorized and continuous exposure models. Models were initially adjusted for age (continuous), sex (male/female), race/ethnicity (non-Hispanic

white, non-Hispanic African-American, Hispanic, or other), hypertension status (yes/no), place of birth (US or non-US born), self-reported smoking history (never, 5+ years since last cigarette, <5 years since last cigarette, infrequent current smoker, daily smoker), education level (less than high school, high school grad, some college or more), total serum lipids (continuous), and survey year. Diabetes status was added to the adjusted model to assess change in estimate, and when estimates substantially changed, diabetes was retained in the model. Due to log transformation being applied to all the outcomes, we back transformed all estimates when presenting results to aid in interpretation.

Interaction terms between analyte concentrations and sex (male/female), variables were added to the model to assess if effect modification was present. Lower order terms were included in the model when interaction terms were added. We considered a p-value less than 0.05 statistically significant when interpreting interaction terms. For statistically significant interactions, we used stratified regression models to assess whether stratum specific estimates of associations were meaningful.

C. Results

1. Polychlorinated biphenyl subsample

Among the 3,851 participants in the PCDDs, PCDFs, and PCBs study sample, the average age was 46.2 years old (SD 0.37) and 50.3% were female. The average eGFR was 93.5 (SD 0.54), and the median UACR was 7.0 (IQR 4.6-13.0) [GM 7.5 (95% CI 7.1, 7.8)]. A majority (85.2%) reported being born in the United States, and 71.9% were non-Hispanic white. As shown in Table XXXIX, eGFR and UACR

varied by age, sex, and race. The average exposure concentrations for the indices of exposures across various demographic characteristics of the study sample are shown in Tables XL and XLI. Exposure concentrations were higher in older participants compared to younger participants, and levels differed by race, diabetes and hypertension status, and survey year.

In multivariable adjusted models, few meaningful associations were observed between indices of PCDD, PCDF, and PCB exposure and measures of kidney function. We observed positive associations between concentrations of total toxic equivalencies and most measures of PCBs with eGFR, but differences were small (Table XLII). Findings were consistent across categorizations of PCBs, indicating that increased concentrations of PCBs were associated with two to three mL/minute/1.73 m^2 higher average eGFR values among those in the highest exposure category relative to the lowest exposure category. This was particularly true for TEQs, total PCBs, total estrogenic PCBs, and all measures of anti-estrogenic and Warner groupings. No association was observed between any concentration measure and low eGFR.

Evaluation of effect modification by sex indicated a statistically significant interactions between sex and total PCBs (p-interaction=0.001), total estrogenic PCBs (p-interaction=0.01), total anti-estrogenic PCBs (p-interaction=0.0001), Group 2a anti-estrogenic PCBs (p-interaction=0.0008), Group 2b anti-estrogenic PCBs (p-interaction=0.0006), Group 3 CYP1A/2B PCBs (p-interaction=0.0006), CYP1A inducer/substrate PCBs (p-interaction=0.004), CYP2B inducer PCBs (p-interaction=0.002), and mixed CYP1A/CYP2B inducing PCBs (p-interaction=0.0002).

Sex-stratified estimates indicated a positive association between concentrations of these analyte groups and eGFR among males, and no association among females (Table XLIII). Other interactions between sex and TEQs (p-interaction=0.07), Group 1a estrogenic PCBs (p-interaction=0.41), Group 1b estrogenic PCBs (p-interaction=0.08) were marginally significant or non-significant. No association was observed between any concentration measure and low eGFR by sex (data not shown).

Few associations were observed between TEQs and categorizations of PCB analytes with UACR. There was a positive association between concentrations group 2A anti-estrogenic PCBs and UACR (GM Q4 8.5 (95% CI 7.5, 9.5) versus Q1 GM 7.2 (95% CI 6.6, 7.9), p=0.06) (Table XLII). This was not observed with total anti-estrogenic or group 2B anti-estrogenic PCBs. A similar positive association was observed with CYP1A PCBs and UACR. There was some evidence of effect modification by sex, and consistent with the findings with eGFR, associations appeared to be present among males and non-significant among females. Despite many significant interaction terms (TEQs (p-interaction=0.03), total PCBs (p-interaction=0.02), total estrogenic PCBs (p-interaction=0.02), Group 1a estrogenic PCBs (p-interaction=0.31), Group 1b estrogenic PCBs (p-interaction=0.07), total anti-estrogenic PCBs (p-interaction=<0.0001), Group 2a anti-estrogenic PCBs (p-interaction=<0.0001), Group 2b anti-estrogenic PCBs (p-interaction=<0.0001), Group 3 CYP1A/2B PCBs (p-interaction=<0.0001), CYP1A inducer/substrate PCBs (p-interaction=0.001), CYP2B inducer PCBs (p-interaction=0.03), and mixed CYP1A/CYP2B inducing PCBs (p-interaction=<0.0001), the magnitude of the associations among males did not appear to be very strong (Table XLIII).

Overall, no associations were observed between TEQs and categorizations of PCB analytes with albuminuria (Table XLII). When modeling the odds of albuminuria, we did observe statistically significant interactions between sex and TEQs (p-interaction=0.02), total anti-estrogenic PCBs (p-interaction=0.06), Group 2a anti-estrogenic PCBs (p-interaction=0.01), Group 2b anti-estrogenic PCBs (p-interaction=0.08), CYP1A inducer/substrate PCBs (p-interaction=0.03), and CYP2B inducer PCBs (p-interaction=0.06). Though not statistically significant, the pattern showed evidence of increased odds of albuminuria among males and no association among females (Table XLIV).

2. Pesticide subsample

Among the 3,134 participants in the pesticide study sample, the average age was 46.1 years old (SD 0.44) and 51.3% were female. The average eGFR was 93.3 (SD 0.66), and the median UACR was 5.8 (IQR 3.9-10.5) [GM 7.4 (95% CI 7.1, 7.8)]. A majority (85.4%) reported being born in the United States, and 72.7% were non-Hispanic white. As shown in Table XLV, eGFR and UACR varied by age, sex, and race. The average pesticide concentrations across various demographic characteristics of the pesticide sample are shown in Tables XLVI and XLVII. Exposure concentrations varied by age, sex, race/ethnicity, diabetes and hypertension status, and survey year.

When assessing the associations between pesticide concentrations and eGFR, p,p' DDE was positively associated with eGFR (p for trend 0.05) but the difference in eGFR by quartile of p,p' DDE was small and may not be clinically meaningful (Table XLVIII). There was a positive trend between dieldrin and eGFR, but none of the average

eGFR levels for the higher quartiles were statistically different from the average eGFR level among those in the first quartile. None of the other pesticide concentrations were associated with eGFR, nor did we observe meaningful evidence of effect modification by sex (data not shown). When evaluating the association between pesticide concentrations with low eGFR, we observed a positive association between concentrations of heptachlor epoxide (p for trend 0.006) and oxychlordane (p for trend 0.10).

Few associations were observed between pesticide concentrations with UACR, particularly after adjustment for diabetes status. Prior to adjustment for diabetes status, we observed a positive association between heptachlor epoxide and UACR (UACR Q4 GM 8.7 mg/g (95% CI 7.7, 9.8) vs. Q1 GM 7.2 mg/g (95% CI 6.7, 7.6), p-trend 0.03). However, after adding diabetes status to the model, p for trend was 0.36 and the geometric mean UACR values were similar among the quartiles of heptachlor epoxide concentration (Table XLVIII). In the fully adjusted model, we observed a slight inverse association between β-hexachlorocyclohexane and UACR (p for trend=0.05), but none of the quartile estimates were significantly different. There was some evidence that suggested positive associations with UACR among males in the highest concentration categories of β-hexachlorocyclohexane (p-interaction 0.06), oxychlordane (p=0.09), and trans-nonachlor, but these patterns lacked statistical significance after multivariable adjustment (data not shown). Similar to continuous UACR, few associations were observed with odds of albuminuria. Prior to adding diabetes status to the model, heptachlor epoxide was positively associated with increased odds of albuminuria (OR Q4 vs. Q1= 1.4 (95% CI 1.1, 1.8), p=0.03; p for trend=0.02), but the association did not

persist after adjustment for diabetes (OR Q4 vs. Q1= 1.1 (95% CI 0.81, 1.6), p=0.45; p for trend=0.28). There was no evidence of effect modification by diabetes for this association (p-interaction=0.37). No other pesticide concentrations were associated with odds of albuminuria, nor was there evidence of effect modification by sex.

TABLE XXXVIII.
SUMMARY OF DIFFERENT SUBSAMPLES OF MEASURED ANALYTES AMONG NHANES 1999-2004 PARTICIPANTS AGED 20 AND OVER, WITH MEASURES OF EGFR AND UACR.

	1999-2000 cycle	2001-2002 cycle	2003-2004 cycle
	subsample	**subsample**	**subsample**
Polychlorinated dibenzo-p-dioxins (PCDDs) (n=7)	Dioxins	Dioxins	C
1,2,3,7,8 Pentachlorodibenzo-p-dioxin (pncdd)			
1,2,3,4,7,8-Hexachlorodibenzo-p-dioxin (hxcdd)	Not measured		
1,2,3,6,7,8 Hexachlorodibenzo-p-dioxin (hxcdd2)			
1,2,3,7,8,9 Hexachlorodibenzo-p- dioxin (hxcdd3)			
1,2,3,4,6,7,8 Heptachlorodibenzo-p-dioxin (hpcdd)			
1,2,3,4,6,7,8,9 Octachlorodibenzo-p-dioxin (ocdd)			
2,3,7,8 Tetrachlorodibenzo-p-dioxin (tcdd)			
Polychlorinated dibenzofurans (PCDFs) (n=10)	Dioxins	Dioxins	C
2,3,7,8 Tetrachlorodibenzofuran (tcdf)			
1,2,3,7,8 Pentachlorodibenzofuran (pncdf)			
2,3,4,7,8 Pentachlorodibenzofuran (pncdf2)			
1,2,3,4,7,8 Hexachlorodibenzofuran (hcxdf)			
1,2,3,6,7,8 Hexachlorodibenzofuran (hcxdf2)			
1,2,3,7,8,9 Hexachlorodibenzofuran (hcxdf3)			
2,3,4,6,7,8 Hexachlorodibenzofuran (hcxdf4)			
1,2,3,4,6,7,8 Heptachlorodibenzofuran (hpcdf)			
1,2,3,4,7,8,9-Heptachlorodibenzofuran (hpcdf2)	Not measured		
1,2,3,4,6,7,8,9 Octachlorodibenzofuran (ocdf)			
Polychlorinated Biphenyls (PCBs) (n=38)	Dioxins	Dioxins	C
3,3',4,4',5,5' Hexachlorobiphenyl (HXCB) (PCB 169)			
3,3',4,4',5 Pentachlorobiphenyl (pncb) (PCB 126)			
3,4,4',5 Tetrachlorobiphenyl (TCB) (PCB 81)			
2,4,4'-Trichloro biphenyl (PCB 28) (ng/g)		Not measured	
2,2'3,5'-Tetrachloro biphenyl (PCB 44)	Not measured	Not measured	
2,2',4,5'-Tetrachloro biphenyl (PCB 49)	Not measured	Not measured	
2,2',5,5'-Tetrachloro biphenyl (PCB 52)			
2,3',4,4'-Tetrachloro biphenyl (PCB 66)			
2,4,4',5-Tetrachloro biphenyl (PCB 74)			
2,2',3,4,5'-Pentachloro biphenyl (PCB 87)	Not measured		
2,2',4,4',5-Pentachloro biphenyl (PCB 99)			
2,2',4,5,5'-Pentachloro biphenyl (PCB 101)			
2,3,3',4,4'-Pentachloro biphenyl (PCB 105)			
2,3,3',4',6-Pentachloro biphenyl (PCB 110)	Not measured		
2,3',4,4',5-Pentachloro biphenyl (PCB 118)			

TABLE XXXVIII (continued).
SUMMARY OF DIFFERENT SUBSAMPLES OF MEASURED ANALYTES AMONG NHANES 1999-2004 PARTICIPANTS AGED 20 AND OVER, WITH MEASURES OF EGFR AND UACR.

	1999-2000 cycle	2001-2002 cycle	2003-2004 cycle
	subsample	subsample	subsample
2,2',3,3',4,4'-Hexachloro biphenyl (PCB 128)			
2,2',3,4,4',5' and 2,3,3',4,4',6- Hexachloro biphenyl (PCB 138/158)			
2,2',3,4',5,5-Hexachloro biphenyl (PCB 146)			
2,2',3,4',5',6-Hexachloro biphenyl (PCB 149)	Not measured		
2,2',3,5,5',6-Hexachloro biphenyl (PCB 151)	Not measured		
2,2',4,4',5,5'-Hexachloro biphenyl (PCB 153)			
2,3,3',4,4',5-Hexachloro biphenyl (PCB 156)			
2,3,3',4,4',5'-Hexachloro biphenyl (PCB 157)			
2,3',4,4',5,5'-Hexachloro biphenyl (PCB 167)			
2,2',3,3',4,4',5-Heptachloro biphenyl (PCB 170)			
2,2',3,3',4,5,5'-Heptachloro biphenyl (PCB 172)			
2,2',3,3',4,5',6'-Heptachloro biphenyl (PCB 177)			
2,2,3,3',5',5',6-Heptachloro biphenyl (PCB 178)			
2,2',3,4,4',5,5'-Heptachloro biphenyl (PCB 180)			
2,2',3,4,4',5',6-Heptachloro biphenyl (PCB 183)			
2,2',3,4',5,5',6-Heptachloro biphenyl (PCB 187)			
2,3,3',4,4',5,5' –Heptachloro biphenyl (PCB 189)	Not measured		
2,2',3,3',4,4',5,5'-Octachloro biphenyl (PCB 194)	Not measured		
2,2'3,3',4,4',5,6-Octchloro biphenyl (PCB 195)	Not measured		
2,2',3,3,4,4',5,6'- and 2,2',3,4,4',5,5'6-Octachloro biphenyl (PCB 196/203)	Not measured		
2,2',3,3',4,5,5',6'-Octachloro biphenyl (PCB 199)	Not measured		
2,2',3,3',4,4',5,5,6'-Nonachloro biphenyl (PCB 206)	Not measured		
2,2',3,3',4,4',5,5',6,6'-Decachloro biphenyl (PCB 209)	Not measured	Not measured	
Persistent Pesticides and Metabolites (n=13)	Dioxins	Dioxins	B
β-hexachlorocyclohexane			
Gamma-hexachlorocyclohexane			
Hexachlorobenzene			
Heptachlor epoxide			
Oxychlordane			
o,p'-DDT			
p,p'-DDT			
p,p'-DDE			
trans-Nonachlor			
Mirex			
Aldrin	Not Measured		
Dieldrin	Not Measured		
Endrin	Not Measured		

TABLE XXXIX.
OVERALL WEIGHTED DEMOGRAPHIC AND CLINICAL CHARACTERISTICS WITH DISTRIBUTIONS OF EACH OUTCOME BY LEVELS OF COVARIATES AMONG NHANES 1999-2004 PARTICIPANTS IN THE PCDD, PCDF, AND PCB SUBSAMPLE

	Overall	Continuous eGFR (mL/minute/1.73 m²)[a]		Low eGFR (eGFR < 60)		Urine Albumin to Creatinine Ratio (mg/g)[a]		Albuminuria (UACR ≥ 17/25 males and females mg/g)	
	n (%)	Mean (95% CI)[a]	p-value	% (95% CI)	p-value	GM (95% CI)[a]	p-value	% (95% CI)	p-value
Overall		93.5 (92.6, 94.3)		381 (6.3)		7.5 (7.1, 7.8)		662 (13.0)	
Age in years, 20-39	1278 (38.9)	107.2 (105.9, 108.5)	<0.0001	0.21 (0.0, 0.56)		6.1 (5.7, 6.4)	<0.0001	7.9 (5.9, 9.9)	
40-59	1185 (38.5)	92.4 (91.3, 93.5)	<0.0001	2.0 (1.1, 2.9)		6.9 (6.3, 7.4)	<0.0001	10.6 (8.4, 12.9)	
60+	1388 (22.6)	71.6 (70.4, 72.8)	ref	24.3 (21.0, 27.6)	<0.0001	12.5 (11.4, 13.7)	ref	25.9 (22.8, 28.9)	<0.0001
Sex, Male	1958 (49.7)	92.4 (91.6, 93.3)	ref	5.2 (4.1, 6.2)		6.7 (6.4, 7.1)	ref	13.9 (12.1, 15.8)	
Female	1893 (50.3)	94.5 (93.3, 95.7)	0.001	7.5 (6.0, 9.0)	0.006	8.3 (7.8, 8.9)	<0.0001	12.1 (10.0, 14.2)	0.12
Race/ethnicity		99.2 (97.7, 100.6)				8.5 (7.6, 9.6)			
African-American, nH	683 (10.1)	91.7 (90.6, 92.7)	<0.0001	5.6 (3.9, 7.3)		7.1 (6.7, 7.5)	0.006	15.8 (13.1, 18.5)	
White, nH	1985 (71.9)	98.4 (96.7, 100.1)	ref	7.3 (6.2, 8.4)		8.5 (7.7, 9.3)	ref	12.6 (10.5, 14.7)	
Hispanic	1032 (12.7)	95.0 (91.9, 98.1)	<0.0001	1.8 (0.9, 2.7)		8.7 (7.1, 10.8)	0.003	12.9 (10.1, 15.8)	
Other	151 (5.3)	96.2 (94.8, 97.5)	0.04	5.9 (2.0, 9.7)	<0.0001	8.5 (7.9, 9.2)	0.05	13.4 (6.1, 20.6)	0.53
Education, < High school	1237 (20.2)	94.0 (92.6, 95.5)	<0.0001	11.8 (9.7, 13.9)		7.5 (6.9, 8.2)	<0.0001	17.4 (14.7, 20.2)	
High school graduate	878 (24.7)	93.2 (91.8, 94.6)	0.001	5.7 (4.2, 7.2)		7.6 (7.0, 8.3)	0.001	13.4 (10.7, 16.1)	
Some college	1021 (30.4)	91.0 (89.5, 92.6)	0.02	4.9 (3.2, 6.6)		6.5 (6.1, 7.0)	0.003	12.5 (9.6, 15.4)	
≥ College graduate	715 (24.7)	92.6 (91.7, 93.5)	ref	4.2 (2.9, 5.5)	<0.0001	7.4 (7.0, 7.8)	ref	9.7 (7.3, 12.1)	0.0007
Born in the United States, Yes	2983 (85.2)	98.3 (97.1, 99.5)	<0.0001	6.8 (5.8, 7.8)		8.1 (7.5, 8.7)	0.04	12.8 (11.0, 14.7)	
No	868 (14.8)	93.9 (92.8, 95.1)		3.5 (2.2, 4.8)	<0.0001	7.8 (7.2, 8.4)		13.9 (10.9, 16.9)	0.56
Body mass index, kg/m², <25	1276 (36.3)	92.8 (91.4, 94.2)	0.69	5.0 (3.9, 6.2)		6.7 (6.2, 7.1)	0.30	11.7 (9.3, 14.0)	
25 to <30	1379 (34.2)	93.6 (92.3, 94.9)	0.37	7.2 (5.6, 8.9)		8.2 (7.6, 8.8)	0.0001	12.4 (9.9, 15.0)	
≥30	1196 (29.5)	92.2 (90.7, 93.7)	ref	6.9 (5.3, 8.5)	0.03	7.9 (7.2, 8.7)	ref	15.3 (12.7, 18.0)	0.07
High triglycerides ≥ 200 mg/dL	683 (17.6)	93.7 (92.8, 94.7)	0.05	9.9 (7.3, 12.5)		8.5 (7.5, 9.5)	0.02	17.1 (13.5, 20.6)	
<200 mg/dL	3168 (82.4)	93.4 (92.5, 94.3)		5.6 (4.7, 6.5)	0.0004	7.3 (6.9, 7.7)		12.1 (10.4, 13.9)	0.01
High total cholesterol ≥ 200 mg/dL	1942 (50.7)	93.5 (92.4, 94.7)	0.78	7.1 (5.6, 8.7)		7.1 (6.7, 7.5)	0.02	13.5 (11.3, 15.7)	
<200 mg/dL	1909 (49.3)	93.7 (91.2, 96.3)		5.5 (4.3, 6.7)	0.08	7.9 (7.4, 8.5)		12.5 (10.3, 14.6)	0.45
Diabetes	459 (8.1)	93.5 (92.6, 94.3)	0.85	15.7 (10.9, 20.4)		15.6 (12.6, 19.5)		37.5 (30.9, 44.1)	
Non-diabetic	3392 (91.9)	93.0 (91.8, 94.2)		5.5 (4.6, 6.4)	0.0001	7.0 (6.7, 7.3)	<0.0001	10.8 (9.3, 12.4)	<0.0001

[a] age-adjusted

TABLE XXXIX (continued).
OVERALL WEIGHTED DEMOGRAPHIC AND CLINICAL CHARACTERISTICS WITH DISTRIBUTIONS OF EACH OUTCOME BY LEVELS OF COVARIATES AMONG NHANES 1999-2004 PARTICIPANTS IN THE PCDD, PCDF, AND PCB SUBSAMPLE

	Overall	Continuous eGFR (mL/minute/1.73 m^2)[a]		Low eGFR (eGFR < 60)		Urine Albumin to Creatinine Ratio (mg/g)[a]		Albuminuria (UACR ≥ 17/25 males and females mg/g)	
	n (%)	Mean (95% CI)[a]	p-value	% (95% CI)	p-value	GM (95% CI)[a]	p-value	% (95% CI)	p-value
Hypertension	1717 (37.1)	93.7 (92.8, 94.7)	0.28	13.5 (11.4, 15.7)		8.9 (8.2, 9.7)		20.3 (17.3, 23.3)	
Non-hypertensive	2134 (62.9)	93.0 (91.9, 94.0)		2.1 (1.5, 2.7)	<0.0001	6.7 (6.4, 7.1)	<0.0001	8.7 (7.1, 10.2)	<0.0001
Smoking history, Never	1913 (49.4)	91.6 (90.3, 93.0)	0.0001	6.3 (4.9, 7.7)		7.5 (7.1, 8.0)	0.37	11.6 (9.5, 13.8)	
Former (5+ years)	850 (20.2)	94.1 (91.8, 96.4)	<0.0001	12.5 (10.2, 14.8)		6.9 (6.2, 7.8)	0.07	17.0 (13.4, 20.5)	
Former (<5 years)	211 (5.6)	95.4 (92.6, 98.2)	0.21	3.6 (0.7, 6.5)		8.0 (6.8, 9.4)	0.89	14.4 (8.4, 20.5)	
Current (infrequent)	158 (3.9)	95.9 (94.4, 97.3)	0.75	2.8 (0.3, 5.4)		6.8 (6.0, 7.8)	0.07	8.2 (3.4, 13.1)	
Current (daily)	717 (20.9)	95.3 (94.0, 96.6)	ref	1.7 (0.9, 2.60		7.9 (7.2, 8.7)	ref	12.9 (10.2, 15.7)	0.01
Cotinine ≥ 10 ng/ml	1009 (28.8)	92.8 (91.9, 93.7)		2.6 (1.7, 3.4)		7.8 (7.1, 8.5)		13.9 (11.5, 16.3)	
< 10 ng/ml	2817 (71.2)	99.2 (97.7, 100.6)	0.0001	7.9 (6.6, 9.2)	<0.0001	7.4 (7.0, 7.8)	0.28	12.8 (11.0, 14.5)	0.39
Total toxic equivalency (TEQ) (range), Q1 (0-0.009 ng/g lipid)	914 (25.6)	92.8 (91.2, 94.5)	ref	4.2 (2.7, 5.8)		7.4 (6.9, 7.9)	ref	10.4 (8.0, 12.8)	
Q2 (0.009-0.014 ng/g lipid)	979 (28.2)	92.8 (91.8, 93.8)	0.93	2.7 (1.7, 3.8)		6.9 (6.5, 7.5)	0.50	9.3 (6.9, 11.7)	
Q3 (0.015-0.02 ng/g lipid)	979 (26.0)	94.3 (93.1, 95.5)	0.15	4.6 (3.3, 5.8)		7.8 (7.1, 8.5)	0.87	13.3 (10.6, 16.0)	
Q4 (0.02-0.18 ng/g lipid)	979 (20.2)	94.2 (92.8, 95.6)	0.18	16.3 (13.4, 19.3)	<0.0001	8.0 (7.3, 8.8)	0.44	21.1 (17.6, 24.6)	<0.0001
Total PCBs (range), Q1 (0-131 ng/g lipid)	914 (25.1)	92.3 (90.8, 93.8)	ref	2.0 (0.8, 3.2)		7.8 (7.3, 8.4)	ref	10.6 (7.7, 13.5)	
Q2 (132-206 ng/g lipid)	979 (29.1)	92.9 (91.8, 94.1)	0.47	2.4 (1.4, 3.5)		7.1 (6.5, 7.8)	0.10	8.8 (5.9, 11.7)	
Q3 (207-339 ng/g lipid)	979 (25.9)	94.0 (92.8, 95.2)	0.07	6.5 (4.8, 8.3)		7.2 (6.5, 7.9)	0.15	13.8 (11.2, 16.4)	
Q4 (339-3785 ng/g lipid)	979 (19.8)	95.1 (93.7, 96.6)	0.01	17.3 (14.3, 20.3)	<0.0001	8.0 (7.3, 8.9)	0.67	21.3 (18.0, 24.6)	<0.0001
Total Estrogenic PCBs (range), Q1 (0-15 ng/g lipid)	913 (26.3)	92.7 (91.4, 94.1)	ref	2.6 (1.4, 3.7)		7.6 (7.1, 8.1)	ref	9.8 (7.0, 12.6)	
Q2 (15-21 ng/g lipid)	982 (28.6)	92.9 (91.8, 94.0)	0.78	2.8 (1.6, 4.0)		7.4 (6.8, 8.1)	0.70	11.2 (9.1, 13.4)	
Q3 (21-29 ng/g lipid)	976 (25.6)	93.1 (91.8, 94.4)	0.63	8.3 (6.7, 9.9)		7.3 (6.5, 8.1)	0.54	13.5 (9.8, 17.3)	
Q4 (30-477 ng/g lipid)	980 (19.5)	95.8 (94.1, 97.4)	0.004	14.1 (11.2, 17.0)	<0.0001	7.7 (7.0, 8.5)	0.74	19.2 (15.8, 22.5)	<0.0001
1A Estrogenic PCBs (range), Q1 (0-3.2 ng/g lipid)	908 (23.6)	93.5 (92.0, 95.1)	ref	7.1 (5.0, 9.1)		7.6 (7.0, 8.3)	ref	12.3 (10.2, 14.5)	
Q2 (3.3-4.9 ng/g lipid)	980 (26.2)	92.5 (91.5, 93.6)	0.27	6.2 (4.7, 7.6)		7.5 (6.8, 8.2)	0.68	14.0 (10.7, 17.4)	
Q3 (5.0-7.3 ng/g lipid)	984 (24.8)	93.7 (92.3, 95.0)	0.89	6.4 (4.7, 8.2)		7.3 (6.8, 7.9)	0.45	13.2 (11.2, 15.3)	
Q4 (7.4-272 ng/g lipid)	979 (25.4)	94.2 (92.9, 95.5)	0.45	5.7 (4.1, 7.3)	0.68	7.5 (6.9, 8.3)	0.85	12.3 (9.1, 15.5)	0.74

[a] age-adjusted

TABLE XXXIX (continued).
OVERALL WEIGHTED DEMOGRAPHIC AND CLINICAL CHARACTERISTICS WITH DISTRIBUTIONS OF EACH OUTCOME BY LEVELS OF COVARIATES AMONG NHANES 1999-2004 PARTICIPANTS IN THE PCDD, PCDF, AND PCB SUBSAMPLE

	Overall	Continuous eGFR (mL/minute/1.73 m^2)[a]		Low eGFR (eGFR < 60)		Urine Albumin to Creatinine Ratio (mg/g)[a]		Albuminuria (UACR ≥ 17/25 males and females mg/g)	
	n (%)	Mean (95% CI)[a]	p-value	% (95% CI)	p-value	GM (95% CI)[a]	p-value	% (95% CI)	p-value
1B Estrogenic PCBs (range), Q1 (0-10.1 ng/g lipid)	908 (25.5)	93.1 (91.7, 94.5)	ref	2.4 (1.2, 3.7)		7.5 (7.0, 8.1)	ref	9.8 (6.7, 12.8)	
Q2 (10.2-16.2 ng/g lipid)	986 (29.3)	93.2 (91.8, 94.7)	0.82	3.2 (2.1, 4.3)		7.3 (6.9, 7.8)	0.58	10.4 (8.5, 12.3)	
Q3 (16.2-23.8 ng/g lipid)	977 (25.8)	92.7 (91.7, 93.7)	0.55	6.6 (5.1, 8.0)		7.5 (6.7, 8.4)	0.96	14.1 (10.5, 17.6)	
Q4 (23.8-219 ng/g lipid)	980 (19.4)	95.4 (93.7, 97.1)	0.05	15.9 (13.0, 18.7)	<0.0001	7.6 (6.8, 8.5)	0.96	19.8 (16.8, 22.8)	<0.0001
Total Anti-Estrogenic PCBs (range), Q1 (0-41.0 ng/g lipid)	914 (24.8)	92.5 (91.0, 93.9)	ref	2.2 (0.9, 3.4)		7.6 (7.1, 8.1)	ref	10.0 (6.9, 13.1)	
Q2 (41.0-66.7 ng/g lipid)	979 (29.2)	92.4 (91.3, 93.4)	0.86	2.5 (1.6, 3.4)		6.9 (6.3, 7.5)	0.08	8.8 (6.3, 11.4)	
Q3 (66.8-116.1) ng/g lipid)	979 (25.9)	94.7 (93.5, 95.9)	0.01	5.9 (4.1, 7.6)		7.3 (6.6, 8.0)	0.53	14.1 (11.3, 16.9)	
Q4 (116.2-1675 ng/g lipid)	979 (20.1)	94.7 (93.4, 96.1)	0.01	17.7 (14.6, 20.8)	<0.0001	8.6 (7.6, 9.7)	0.11	21.4 (17.5, 25.3)	<0.0001
2A Anti-Estrogenic PCBs (range), Q1 (0-20.8 ng/g lipid)	914 (25.4)	92.8 (91.5, 94.1)	ref	2.7 (1.4, 4.0)		7.3 (6.7, 7.9)	ref	9.7 (6.6, 12.8)	
Q2 (20.8-31.6 ng/g lipid)	979 (28.2)	92.2 (91.0, 93.3)	0.51	2.0 (1.1, 2.9)		6.8 (6.3, 7.4)	0.25	8.8 (6.7, 11.0)	
Q3 (31.7-52.5 ng/g lipid)	979 (26.2)	94.9 (93.8, 95.9)	0.02	5.1 (3.8, 6.4)		7.5 (6.9, 8.2)	0.56	14.7 (12.2, 17.3)	
Q4 (52.6-698 ng/g lipid)	979 (20.2)	94.4 (92.8, 96.0)	0.12	18.5 (15.2, 21.8)	<0.0001	8.8 (7.8, 9.9)	0.02	20.7 (16.3, 25.0)	<0.0001
2B Anti-Estrogenic PCBs (range), Q1 (0-18.9 ng/g lipid)	914 (24.3)	92.1 (90.5, 93.7)	ref	1.9 (0.7, 3.1)		7.7 (7.1, 8.4)	ref	9.9 (7.3, 12.5)	
Q2 (19.0-34.5 ng/g lipid)	979 (29.8)	92.5 (91.4, 93.5)	0.73	3.1 (2.0, 4.2)		6.9 (6.4, 7.5)	0.03	8.3 (5.6, 11.0)	
Q3 (34.6-62.7 ng/g lipid)	980 (25.6)	94.6 (93.4, 95.9)	0.009	6.4 (4.8, 7.9)		7.3 (6.7, 7.9)	0.33	14.6 (11.9, 17.3)	
Q4 (62.8-1072 ng/g lipid)	978 (20.3)	95.1 (93.9, 96.4)	0.001	16.3 (13.4, 19.3)	<0.0001	8.3 (7.4, 9.4)	0.36	21.6 (18.2, 25.1)	<0.0001
Group 3 CYP1A/2B PCBs (range), Q1 (0-35.3 ng/g lipid)	914 (23.3)	92.4 (91.0, 93.9)	ref	1.7 (0.5, 2.9)		8.2 (7.6, 8.8)	ref	10.4 (7.5, 13.4)	
Q2 (35.3-71.5 ng/g lipid)	979 (31.0)	92.5 (91.2, 93.7)	0.95	2.5 (1.5, 3.5)		7.0 (6.5, 7.5)	0.001	7.6 (5.2, 9.9)	
Q3 (71.5-134.8 ng/g lipid)	979 (26.2)	93.7 (92.6, 94.9)	0.13	7.5 (5.4, 9.5)		7.4 (6.6, 8.2)	0.10	15.6 (12.6, 18.7)	
Q4 (134.9-1769 ng/g lipid)	979 (19.5)	96.0 (94.8, 97.2)	0.001	16.4 (13.4, 19.5)	<0.0001	7.7 (7.0, 8.5)	0.39	21.1 (18.1, 24.1)	<0.0001
Warner CYP1A PCBs (range), Q1 (0-22.2 ng/g lipid)	914 (25.6)	92.6 (91.2, 94.0)	ref	2.3 (1.0, 3.5)		7.2 (6.7, 7.8)	ref	9.8 (6.7, 12.9)	
Q2 (22.2-33.7 ng/g lipid)	979 (27.7)	92.3 (91.1, 93.5)	0.81	2.8 (1.7, 3.8)		6.7 (6.2, 7.2)	0.13	8.9 (6.8, 11.1)	
Q3 (33.7-54.7 ng/g lipid)	979 (26.4)	94.7 (93.5, 95.9)	0.06	5.0 (3.5, 6.6)		7.5 (6.9, 8.2)	0.52	14.2 (11.8, 16.6)	
Q4 (54.8-704 ng/g lipid)	979 (20.2)	94.6 (93.0, 96.2)	0.001	18.1 (14.9, 21.2)	<0.0001	9.0 (7.9, 10.2)	0.01	21.0 (16.5, 25.5)	<0.0001

[a] age-adjusted

TABLE XXXIX (continued).
OVERALL WEIGHTED DEMOGRAPHIC AND CLINICAL CHARACTERISTICS WITH DISTRIBUTIONS OF EACH OUTCOME BY LEVELS OF COVARIATES AMONG NHANES 1999-2004 PARTICIPANTS IN THE PCDD, PCDF, AND PCB SUBSAMPLE

	Overall	Continuous eGFR (mL/minute/1.73 m^2)[a]		Low eGFR (eGFR < 60)		Urine Albumin to Creatinine Ratio (mg/g)[a]		Albuminuria (UACR ≥ 17/25 males and females mg/g)	
	n (%)	Mean (95% CI)[a]	p-value	% (95% CI)	p-value	GM (95% CI)[a]	p-value	% (95% CI)	p-value
Warner mixed PCBs (range), Q1 (0-31.1 ng/g lipid)	913 (24.9)	92.5 (91.1, 94.0)	ref	2.2 (0.9, 3.4)		7.7 (7.1, 8.3)	ref	10.1 (7.1, 13.1)	
Q2 (31.1-50.5 ng/g lipid)	980 (29.3)	92.2 (90.9, 93.5)	0.77	3.5 (2.3, 4.7)		6.9 (6.4, 7.5)	0.05	8.4 (6.1, 10.7)	
Q3 (50.5-82.9 ng/g lipid)	979 (25.6)	94.5 (93.2, 95.8)	0.01	5.8 (4.3, 7.3)		7.6 (6.8, 8.4)	0.79	15.1 (11.9, 18.3)	
Q4 (83.0-1271 ng/g lipid)	979 (20.2.)	95.2 (94.0, 96.4)	0.06	16.3 (13.3, 19.2)	<0.0001	8.0 (7.2, 8.9)	0.59	20.6 (17.3, 23.8)	<0.0001
Warner CYP2B PCBs (range), Q1 (0-67.4 ng/g lipid)	914 (25.8)	92.0 (90.7, 93.3)	ref	2.0 (0.7, 3.3)		8.0 (7.4, 8.6)	ref	11.2 (8.2, 14.1)	
Q2 (67.5-116.3 ng/g lipid)	979 (27.9)	93.6 (92.3, 94.9)	0.03	3.3 (2.1, 4.5)		7.0 (6.5, 7.6)	0.002	9.2 (7.0, 11.3)	
Q3 (116.3-196.1 ng/g lipid)	979 (26.0)	93.8 (92.4, 95.2)	0.07	6.2 (4.6, 7.7)		7.1 (6.5, 7.8)	0.04	12.4 (9.6, 15.1)	
Q4 (196.1-2253 ng/g lipid)	979 (20.2)	94.7 (93.3, 96.2)	0.009	16.2 (13.0, 19.5)	<0.0001	8.0 (7.4, 8.7)	0.95	21.5 (18.4, 24.5)	<0.0001
Survey year, 1999-2000	1173 (30.5)	93.2 (91.9, 94.4)	ref	5.9 (4.4, 7.5)		7.5 (6.8, 8.3)	ref	13.5 (10.4, 16.6)	
2001-2002	1371 (35.7)	93.4 (91.5, 95.2)	0.84	6.3 (4.3, 8.2)		7.6 (7.0, 8.1)	0.95	12.8 (10.2, 15.3)	
2003-2004	1307 (33.8)	93.9 (92.7, 95.0)	0.41	6.8 (5.2, 8.3)	0.79	7.4 (6.9, 7.9)	0.75	12.8 (10.1, 15.5)	0.91

[a] age-adjusted

TABLE XL.
WEIGHTED GEOMETRIC MEAN LIPID ADJUSTED TEQ, TOTAL PCB, TOTAL ESTROGENIC, AND TOTAL ANTI-ESTROGENIC POLLUTANT CONCENTRATION LEVELS AMONG NHANES 1999-2004 PARTICIPANTS, OVERALL AND BY COVARIATES

	Total toxic equivalency (TEQ) (ng/g lipid)		**Total PCBs (ng/g lipid)**		**Total Estrogenic PCBs (ng/g lipid)**		**Total Anti-Estrogenic PCBs (ng/g lipid)**	
	GM (95% CI)	**p-value**	**GM (95% CI)**	**p-value**	**GM (95% CI)**	**p-value**	**GM (95% CI)**	**p-value**
Overall	0.12 (0.11, 0.12)		147 (123, 174)		16.8 (14.9, 19.0)		50.6 (43.6, 58.6)	
Age in years, 20-39	0.111 (0.111, 0.112)	<0.0001	101 (86, 118)	<0.0001	13.8 (12.4, 15.4)	<0.0001	33.2 (29.1, 37.8)	<0.0001
40-59	0.115 (0.115, 0.116)	<0.0001	162 (134, 196)	0.0004	17.4 (15.2, 19.8)	0.0007	56.0 (47.7, 65.9)	<0.0001
60+	0.123 (0.123, 0.124)	ref	237 (176, 317)	ref	22.4 (18.3, 27.5)	ref	87.8 (68.0, 113.4)	ref
Male	0.115 (0.115, 0.115)		146 (120, 177)		17.0 (14.9, 19.4)		48.1 (40.9, 56.6)	
Female	0.116 (0.116, 0.117)	0.002	148 (125, 175)	0.76	16.7 (14.8, 18.8)	0.64	53.1 (45.9, 61.4)	0.03
Premenopausal	0.113 (0.113, 0.113)		112 (94, 133)		14.3 (12.6, 16.1)		38.9 (33.5, 45.1)	
Postmenopausal	0.122 (0.122, 0.123)	<0.0001	232 (190, 283)	<0.0001	21.5 (18.7, 24.7)	<0.0001	88.1 (73.7, 105.3)	<0.0001
Race/ethnicity								
African-American, nH	0.117 (0.117, 0.118)	0.05	167 (126, 223)	0.35	19.6 (16.0, 24.1)	0.03	57.1 (45.3, 71.9)	0.06
White, nH	0.116 (0.116, 0.116)	ref	152 (127, 183)	ref	16.8 (14.8, 19.0)	ref	52.8 (45.0, 61.9)	ref
Hispanic	0.113 (0.113, 0.114)	<0.0001	112 (93, 134)	0.004	14.9 (13.1, 16.9)	0.10	37.9 (32.2, 44.5)	0.001
Other	0.114 (0.114, 0.116)	0.13	132 (95, 183)	0.31	17.3 (13.5, 22.1)	0.81	44.7 (33.4, 59.8)	0.20
Education, < High school	0.117 (0.117, 0.118)	0.01	169 (143, 200)	0.11	19.4 (17.2, 21.9)	0.01	57.8 (49.8, 67.2)	0.11
High school graduate	0.115 (0.115, 0.117)	0.41	135 (106, 173)	0.39	15.6 (13.2, 18.5)	0.43	47.3 (38.3, 58.4)	0.42
Some college	0.115 (0.115, 0.116)	0.65	142 (110, 182)	0.72	16.5 (13.8, 19.7)	0.96	48.5 (39.0, 60.3)	0.65
≥ College graduate	0.115 (0.115, 0.116)	ref	148 (126, 174)	ref	16.6 (14.8, 18.6)	ref	51.0 (44.1, 59.1)	ref
Born in the United States, Yes	0.115 (0.115, 0.116)		149 (123, 180)		16.8 (14.8, 19.1)		51.4 (43.8, 60.5)	
No	0.114 (0.114, 0.115)	0.07	135 (112, 163)	0.36	17.1 (14.8, 19.8)	0.79	45.8 (38.8, 54.1)	0.23
BMI, kg/m², <25	0.115 (0.115, 0.116)	0.06	149 (124, 179)	0.51	17.2 (15.1, 19.6)	0.26	49.8 (42.6, 58.2)	0.83
25 to <30	0.115 (0.115, 0.116)	0.54	150 (125, 180)	0.25	17.1 (15.2, 19.4)	0.12	51.4 (44.0, 60.0)	0.78
≥30	0.116 (0.116, 0.117)	ref	140 (112, 176)	ref	16.0 (13.7, 18.7)	ref	50.6 (41.6, 61.6)	ref

TABLE XL (continued).
WEIGHTED GEOMETRIC MEAN LIPID ADJUSTED TEQ, TOTAL PCB, TOTAL ESTROGENIC, AND TOTAL ANTI-ESTROGENIC POLLUTANT CONCENTRATION LEVELS AMONG NHANES 1999-2004 PARTICIPANTS, OVERALL AND BY COVARIATES

	Total toxic equivalency (TEQ) (ng/g lipid)		Total PCBs (ng/g lipid)		Total Estrogenic PCBs (ng/g lipid)		Total Anti-Estrogenic PCBs (ng/g lipid)	
	GM (95% CI)	p-value	GM (95% CI)	p-value	GM (95% CI)	p-value	GM (95% CI)	p-value
Triglycerides ≥ 200 mg/dL, Yes	0.115 (0.115, 0.116)		131 (102, 168)		14.3 (12.0, 17.0)		46.9 (37.7, 58.2)	
No	0.115 (0.115, 0.116)	0.78	150 (128, 177)	0.07	17.4 (15.6, 19.5)	0.001	51.4 (44.7, 59.1)	0.17
Total cholesterol ≥ 200 mg/dL, Yes	0.116 (0.116, 0.116)		147 (125, 173)		16.4 (14.7, 18.3)		51.4 (44.7, 59.1)	
No	0.115 (0.115, 0.116)	0.29	146 (118, 181)	0.92	17.3 (14.9, 20.1)	0.29	49.7 (41.5, 59.6)	0.61
Diabetes	0.121 (0.121, 0.123)		225 (175, 288)		21.7 (18.1, 26.0)		81.6 (65.5, 101.7)	
Non-diabetic	0.115 (0.115, 0.115)	<0.0001	141 (119, 167)	<0.0001	16.5 (14.7, 18.5)	<0.0001	48.5 (41.9, 56.1)	<0.0001
Hypertension	0.119 (0.119, 0.120)		176 (140, 223)		18.5 (15.8, 21.7)		63.7 (52.0, 78.0)	
Non-hypertensive	0.113 (0.113, 0.114)	<0.0001	132 (113, 153)	0.0001	15.9 (14.3, 17.7)	0.002	44.2 (38.8, 50.2)	<0.0001
Smoking status, Never	0.116 (0.116, 0.117)	<0.0001	134 (107, 166)	0.27	15.9 (13.7, 18.5)	0.34	47.1 (39.1, 56.8)	0.71
Former (5+ years)	0.118 (0.118, 0.120)	<0.0001	204 (170, 245)	0.001	20.5 (17.9, 23.4)	0.01	70.7 (60.4, 82.9)	<0.0001
Former (<5 years)	0.112 (0.112, 0.113)	0.60	108 (77, 152)	0.04	13.9 (10.7, 18.1)	0.10	37.4 (27.8, 50.3)	0.05
Current (infrequent)	0.113 (0.113, 0.114)	0.86	124 (90, 171)	0.30	15.1 (11.9, 19.2)	0.39	41.7 (31.5, 55.4)	0.33
Current (daily)	0.113 (0.113, 0.113)	ref	149 (127, 175)	ref	17.1 (15.2, 19.2)	ref	48.6 (42.0, 56.3)	ref
Survey year, 1999-2000	0.118 (0.118, 0.119)	<0.0001	175 (150, 205)	0.003	22.2 (19.9, 24.8)	0.0002	66.8 (57.7, 77.3)	0.0002
2001-2002	0.116 (0.116, 0.117)	0.002	232 (215, 250)	<0.0001	20.5 (19.5, 21.6)	0.0005	73.2 (67.4, 79.5)	<0.0001
2003-2004	0.113 (0.113, 0.114)	ref	77 (46, 129)	ref	10.6 (7.5, 15.1)	ref	26.6 (17.3, 41.0)	ref

TABLE XLI.
WEIGHTED GEOMETRIC MEAN LIPID ADJUSTED CYP GROUPED POLLUTANT CONCENTRATION LEVELS AMONG NHANES 1999-2004 PARTICIPANTS, OVERALL AND BY COVARIATES

	Group 3 CYP1A/2B PCBs (ng/g lipid)		Warner CYP1A PCBs (ng/g lipid)		Warner CYP2B PCBs (ng/g lipid)		Warner mixed PCBs (ng/g lipid)	
	GM (95% CI)	p-value	GM (95% CI)	p-value	GM (95% CI)	p-value	GM (95% CI)	p-value
Overall	50.9 (43.8, 59.2)		26.2 (23.0, 29.9)		82.9 (70.7, 97.2)		37.6 (32.7, 43.2)	
Age in years, 20-39	29.2 (25.7, 33.2)	<0.0001	18.8 (16.7, 21.2)	<0.0001	55.0 (47.7, 63.5)	<0.0001	25.2 (22.2, 28.5)	<0.0001
40-59	61.8 (52.3, 73.1)	<0.0001	27.3 (23.6, 31.5)	<0.0001	94.4 (79.2, 112.7)	0.0005	42.3 (36.4, 49.3)	<0.0001
60+	95.9 (74.0, 124.4)	ref	43.6 (34.7, 54.8)	ref	134.4 (102.3, 176.6)	ref	61.4 (48.2, 78.2)	ref
Male	51.6 (43.6, 61.1)		23.8 (20.6, 27.5)		83.9 (70.3, 100.2)		37.2 (31.9, 43.4)	
Female	50.3 (43.5, 58.2)	0.58	28.9 (25.4, 32.9)	<0.0001	81.8 (70.1, 95.5)	0.60	38.0 (33.2, 43.5)	0.61
Premenopausal	35.9 (30.9, 41.8)		21.6 (18.9, 24.6)		62.1 (53.0, 72.8)		28.7 (24.9, 33.0)	
Postmenopausal	86.9 (72.7, 103.8)	<0.0001	46.5 (39.6, 54.7)	<0.0001	127.9 (106.3, 153.8)	<0.0001	59.9 (50.7, 70.8)	<0.0001
Race/ethnicity								
African-American, nH	59.8 (47.3, 75.7)	0.23	28.4 (23.1, 34.9)	0.62	95.6 (73.8, 123.8)	0.28	44.2 (35.4, 55.0)	0.13
White, nH	53.9 (45.9, 63.4)	ref	27.3 (23.7, 31.5)	ref	86.3 (72.8, 102.2)	ref	38.9 (33.5, 45.2)	ref
Hispanic	33.6 (28.9, 39.1)	<0.0001	21.0 (18.0, 24.4)	0.005	60.9 (51.5, 71.9)	0.001	28.2 (24.0, 33.2)	0.001
Other	46.7 (34.5, 63.3)	0.29	22.4 (17.4, 29.0)	0.09	76.5 (56.2, 104.1)	0.38	34.7 (25.9, 46.4)	0.39
Education, < High school	59.0 (50.2, 69.3)	0.20	29.3 (25.8, 33.3)	0.17	95.4 (81.3, 112.0)	0.14	43.2 (37.3, 50.0)	0.07
High school graduate	46.5 (37.5, 57.7)	0.19	24.6 (20.3, 29.7)	0.36	75.5 (60.2, 94.7)	0.25	35.3 (29.0, 43.0)	0.51
Some college	48.3 (38.9, 59.9)	0.40	25.4 (20.9, 31.0)	0.67	80.1 (63.4, 101.0)	0.63	36.1 (29.4, 44.4)	0.72
≥ College graduate	52.9 (45.7, 61.3)	ref	26.6 (23.2, 30.4)	ref	84.6 (72.9, 98.2)	ref	37.5 (32.6, 43.1)	ref
Born in the United States, Yes	52.2 (44.3, 61.5)		26.7 (23.2, 30.8)		84.3 (70.9, 100.2)		38.1 (32.7, 44.3)	
No	44.2 (37.2, 52.5)	0.09	23.5 (20.2, 27.4)	0.15	75.1 (62.7, 89.9)	0.25	35.0 (29.8, 41.1)	0.37
BMI, kg/m², <25	51.5 (43.6, 60.8)	0.41	25.7 (22.4, 29.5)	0.56	84.9 (71.5, 100.9)	0.29	37.4 (32.3, 43.4)	0.87
25 to <30	52.9 (45.1, 62.1)	0.08	26.3 (22.9, 30.2)	0.70	85.5 (72.3, 101.0)	0.09	38.3 (33.1, 44.3)	0.51
≥30	48.1 (39.5, 58.5)	ref	26.8 (22.5, 31.9)	ref	77.6 (63.2, 95.3)	ref	37.0 (30.7, 44.6)	ref
Triglycerides ≥ 200 mg/dL, Yes	49.1 (39.3, 61.4)		23.4 (19.3, 28.3)		75.3 (59.6, 95.2)		34.7 (28.2, 42.7)	
No	51.3 (44.5, 59.3)	0.55	26.9 (23.7, 30.4)	0.02	84.6 (72.8, 98.3)	0.11	38.2 (33.5, 43.6)	0.15

TABLE XLI (continued).
WEIGHTED GEOMETRIC MEAN LIPID ADJUSTED CYP GROUPED POLLUTANT CONCENTRATION LEVELS AMONG NHANES 1999-2004 PARTICIPANTS, OVERALL AND BY COVARIATES

	Group 3 CYP1A/2B PCBs (ng/g lipid)		Warner CYP1A PCBs (ng/g lipid)		Warner CYP2B PCBs (ng/g lipid)		Warner mixed PCBs (ng/g lipid)	
	GM (95% CI)	p-value	GM (95% CI)	p-value	GM (95% CI)	p-value	GM (95% CI)	p-value
Total cholesterol ≥ 200 mg/dL, Yes	53.7 (46.5, 62.1)		26.1 (23.1, 29.5)		83.9 (72.1, 97.6)		37.9 (33.2, 43.3)	
No	48.2 (40.1, 57.9)	0.12	26.4 (22.5, 31.0)	0.82	81.9 (67.3, 99.6)	0.74	37.2 (31.5, 44.1)	0.77
Diabetes	86.3 (69.0, 107.9)		39.9 (32.6, 48.7)		127.1 (100.6, 160.5)		58.4 (47.3, 72.0)	
Non-diabetic	48.6 (42.0, 56.3)	<0.0001	25.3 (22.2, 28.7)	<0.0001	79.8 (68.3, 93.2)	<0.0001	36.2 (31.6, 41.4)	<0.0001
Hypertension	66.0 (53.7, 81.1)		32.6 (27.2, 39.0)		99.8 (80.5, 123.8)		45.7 (37.7, 55.3)	
Non-hypertensive	43.7 (38.3, 50.0)	<0.0001	23.1 (20.6, 25.9)	<0.0001	74.3 (64.5, 85.5)	<0.0001	33.5 (29.7, 37.9)	0.0001
Smoking status, Never	45.4 (37.7, 54.6)	0.19	25.7 (21.7, 30.4)	0.25	74.9 (61.5, 91.3)	0.18	34.3 (28.8, 40.8)	0.21
Former (5+ years)	77.5 (66.1, 91.0)	<0.0001	34.6 (29.9, 40.0)	<0.0001	116.3 (97.9, 138.1)	0.001	51.9 (44.6, 60.3)	0.0005
Former (<5 years)	37.6 (28.0, 50.4)	0.03	19.7 (15.0, 25.7)	0.15	62.3 (45.8, 84.8)	0.03	28.3 (21.3, 37.6)	0.02
Current (infrequent)	39.5 (29.6, 52.8)	0.13	22.2 (17.2, 28.5)	0.70	69.7 (51.6, 94.3)	0.25	31.5 (23.9, 41.5)	0.22
Current (daily)	50.8 (43.3, 59.6)	ref	23.4 (20.6, 26.7)	ref	84.5 (72.2, 98.9)	ref	38.1 (32.9, 44.1)	ref
Survey year, 1999-2000	60.6 (52.1, 70.5)	0.005	33.6 (29.5, 38.3)	<0.0001	83.3 (71.6, 96.9)	0.02	50.1 (43.6, 57.6)	<0.0001
2001-2002	71.0 (65.1, 77.3)	0.0004	39.5 (36.6, 42.7)	<0.0001	141.8 (132.5, 151.8)	<0.0001	54.2 (50.2, 58.6)	<0.0001
2003-2004	30.7 (19.8, 47.4)	ref	13.6 (9.3, 20.0)	ref	46.8 (29.3, 74.6)	ref	19.7 (13.1, 29.6)	ref

TABLE XLII.
MULTIVARIABLE ADJUSTED ASSOCIATIONS BETWEEN CATEGORIZED LEVELS OF LIPID ADJUSTED PCDD, PCDF, AND PCB INDEXES AND KIDNEY OUTCOMES AMONG NHANES 1999-2004 PARTICIPANTS

Serum concentrations (lipid adjusted ng/g)	**Continuous eGFR (mL/minute/1.73 m^2)**	**Low eGFR (eGFR <60 vs. ≥60)**	**Continuous UACR (mg/g)**	**Albuminuria (UACR ≥ 17/25 males and females mg/g)**
	Mean (95% CI)[a]	**OR (95% CI)[a]**	**GM (95% CI)[a]**	**OR (95% CI)[a]**
Total toxic equivalency (TEQ), Q1 (ref)	92.6 (91.1, 94.1)	1.0 (ref)	7.4 (6.9, 7.9)	1.0 (ref)
Q2 (0.009-0.014 ng/g lipid)	92.8 (91.7, 93.9)	1.04 (0.66, 1.62)	7.0 (6.5, 7.5)	0.88 (0.65, 1.20)
Q3 (0.015-0.02 ng/g lipid)	94.6 (93.5, 95.7)[b]	0.67 (0.41, 1.08)	7.8 (7.2, 8.5)	1.08 (0.74, 1.56)
Q4 (0.02-0.18 ng/g lipid)	94.7 (93.3, 96.0)[b]	0.70 (0.42, 1.16)	7.9 (7.2, 8.6)	1.20 (0.90, 1.61)
p-value trend	0.01	0.14	0.10	0.19
Total PCBs, Q1 (ref)	92.0 (90.5, 93.5)	1.0 (ref)	7.7 (7.1, 8.3)	1.0 (ref)
Q2 (132-206 ng/g lipid)	93.4 (92.3, 94.5)	1.28 (0.55, 3.01)	7.1 (6.5, 7.8)	0.73 (0.46, 1.15)
Q3 (207-339 ng/g lipid)	94.4 (93.2, 95.5)[b]	0.95 (0.46, 1.99)	7.3 (6.7, 8.0)	0.80 (0.55, 1.16)
Q4 (339-3785 ng/g lipid)	95.0 (93.4, 96.5)[b]	1.03 (0.52, 2.02)	8.1 (7.3, 8.9)	0.94 (0.65, 1.36)
p-value trend	0.005	0.78	0.55	0.94
Total Estrogenic PCBs, Q1 (ref)	92.5 (91.1, 93.9)	1.0 (ref)	7.4 (6.9, 8.0)	1.0 (ref)
Q2 (15-21 ng/g lipid)	93.4 (92.4, 94.5)	1.04 (0.51, 2.12)	7.5 (6.9, 8.1)	1.10 (0.78, 1.56)
Q3 (21-29 ng/g lipid)	93.5 (92.3, 94.7)	1.30 (0.75, 2.27)	7.3 (6.6, 8.2)	1.03 (0.69, 1.54)
Q4 (30-477 ng/g lipid)	95.5 (93.9, 97.1)[b]	0.91 (0.49, 1.69)	7.8 (7.1, 8.6)	1.08 (0.69, 1.70)
p-value trend	0.01	0.65	0.50	0.83
1A Estrogenic PCBs, Q1 (ref)	93.4 (91.9, 94.9)	1.0 (ref)	7.4 (6.8, 8.0)	1.0 (ref)
Q2 (3.3-4.9 ng/g lipid)	92.7 (91.6, 93.9)	0.76 (0.49, 1.16)	7.4 (6.7, 8.2)	1.20 (0.83, 1.73)
Q3 (5.0-7.3 ng/g lipid)	93.7 (92.4, 95.0)	0.83 (0.48, 1.43)	7.3 (6.8, 7.8)	1.12 (0.86, 1.47)
Q4 (7.4-272 ng/g lipid)	94.6 (93.3, 95.8)	0.77 (0.47, 1.24)	7.8 (7.1, 8.6)	1.18 (0.80, 1.75)
p-value trend	0.10	0.37	0.49	0.47
1B Estrogenic PCBs, Q1 (ref)	92.9 (91.4, 94.4)	1.0 (ref)	7.4 (6.8, 8.1)	1.0 (ref)
Q2 (10.2-16.2 ng/g lipid)	93.6 (92.2, 95.0)	1.14 (0.66, 1.99)	7.3 (6.9, 7.8)	0.96 (0.63, 1.45)
Q3 (16.2-23.8 ng/g lipid)	93.3 (92.2, 94.4)	0.96 (0.52, 1.75)	7.6 (6.8, 8.5)	1.11 (0.74, 1.66)
Q4 (23.8-219 ng/g lipid)	94.9 (93.2, 96.7)	0.93 (0.50, 1.73)	7.6 (6.8, 8.5)	1.05 (0.69, 1.58)
p-value trend	0.16	0.63	0.65	0.66

[a]Model adjusts for age, sex, race, education level, serum lipids (continuous), self-reported smoking history (never, 5+ years since last cigarette, <5 years since last cigarette, infrequent current smoker, daily smoker), hypertension status (yes/no), nativity (born in the US, yes/no), and survey cycle; [b]Statistically significant ($p<0.05$)

TABLE XLII (continued).
MULTIVARIABLE ADJUSTED ASSOCIATIONS BETWEEN CATEGORIZED LEVELS OF LIPID ADJUSTED PCDD, PCDF, AND PCB INDEXES AND KIDNEY OUTCOMES AMONG NHANES 1999-2004 PARTICIPANTS

Serum concentrations (lipid adjusted ng/g)	**Continuous eGFR (mL/minute/1.73 m^2)**	**Low eGFR (eGFR <60 vs. ≥60)**	**Continuous UACR (mg/g)**	**Albuminuria (UACR ≥ 17/25 males and females mg/g)**
	Mean (95% CI)[a]	**OR (95% CI)**[a]	**GM (95% CI)**[a]	**OR (95% CI)**[a]
Total Anti-Estrogenic PCBs, Q1 (ref)	91.9 (90.5, 93.3)	1.0 (ref)	7.5 (6.9, 8.2)	1.0 (ref)
Q2 (41.0-66.7 ng/g lipid)	93.0 (92.0, 93.9)	1.31 (0.66, 2.58)	7.0 (6.4, 7.6)	0.82 (0.52, 1.28)
Q3 (66.8-116.1) ng/g lipid)	95.0 (93.9, 96.2)[b]	0.79 (0.37, 1.67)	7.3 (6.6, 8.1)	0.91 (0.56, 1.47)
Q4 (116.2-1675 ng/g lipid)	94.7 (93.3, 96.1)[b]	0.92 (0.48, 1.79)	8.4 (7.4, 9.4)	1.05 (0.66, 1.68)
p-value trend	0.001	0.52	0.20	0.67
2A Anti-Estrogenic PCBs, Q1 (ref)	92.1 (90.8, 93.4)	1.0 (ref)	7.2 (6.6, 7.9)	1.0 (ref)
Q2 (20.8-31.6 ng/g lipid)	92.7 (91.6, 93.8)	1.03 (0.51, 2.07)	7.0 (6.4, 7.5)	0.98 (0.60, 1.59)
Q3 (31.7-52.5 ng/g lipid)	95.2 (94.2, 96.1)[b]	0.76 (0.42, 1.37)	7.6 (7.1, 8.2)	1.28 (0.84, 1.93)
Q4 (52.6-698 ng/g lipid)	94.7 (93.1, 96.3)[b]	0.93 (0.53, 1.64)	8.5 (7.5, 9.5) p=0.06	1.26 (0.76, 2.11)
p-value trend	0.001	0.83	0.04	0.23
2B Anti-Estrogenic PCBs, Q1 (ref)	91.6 (90.0, 93.1)	1.0 (ref)	7.7 (7.0, 8.4)	1.0 (ref)
Q2 (19.0-34.5 ng/g lipid)	93.2 (92.2, 94.2)[b]	1.64 (0.71, 3.75)	6.9 (6.4, 7.4)	0.68 (0.45, 1.04)
Q3 (34.6-62.7 ng/g lipid)	94.9 (93.7, 96.2)[b]	0.78 (0.37, 1.67)	7.4 (6.8, 8.1)	0.87 (0.57, 1.32)
Q4 (62.8-1072 ng/g lipid)	94.9 (93.6, 96.2)[b]	0.92 (0.45, 1.90)	8.3 (7.4, 9.3)	1.02 (0.68, 1.52)
p-value trend	0.001	0.27	0.21	0.52
Group 3 CYP1A/2B PCBs, Q1 (ref)	91.7 (90.3, 93.2)	1.0 (ref)	7.9 (7.3, 8.5)	1.0 (ref)
Q2 (35.3-71.5 ng/g lipid)	93.0 (91.8, 94.1)	1.81 (0.80, 4.11)	7.0 (6.5, 7.5)[b]	0.61 (0.39, 0.95)[b]
Q3 (71.5-134.8 ng/g lipid)	94.2 (93.1, 95.4)[b]	1.11 (0.54, 2.28)	7.5 (6.8, 8.3)	0.84 (0.56, 1.26)
Q4 (134.9-1769 ng/g lipid)	95.9 (94.6, 97.2)[b]	1.00 (0.51, 1.96)	7.8 (7.1, 8.7)	0.88 (0.59, 1.31)
p-value trend	<0.0001	0.24	0.92	0.98

[a]Model adjusts for age, sex, race, education level, serum lipids (continuous), self-reported smoking history (never, 5+ years since last cigarette, <5 years since last cigarette, infrequent current smoker, daily smoker), hypertension status (yes/no), nativity (born in the US, yes/no), and survey cycle; [b]Statistically significant (p<0.05)

TABLE XLII (continued).
MULTIVARIABLE ADJUSTED ASSOCIATIONS BETWEEN CATEGORIZED LEVELS OF LIPID ADJUSTED PCDD, PCDF, AND PCB INDEXES AND KIDNEY OUTCOMES AMONG NHANES 1999-2004 PARTICIPANTS

Serum concentrations (lipid adjusted ng/g)	**Continuous eGFR (mL/minute/1.73 m^2)**	**Low eGFR (eGFR <60 vs. ≥60)**	**Continuous UACR (mg/g)**	**Albuminuria (UACR ≥ 17/25 males and females mg/g)**
	Mean (95% CI)[a]	**OR (95% CI)**[a]	**GM (95% CI)**[a]	**OR (95% CI)**[a]
Warner mixed PCBs, Q1 (ref)	92.1 (90.5, 93.6)	1.0 (ref)	7.7 (7.0, 8.3)	1.0 (ref)
Q2 (31.1-50.5 ng/g lipid)	92.9 (91.6, 94.1)	1.56 (0.80, 3.06)	6.9 (6.3, 7.4)[b]	0.71 (0.48, 1.07)
Q3 (50.5-82.9 ng/g lipid)	94.8 (93.7, 96.0)[b]	0.70 (0.33, 1.50)	7.7 (7.0, 8.5)	0.97 (0.61, 1.55)
Q4 (83.0-1271 ng/g lipid)	95.0 (93.7, 96.2)[b]	0.87 (0.45, 1.71)	7.9 (7.2, 8.8)	0.98 (0.66, 1.45)
p-value trend	0.002	0.23	0.33	0.62
Warner CYP1A PCBs, Q1 (ref)	92.0 (90.6, 93.4)	1.0 (ref)	7.2 (6.6, 7.8)	1.0 (ref)
Q2 (22.2-33.7 ng/g lipid)	92.7 (91.5, 93.9)	1.53 (0.75, 3.12)	6.8 (6.4, 7.3)	0.91 (0.59, 1.41)
Q3 (33.7-54.7 ng/g lipid)	95.0 (94.0, 96.1)[b]	0.89 (0.46, 1.74)	7.6 (7.1, 8.3)	1.22 (0.79, 1.89)
Q4 (54.8-704 ng/g lipid)	94.9 (93.2, 96.5)[b]	1.04 (0.57, 1.89)	8.7 (7.7, 9.8)[b]	1.28 (0.77, 2.13)
p-value trend	0.001	0.66	0.02	0.21
Warner CYP2B PCBs, Q1 (ref)	91.9 (90.7, 93.2)	1.0 (ref)	7.8 (7.3, 8.4)	1.0 (ref)
Q2 (67.5-116.3 ng/g lipid)	93.8 (92.6, 95.0)[b]	1.16 (0.53, 2.54)	6.9 (6.5, 7.4)[b]	0.63 (0.45, 0.88)[b]
Q3 (116.3-196.1 ng/g lipid)	94.2 (92.9, 95.5)[b]	0.74 (0.35, 1.60)	7.2 (6.6, 7.9)	0.62 (0.41, 0.94)[b]
Q4 (196.1-2253 ng/g lipid)	94.6 (93.1, 96.1)[b]	0.87 (0.45, 1.68)	8.2 (7.6, 8.9)	0.84 (0.59, 1.19)
p-value trend	0.02	0.41	0.55	0.50

[a]Model adjusts for age, sex, race, education level, serum lipids (continuous), self-reported smoking history (never, 5+ years since last cigarette, <5 years since last cigarette, infrequent current smoker, daily smoker), hypertension status (yes/no), nativity (born in the US, yes/no), and survey cycle; [b]Statistically significant ($p<0.05$)

TABLE XLIII.
SEX-STRATIFIED MULTIVARIABLE ADJUSTED ASSOCIATIONS BETWEEN CATEGORIZED LEVELS OF LIPID ADJUSTED PCDD, PCDF, AND PCB SUMMARY MEASURES AND CONTINUOUS OUTCOMES AMONG NHANES 1999-2004 PARTICIPANTS

	Males	Females		Males	Females	
Serum concentrations (lipid adjusted ng/g)	**Continuous eGFR (mL/minute/1.73 m^2)**	**Continuous eGFR (mL/minute/1.73 m^2)**		**Continuous UACR (mg/g)**	**Continuous UACR (mg/g)**	
	Mean (95% CI)[a]	**Mean (95% CI)[a]**	**p-interaction**	**GM (95% CI)[a]**	**GM (95% CI)[a]**	**p-interaction**
Total toxic equivalency (TEQ), Q1 (ref)	91.2 (89.6, 92.8)	93.9 (91.9, 95.9)		6.5 (5.9, 7.1)	8.7 (7.7, 9.7)	
Q2 (0.009-0.014 ng/g lipid)	91.3 (89.9, 92.7)	94.4 (92.9, 95.8)		6.2 (5.7, 6.8)	7.9 (7.2, 8.7)	
Q3 (0.015-0.02 ng/g lipid)	93.4 (91.8, 95.0)[b]	95.5 (93.7, 97.3)	0.07	7.3 (6.5, 8.2)	8.6 (7.5, 9.7)	0.03
Q4 (0.02-0.18 ng/g lipid)	94.7 (93.0, 96.4)[b]	94.7 (92.6, 96.9)		7.3 (6.1, 8.7)	8.9 (7.8, 10.1)	
p-value trend	0.004	0.40		0.09	0.61	
Total PCBs, Q1 (ref)	89.9 (88.2, 91.6)	93.9 (91.9, 95.9)		6.6 (5.9, 7.4)	9.1 (8.2, 10.1)	
Q2 (132-206 ng/g lipid)	91.7 (90.3, 93.1)	94.9 (93.3, 96.5)		6.5 (5.8, 7.2)	7.9 (7.0, 8.9)	
Q3 (207-339 ng/g lipid)	93.7 (92.2, 95.2)[b]	94.8 (93.1, 96.6)	0.001	6.8 (6.1, 7.7)	7.9 (7.1, 8.8)	0.02
Q4 (339-3785 ng/g lipid)	95.1 (93.4, 96.7)[b]	94.8 (92.9, 96.7)		7.2 (6.1, 8.5)	9.4 (8.2, 10.7)	
p-value trend	<0.0001	0.48		0.42	0.95	
Total Estrogenic PCBs, Q1 (ref)	90.4 (88.8, 91.9)	94.3 (92.4, 96.3)		6.3 (5.7, 6.8)	8.8 (7.8, 9.9)	
Q2 (15-21 ng/g lipid)	91.9 (90.6, 93.2)	94.8 (93.4, 96.3)		6.8 (6.1, 7.6)	8.3 (7.5, 9.2)	
Q3 (21-29 ng/g lipid)	93.5 (92.1, 95.0)[b]	93.6 (91.8, 95.5)	0.01	7.0 (6.2, 7.9)	8.0 (6.9, 9.3)	0.02
Q4 (30-477 ng/g lipid)	94.3 (92.5, 96.2)[b]	96.2 (94.3, 98.0)		7.0 (6.1, 8.2)	8.9 (7.7, 10.3)	
p-value trend	0.003	0.30		0.19	0.86	
1B Estrogenic PCBs, Q1 (ref)	91.6 (89.7, 93.5)	94.1 (92.4, 95.8)		6.2 (5.5, 7.1)	9.0 (7.9, 10.4)	
Q2 (10.2-16.2 ng/g lipid)	91.8 (90.1, 93.4)	95.3 (93.6, 97.0)		6.8 (6.1, 7.6)	8.0 (7.4, 8.6)	
Q3 (16.2-23.8 ng/g lipid)	92.7 (91.2, 94.2)	93.8 (92.3, 95.4)	0.08	7.0 (6.3, 7.9)	8.4 (7.2, 9.8)	0.07
Q4 (23.8-219 ng/g lipid)	94.1 (92.1, 96.2)	95.3 (93.1, 97.5)		6.9 (5.9, 8.1)	8.5 (7.3, 9.9)	
p-value trend	0.10	0.65		0.36	0.75	

[a]Model adjusts for age (continuous), sex (male/female), race (non-Hispanic white, non-Hispanic African-American, Hispanic, or other), education level (less than high school, high school grad, some college or more), serum lipids (continuous), self-reported smoking history (never, 5+ years since last cigarette, <5 years since last cigarette, infrequent current smoker, daily smoker), hypertension status (yes/no), nativity (born in the US, yes/no), and survey cycle; [b]Statistically significant (p<0.05);

TABLE XLIII (continued).
SEX-STRATIFIED MULTIVARIABLE ADJUSTED ASSOCIATIONS BETWEEN CATEGORIZED LEVELS OF LIPID ADJUSTED PCDD, PCDF, AND PCB SUMMARY MEASURES AND CONTINUOUS OUTCOMES AMONG NHANES 1999-2004 PARTICIPANTS

	Males	Females		Males	Females	
Serum concentrations (lipid adjusted ng/g)	**Continuous eGFR (mL/minute/1.73 m^2)**	**Continuous eGFR (mL/minute/1.73 m^2)**		**Continuous UACR (mg/g)**	**Continuous UACR (mg/g)**	
	Mean (95% CI)[a]	**Mean (95% CI)[a]**	**p-interaction**	**GM (95% CI)[a]**	**GM (95% CI)[a]**	**p-interaction**
Total Anti-Estrogenic PCBs, Q1 (ref)	90.0 (88.2, 91.8)	93.6 (91.9, 95.4)	0.0001	6.4 (5.7, 7.2)	9.2 (8.2, 10.3)	<0.0001
Q2 (41.0-66.7 ng/g lipid)	91.4 (90.3, 92.4)	94.6 (92.7, 96.4)		6.4 (5.8, 7.1)	7.7 (6.9, 8.7)	
Q3 (66.8-116.1) ng/g lipid)	94.2 (92.8, 95.6)[b]	95.7 (93.9, 97.5)		6.8 (6.1, 7.7)	7.9 (7.0, 9.0)	
Q4 (116.2-1675 ng/g lipid)	95.2 (93.4, 96.9)[b]	94.5 (92.8, 96.2)		7.9 (6.4, 9.7)	9.4 (8.0, 11.1)	
p-value trend	<0.0001	0.26		0.11	0.76	
2A Anti-Estrogenic PCBs, Q1 (ref)	90.1 (88.7, 91.6)	94.1 (91.9, 96.3)	0.0008	5.9 (5.4, 6.6)	9.0 (7.9, 10.3)	<0.0001
Q2 (20.8-31.6 ng/g lipid)	91.4 (90.1, 92.8)	93.8 (92.0, 95.6)		6.4 (5.7, 7.1)	7.6 (6.8, 8.5)[b]	
Q3 (31.7-52.5 ng/g lipid)	94.8 (93.5, 96.2)[b]	95.4 (94.0, 96.8)		7.5 (6.7, 8.4)[b]	7.8 (7.1, 8.5)	
Q4 (52.6-698 ng/g lipid)	94.8 (92.7, 96.8)[b]	95.1 (93.2, 97.0)		8.0 (6.2, 10.3)	9.8 (8.5, 11.3)	
p-value trend	<0.0001	0.27		0.02	0.41	
2B Anti-Estrogenic PCBs, Q1 (ref)	89.7 (87.8, 91.7)	93.2 (91.1, 95.3)	0.0006	6.7 (6.1, 7.4)	8.9 (7.8, 10.1)	<0.0001
Q2 (19.0-34.5 ng/g lipid)	91.8 (90.6, 93.1)	94.5 (92.9, 96.2)		6.3 (5.6, 7.0)	7.8 (7.0, 8.6)	
Q3 (34.6-62.7 ng/g lipid)	93.5 (92.0, 95.0)[b]	96.2 (94.4, 97.9)		6.8 (6.1, 7.7)	8.1 (7.3, 9.1)	
Q4 (62.8-1072 ng/g lipid)	95.2 (93.6, 96.8)[b]	94.5 (92.8, 96.3)		7.5 (6.3, 8.8)	9.5 (8.1, 11.1)	
p-value trend	<0.0001	0.18		0.30	0.47	
Group 3 CYP1A/2B PCBs, Q1 (ref)	89.8 (88.1, 91.6)	93.4 (91.3, 95.6)	0.0006	7.0 (6.1, 8.0)	9.1 (8.2, 10.2)	<0.0001
Q2 (35.3-71.5 ng/g lipid)	91.5 (90.0, 92.9)	94.3 (92.7, 96.0)		6.3 (5.7, 7.0)	7.7 (6.9, 8.7)[b]	
Q3 (71.5-134.8 ng/g lipid)	93.3 (91.7, 94.9)[b]	95.1 (93.4, 96.8)		6.8 (6.1, 7.6)	8.5 (7.4, 9.7)	
Q4 (134.9-1769 ng/g lipid)	95.5 (93.8, 97.2)[b]	96.1 (94.2, 97.9)		7.0 (5.9, 8.3)	8.9 (7.7, 10.3)	
p-value trend	<0.0001	0.05		0.90	0.99	

[a]Model adjusts for age (continuous), sex (male/female), race (non-Hispanic white, non-Hispanic African-American, Hispanic, or other), education level (less than high school, high school grad, some college or more), serum lipids (continuous), self-reported smoking history (never, 5+ years since last cigarette, <5 years since last cigarette, infrequent current smoker, daily smoker), hypertension status (yes/no), nativity (born in the US, yes/no), and survey cycle; [b]Statistically significant (p<0.05);

TABLE XLIII (continued).
SEX-STRATIFIED MULTIVARIABLE ADJUSTED ASSOCIATIONS BETWEEN CATEGORIZED LEVELS OF LIPID ADJUSTED PCDD, PCDF, AND PCB SUMMARY MEASURES AND CONTINUOUS OUTCOMES AMONG NHANES 1999-2004 PARTICIPANTS

	Males	Females		Males	Females	
Serum concentrations (lipid adjusted ng/g)	**Continuous eGFR (mL/minute/1.73 m^2)**	**Continuous eGFR (mL/minute/1.73 m^2)**		**Continuous UACR (mg/g)**	**Continuous UACR (mg/g)**	
	Mean (95% CI)[a]	**Mean (95% CI)[a]**	**p-interaction**	**GM (95% CI)[a]**	**GM (95% CI)[a]**	**p-interaction**
Warner mixed PCBs, Q1 (ref)	90.0 (88.0, 91.9)	94.0 (92.1, 95.9)		6.6 (5.9, 7.4)	9.1 (8.1, 10.2)	
Q2 (31.1-50.5 ng/g lipid)	91.8 (90.7, 92.8)	94.0 (92.0, 95.9)		6.2 (5.6, 7.0)	7.7 (6.9, 8.5)[b]	
Q3 (50.5-82.9 ng/g lipid)	93.6 (92.3, 95.0)[b]	95.9 (94.3, 97.6)	0.0002	7.2 (6.3, 8.1)	8.4 (7.4, 9.5)	<0.0001
Q4 (83.0-1271 ng/g lipid)	95.1 (93.4, 96.7)[b]	94.8 (93.2, 96.3)		7.2 (6.1, 8.5)	9.1 (7.9, 10.4)	
p-value trend	<0.0001	0.22		0.29	0.76	
Warner CYP1A PCBs, Q1 (ref)	89.8 (88.3, 91.3)	94.2 (92.2, 96.3)		5.9 (5.3, 6.7)	8.8 (7.9, 9.9)	
Q2 (22.2-33.7 ng/g lipid)	92.1 (90.8, 93.4)[b]	93.2 (91.2, 95.1)		6.3 (5.8, 6.9)	7.4 (6.6, 8.3)[b]	
Q3 (33.7-54.7 ng/g lipid)	94.4 (92.8, 95.9)[b]	95.5 (94.2, 96.9)	0.004	7.4 (6.5, 8.3)[b]	7.9 (7.2, 8.7)	0.001
Q4 (54.8-704 ng/g lipid)	94.7 (92.7, 96.8)[b]	95.4 (93.5, 97.3)		8.3 (6.4, 10.6)[b]	10.0 (8.7, 11.6)	
p-value trend	<0.0001	0.13		0.01	0.18	
Warner CYP2B PCBs, Q1 (ref)	90.5 (89.1, 91.8)	93.2 (91.2, 95.2)		6.9 (6.2, 7.6)	9.1 (7.9, 10.4)	
Q2 (67.5-116.3 ng/g lipid)	92.4 (90.7, 94.0)	95.2 (93.7, 96.8)		6.2 (5.6, 6.8)[b]	7.9 (7.2, 8.6)[b]	
Q3 (116.3-196.1 ng/g lipid)	92.9 (91.3, 94.5)[b]	95.4 (93.7, 97.0)	0.002	6.7 (5.9, 7.6)	8.0 (7.2, 8.9)	0.03
Q4 (196.1-2253 ng/g lipid)	94.3 (92.7, 95.9)[b]	94.7 (92.6, 96.8)		7.5 (6.5, 8.7)	9.2 (8.1, 10.4)	
p-value trend	0.003	0.24		0.40	0.93	

[a]Model adjusts for age (continuous), sex (male/female), race (non-Hispanic white, non-Hispanic African-American, Hispanic, or other), education level (less than high school, high school grad, some college or more), serum lipids (continuous), self-reported smoking history (never, 5+ years since last cigarette, <5 years since last cigarette, infrequent current smoker, daily smoker), hypertension status (yes/no), nativity (born in the US, yes/no), and survey cycle; [b]Statistically significant (p<0.05);

TABLE XLIV.
SEX-STRATIFIED MULTIVARIABLE ADJUSTED ASSOCIATIONS BETWEEN SELECT CATEGORIZED LEVELS OF LIPID ADJUSTED PCDD, PCDF, AND PCB INDEXES AND ALBUMINURIA AMONG NHANES 1999-2004 PARTICIPANTS

	Males	**Females**	
Serum concentrations (lipid adjusted ng/g)	**Albuminuria (UACR ≥ 17 mg/g)**	**Albuminuria (UACR ≥ 25 mg/g)**	
	OR (95% CI)[a]	**OR (95% CI)**[a]	**p-interaction**
Total toxic equivalency (TEQ), Q1 (ref)	1.0 (ref)	1.0 (ref)	
Q2 (0.009-0.014 ng/g lipid)	0.85 (0.53, 1.34)	0.84 (0.50, 1.42)	
Q3 (0.015-0.02 ng/g lipid)	1.28 (0.80, 2.06)	0.81 (0.46, 1.43)	0.02
Q4 (0.02-0.18 ng/g lipid)	1.46 (0.87, 2.45)	1.03 (0.62, 1.71)	
p-value trend	0.06	1.0	
Total Anti-Estrogenic PCBs, Q1 (ref)	1.0 (ref)	1.0 (ref)	
Q2 (41.0-66.7 ng/g lipid)	1.10 (0.64, 1.89)	0.57 (0.31, 1.04)	
Q3 (66.8-116.1) ng/g lipid)	1.19 (0.70, 2.03)	0.61 (0.31, 1.18)	0.06
Q4 (116.2-1675 ng/g lipid)	1.26 (0.73, 2.17)	0.92 (0.46, 1.84)	
p-value trend	0.41	0.96	
2A Anti-Estrogenic PCBs, Q1 (ref)	1.0 (ref)	1.0 (ref)	
Q2 (20.8-31.6 ng/g lipid)	1.35 (0.80, 2.26)	0.60 (0.31, 1.14)	
Q3 (31.7-52.5 ng/g lipid)	1.84 (1.20, 2.81)[b]	0.72 (0.40, 1.27)	0.01
Q4 (52.6-698 ng/g lipid)	1.49 (0.87, 2.56)	1.13 (0.57, 2.26)	
p-value trend	0.09	0.58	
2B Anti-Estrogenic PCBs, Q1 (ref)	1.0 (ref)	1.0 (ref)	
Q2 (19.0-34.5 ng/g lipid)	0.85 (0.51, 1.44)	0.54 (0.27, 1.07)	
Q3 (34.6-62.7 ng/g lipid)	1.05 (0.68, 1.63)	0.64 (0.32, 1.28)	0.08
Q4 (62.8-1072 ng/g lipid)	1.15 (0.73, 1.80)	0.91 (0.43, 1.91)	
p-value trend	0.37	0.94	
Warner CYP1A PCBs, Q1 (ref)	1.0 (ref)	1.0 (ref)	
Q2 (22.2-33.7 ng/g lipid)	1.14 (0.67, 1.91)	0.64 (0.35, 1.16)	
Q3 (33.7-54.7 ng/g lipid)	1.63 (0.98, 2.73)	0.76 (0.44, 1.33)	0.03
Q4 (54.8-704 ng/g lipid)	1.43 (0.80, 2.55)	1.23 (0.62, 2.43)	
p-value trend	0.12	0.45	
Warner CYP2B PCBs, Q1 (ref)	1.0 (ref)	1.0 (ref)	
Q2 (67.5-116.3 ng/g lipid)	0.70 (0.44, 1.11)	0.52 (0.32, 0.86)[b]	
Q3 (116.3-196.1 ng/g lipid)	0.74 (0.43, 1.25)	0.51 (0.30, 0.87)[b]	0.06
Q4 (196.1-2253 ng/g lipid)	0.91 (0.56, 1.47)	0.78 (0.44, 1.37)	
p-value trend	0.91	0.43	

[a] Model adjusts for age (continuous), sex (male/female), race (non-Hispanic white, non-Hispanic African-American, Hispanic, or other), education level (less than high school, high school grad, some college or more), serum lipids (continuous), self-reported smoking history (never, 5+ years since last cigarette, <5 years since last cigarette, infrequent current smoker, daily smoker), hypertension status (yes/no), nativity (born in the US, yes/no), and survey cycle

[b] Statistically significant ($p<0.05$)

TABLE XLV.
OVERALL WEIGHTED DEMOGRAPHIC AND CLINICAL CHARACTERISTICS WITH DISTRIBUTIONS OF EACH OUTCOME BY LEVELS OF COVARIATES AMONG NHANES 1999-2004 PARTICIPANTS IN THE PESTICIDE AND PESTICIDE METABOLITE SUBSAMPLE

	Overall	Continuous eGFR (mL/minute/1.73 m^2)[a]		Low eGFR (eGFR < 60)		Urine Albumin to Creatinine Ratio (mg/g)[a]		Albuminuria (UACR ≥ 17/25 males and females mg/g)	
	n (%)	Mean (95% CI)	p-value	% (95% CI)	p-value	GM (95% CI)	p-value	% (95% CI)	p-value
Overall		93.3 (92.3, 94.3)		6.4 (5.5, 7.3)		7.5 (7.1, 7.8)		12.4 (10.9, 14.0)	
Age in years, 20-39	1049 (38.5)	107.3 (105.9, 108.6)	<0.0001	0.27 (0.0, 0.72)		5.9 (5.6, 6.2)	<0.0001	7.8 (6.2, 9.5)	
40-59	986 (39.7)	92.4 (91.1, 93.7)	<0.0001	1.5 (0.70, 2.4)		7.1 (6.6, 7.5)	<0.0001	10.9 (8.5, 13.2)	
60+	1099 (21.8)	70.4 (68.9, 71.8)	ref	26.2 (23.3, 29.1)	<0.0001	12.3 (11.1, 13.6)	ref	23.5 (20.3, 26.6)	<0.0001
Sex, Male	1562 (48.7)	92.6 (91.6, 93.7)		4.6 (3.5, 5.6)		6.9 (6.5, 7.3)		13.7 (11.9, 15.5)	
Female	1572 (51.3)	94.0 (92.7, 95.3)	0.03	8.2 (6.6, 9.7)	0.0002	8.0 (7.5, 8.6)	0.001	11.2 (9.2, 13.3)	0.05
Premenopausal female	858 (63.7)	92.0 (90.5, 93.5)		1.5 (0.61, 2.5)		7.7 (7.1, 8.4)		8.7 (6.6, 10.7)	
Postmenopausal female	714 (36.3)	94.7 (92.5, 97.0)	0.05	19.8 (15.8, 23.8)	<0.0001	9.0 (7.8, 10.4)	0.11	15.8 (12.4, 19.2)	<0.0001
Race/ethnicity									
African-American, nH	561 (10.0)	99.3 (97.5, 101.2)	<0.0001	5.2 (3.3, 7.1)		8.4 (7.4, 9.6)	0.02	14.9 (11.6, 18.2)	
White, nH	1598 (72.7)	91.6 (90.4, 92.8)	ref	7.2 (6.2, 8.3)		7.1 (6.7, 7.4)	ref	11.7 (9.7, 13.7)	
Hispanic	852 (12.1)	98.5 (97.6, 99.5)	<0.0001	2.1 (1.0, 3.1)		8.8 (8.2, 9.5)	<0.0001	14.0 (11.7, 16.4)	
Other	123 (5.2)	93.7 (89.9, 97.6)	0.31	7.4 (2.9, 11.9)	<0.0001	8.6 (6.9, 10.8)	0.08	14.1 (7.2, 21.0)	0.31
Education, < High school	1000 (19.6)	95.9 (94.3, 97.6)	0.002	10.5 (8.0, 13.0)		9.0 (8.1, 10.0)	<0.0001	19.6 (15.9, 23.3)	
High school graduate	723 (25.2)	93.8 (92.5, 95.1)	0.06	6.5 (5.0, 8.0)		7.3 (6.6, 8.1)	0.15	12.5 (8.8, 16.2)	
Some college	857 (31.5)	92.4 (90.7, 94.2)	0.59	5.6 (3.7, 7.4)		7.3 (6.7, 7.8)	0.12	10.6 (8.5, 12.7)	
≥ College graduate	554 (23.7)	91.9 (90.1, 93.7)	ref	4.1 (2.6, 5.6)	<0.0001	6.7 (6.2, 7.3)	ref	8.9 (6.5, 11.4)	<0.0001
Born in the United States, Yes	2439 (85.4)	92.5 (91.5, 93.6)		6.8 (5.8, 7.8)		7.4 (7.0, 7.8)		12.5 (10.7, 14.3)	
No	695 (14.6)	98.0 (96.5, 99.5)	<0.0001	4.1 (2.6, 5.6)	0.001	7.9 (7.3, 8.6)	0.15	12.0 (9.2, 14.9)	0.79
Body mass index, kg/m^2, <25	1005 (34.8)	93.2 (91.8, 94.5)	0.82	6.0 (4.6, 7.5)		7.5 (7.0, 8.0)	0.13	10.9 (8.5, 13.2)	
25 to <30	1126 (34.2)	93.8 (92.4, 95.2)	0.30	6.6 (5.0, 8.3)		6.8 (6.4, 7.2)	0.001	11.8 (9.7, 13.9)	
≥30	1003 (31.0)	93.0 (91.8, 94.2)	ref	6.6 (5.1, 8.1)	0.82	8.1 (7.5, 8.9)	ref	14.9 (12.2, 17.7)	0.03
High triglycerides ≥ 200 mg/dL	573 (18.7)	92.3 (90.9, 93.8)		8.8 (6.2, 11.4)		8.3 (7.4, 9.2)		16.3 (12.8, 19.9)	
<200 mg/dL	2561 (81.3)	93.6 (92.4, 94.7)	0.16	5.9 (5.1, 6.7)	0.01	7.3 (6.9, 7.7)	0.05	11.6 (10.0, 13.1)	0.01
High total cholesterol ≥ 200 mg/dL	1560 (50.2)	93.4 (92.4, 94.3)		7.0 (5.6, 8.5)		7.0 (6.6, 7.5)		12.7 (10.4, 15.0)	
<200 mg/dL	1574 (49.8)	93.3 (92.0, 94.6)	0.88	5.8 (4.6, 6.9)	0.18	7.9 (7.4, 8.4)	0.02	12.2 (10.4, 14.0)	0.72
Diabetes	380 (8.0)	93.5 (90.7, 96.4)		16.0 (11.4, 20.6)		16.4 (13.3, 20.2)		36.9 (31.4, 42.4)	
Non-diabetic	2754 (92.0)	93.3 (92.3, 94.3)	0.87	5.6 (4.7, 6.5)	<0.0001	7.0 (6.7, 7.3)	<0.0001	10.3 (8.9, 11.8)	<0.0001

[a] age-adjusted

TABLE XLV (continued).
OVERALL WEIGHTED DEMOGRAPHIC AND CLINICAL CHARACTERISTICS WITH DISTRIBUTIONS OF EACH OUTCOME BY LEVELS OF COVARIATES AMONG NHANES 1999-2004 PARTICIPANTS IN THE PESTICIDE AND PESTICIDE METABOLITE SUBSAMPLE

	Overall	Continuous eGFR (mL/minute/1.73 m^2)[a]		Low eGFR (eGFR < 60)		Urine Albumin to Creatinine Ratio (mg/g)[a]		Albuminuria (UACR ≥ 17/25 males and females mg/g)	
	n (%)	Mean (95% CI)	p-value	% (95% CI)	p-value	GM (95% CI)	p-value	% (95% CI)	p-value
Hypertension	1393 (37.4)	93.2 (91.9, 94.4)		14.1 (11.9, 16.3)		9.1 (8.3, 10.0)		20.1 (16.9, 23.3)	
Non-hypertensive	1741 (62.6)	93.4 (92.4, 94.5)	0.63	1.9 (1.4, 2.3)	<0.0001	6.6 (6.3, 7.0)	<0.0001	7.9 (6.4, 9.4)	<0.0001
Smoking status, Never	1517 (47.5)	93.3 (92.1, 94.4)	<0.0001	6.3 (4.8, 7.8)		7.4 (7.0, 7.8)	0.24	10.3 (8.5, 12.1)	
Former (5+ years)	703 (20.7)	90.5 (89.0, 92.1)	<0.0001	13.2 (11.0, 15.3)		7.0 (6.1, 8.0)	0.16	17.0 (12.8, 21.1)	
Former (<5 years)	177 (5.7)	93.3 (90.9, 95.7)	0.06	3.0 (0.7, 5.3)		8.1 (6.7, 9.7)	0.83	13.8 (8.2, 19.4)	
Current (infrequent)	129 (4.0)	93.3 (89.8, 96.8)	0.12	3.0 (0, 6.1)		7.7 (6.2, 9.6)	0.89	11.4 (4.6, 18.1)	
Current (daily)	605 (22.1)	96.0 (94.7, 97.4)	ref	1.9 (0.8, 2.9)	<0.0001	7.9 (7.1, 8.7)	ref	12.8 (9.9, 15.7)	0.01
Cotinine ≥ 10 ng/ml	857 (31.1)	95.4 (94.2, 96.6)		2.5 (1.6, 3.3)		7.9 (7.2, 8.6)		13.8 (11.4, 16.3)	
< 10 ng/ml	2260 (68.9)	92.4 (91.4, 93.5)	<0.0001	8.2 (6.9, 9.4)	<0.0001	7.3 (6.9, 7.7)	0.13	11.9 (10.3, 13.6)	0.15
β-hexachlorocyclohexane Q1 (<LOD)	686 (26.9)	91.3 (89.2, 93.4)	ref	0.5 (0.1, 1.0)		7.5 (6.8, 8.2)	ref	9.0 (6.3, 11.7)	
Q2 (1.8-7.2 ng/g lipid)	574 (23.6)	91.7 (90.4, 93.0)	0.67	2.0 (0.6, 3.4)		7.1 (6.4, 7.8)	0.43	9.3 (6.0, 12.5)	
Q3 (7.3-30.5 ng/g lipid)	1228 (36.7)	95.0 (94.0, 96.1)	0.002	8.9 (7.4, 10.4)		7.3 (6.7, 7.9)	0.70	14.8 (11.9, 17.6)	
Q4 (30.6-3500.0 ng/g lipid)	646 (12.8)	95.7 (93.8, 97.7)	0.003	19.8 (15.8, 23.8)	<0.0001	8.6 (7.5, 9.9)	0.12	18.9 (14.8, 22.9)	<0.0001
Hexachlorobenzene, Q1 (<LOD)	1820 (59.2)	92.9 (91.3, 94.4)	ref	6.0 (4.7, 7.4)		7.6 (7.1, 8.1)	ref	12.8 (10.7, 14.9)	
Q2 (4.3-12.4 ng/g lipid)	318 (11.4)	93.1 (91.8, 94.5)	0.80	1.2 (0.4, 1.9)		8.0 (7.2, 8.8)	0.39	13.6 (10.2, 17.0)	
Q3 (12.5-21.3 ng/g lipid)	666 (21.1)	94.1 (92.8, 95.4)	0.23	7.2 (5.3, 9.1)		7.0 (6.3, 7.7)	0.16	10.5 (7.6, 13.3)	
Q4 (21.4-381.0 ng/g lipid)	330 (8.3)	94.8 (92.7, 96.9)	0.13	14.4 (12.0, 16.8)	<0.0001	7.1 (6.1, 8.2)	0.40	13.4 (9.8, 17.0)	0.38
Heptachlor epoxide, Q1 (<LOD)	1191 (41.5)	93.4 (92.0, 94.8)	ref	1.7 (1.1, 2.3)		7.0 (6.6, 7.5)	ref	8.4 (6.8, 9.9)	
Q2 (1.8-6.1 ng/g lipid)	497 (17.5)	93.4 (91.7, 95.0)	0.95	6.6 (4.2, 8.9)		7.2 (6.5, 7.9)	0.67	11.0 (7.6, 14.4)	
Q3 (6.2-14.1 ng/g lipid)	958 (28.8)	93.4 (92.1, 94.8)	0.97	7.7 (6.3, 9.1)		7.6 (7.1, 8.2)	0.11	15.6 (12.7, 18.5)	
Q4 (14.2-912.0 ng/g lipid)	488 (12.2)	92.7 (90.8, 94.5)	0.45	19.2 (15.4, 23.0)	<0.0001	9.2 (8.1, 10.5)	0.001	20.9 (17.4, 24.4)	<0.0001

[a] age-adjusted

TABLE XLV (continued).
OVERALL WEIGHTED DEMOGRAPHIC AND CLINICAL CHARACTERISTICS WITH DISTRIBUTIONS OF EACH OUTCOME BY LEVELS OF COVARIATES AMONG NHANES 1999-2004 PARTICIPANTS IN THE PESTICIDE AND PESTICIDE METABOLITE SUBSAMPLE

	Overall	Continuous eGFR (mL/minute/1.73 m^2)[a]		Low eGFR (eGFR < 60)		Urine Albumin to Creatinine Ratio (mg/g)[a]		Albuminuria (UACR ≥ 17/25 males and females mg/g)	
	n (%)	Mean (95% CI)	p-value	% (95% CI)	p-value	GM (95% CI)	p-value	% (95% CI)	p-value
Oxychlordane , Q1 (<LOD)	467 (15.3)	92.9 (90.3, 95.6)	ref	0.3 (0, 0.8)		7.3 (6.4, 8.3)	ref	8.1 (5.3, 10.8)	
Q2 (1.8-10.5 ng/g lipid)	677 (26.1)	92.5 (90.9, 94.2)	0.69	1.4 (0.2, 2.5)		7.0 (6.5, 7.5)	0.53	8.4 (5.8, 11.0)	
Q3 (10.6-30.4 ng/g lipid)	1325 (44.2)	93.8 (92.9, 94.7)	0.49	5.4 (4.3, 6.5)		7.2 (6.7, 7.6)	0.80	12.4 (10.1, 14.7)	
Q4 (30.5-289.0 ng/g lipid)	665 (14.4)	93.7 (91.9, 95.5)	0.60	25.2 (22.1, 28.3)	<0.0001	9.7 (8.4, 11.3)	0.01	24.5 (20.0, 29.1)	<0.0001
p,p'-DDT, Q1 (<LOD)	1352 (51.0)	92.0 (90.6, 93.4)	ref	4.0 (2.9, 5.0)		7.2 (6.8, 7.7)	ref	10.2 (8.4, 12.0)	
Q2 (1.9-5.8 ng/g lipid)	461 (17.4)	93.1 (91.8, 94.4)	0.26	5.1 (3.8, 6.3)		6.8 (6.4, 7.3)	0.24	10.1 (8.1, 12.1)	
Q3 (5.9-19.6 ng/g lipid)	889 (24.5)	95.2 (93.9, 96.5)	<0.0001	9.9 (7.8, 12.0)		7.7 (6.9, 8.7)	0.29	16.3 (12.6, 20.0)	
Q4 (19.7-3450.0 ng/g lipid)	432 (7.1)	96.9 (94.5, 99.3)	0.0005	15.2 (10.1, 20.2)	<0.0001	9.9 (8.0, 12.2)	0.01	21.2 (16.3, 26.1)	<0.0001
p,p'-DDE, Q1 (1.6-177.0 ng/g lipid)	782 (33.6)	90.7 (89.0, 92.4)	ref	2.3 (1.3, 3.2)		7.5 (7.0, 8.1)	ref	10.6 (8.9, 12.2)	
Q2 (178.0-414.0 ng/g lipid)	784 (29.9)	93.1 (92.0, 94.3)	0.01	4.3 (3.0, 5.6)		7.0 (6.5, 7.6)	0.17	9.6 (7.0, 12.2)	
Q3 (415.0-1040.0) ng/g lipid)	783 (22.6)	95.3 (93.9, 96.7)	0.0003	9.7 (7.1, 12.3)		7.4 (6.7, 8.2)	0.83	15.0 (11.4, 18.5)	
Q4 (1050-27900 ng/g lipid)	784 (13.9)	96.9 (94.8, 99.0)	<0.0001	15.7 (12.4, 19.0)	<0.0001	8.4 (7.2, 9.8)	0.23	19.1 (15.1, 23.1)	<0.0001
***trans*-Nonachlor,** Q1 (<LOD)	240 (8.2)	91.7 (88.2, 95.2)	ref	0.4 (0, 1.1)		7.1 (6.0, 8.4)	ref	6.6 (2.3, 10.9)	
Q2 (2.1-14.1 ng/g lipid)	749 (28.2)	93.2 (91.4, 94.9)	0.35	1.0 (0.1, 1.8)		6.9 (6.4, 7.3)	0.66	8.1 (6.2, 9.9)	
Q3 (14.2-46.5 ng/g lipid)	1422 (48.2)	93.3 (92.3, 94.2)	0.37	5.9 (4.8, 7.1)		7.3 (6.8, 7.9)	0.72	12.4 (10.1, 14.7)	
Q4 (46.6-834.0 ng/g lipid)	723 (15.4)	94.7 (92.8, 96.5)	0.11	21.1 (17.5, 24.6)	<0.0001	9.4 (8.1, 10.8)	0.02	23.8 (20.0, 27.7)	<0.0001
Mirex, Q1 (<LOD)	2015 (65.8)	92.8 (91.5, 94.1)	ref	5.2 (4.2, 6.2)		7.5 (7.1, 8.0)	ref	11.4 (9.7, 13.1)	
Q2 (1.2-4.40 ng/g lipid)	294 (9.7)	93.6 (92.4, 94.8)	0.41	7.5 (5.2, 9.9)		6.8 (6.0, 7.9)	0.25	13.3 (9.1, 17.5)	
Q3 (4.50-14.0 ng/g lipid)	546 (16.1)	94.0 (92.8, 95.1)	0.10	9.0 (6.0, 11.9)		7.2 (6.7, 7.8)	0.50	12.8 (10.0, 15.6)	
Q4 (14.1-2960 ng/g lipid)	279 (8.4)	95.7 (94.0, 97.3)	0.002	10.0 (6.8, 13.3)	0.002	8.1 (6.4, 10.4)	0.53	19.0 (11.3, 26.6)	0.11
Dieldrin, Q1 (<LOD)	511 (22.5)	92.9 (90.5, 95.2)	ref	2.1 (0.8, 3.4)		7.4 (6.7, 8.2)	ref	8.6 (6.1, 11.1)	
Q2 (1.9-5.6 ng/g lipid)	453 (21.2)	94.1 (92.4, 95.7)	0.36	4.3 (2.7, 5.8)		6.1 (5.6, 6.8)	0.04	7.3 (3.9, 10.7)	
Q3 (5.7-11.9 ng/g lipid)	914 (38.6)	94.1 (92.7, 95.4)	0.23	6.9 (4.8, 9.0)		7.6 (7.0, 8.4)	0.81	13.8 (11.0, 16.6)	
Q4 (12.0-448.0 ng/g lipid)	464 (17.7)	94.3 (92.2, 96.3)	0.35	13.4 (9.5, 17.3)	<0.0001	8.2 (7.4, 9.0)	0.16	18.0 (14.5, 21.4)	<0.0001
Survey year, 1999-2000	705 (20.3)	92.2 (90.3, 94.0)	0.13	7.1 (5.2, 8.9)		7.9 (7.0, 8.8)	0.18	14.5 (10.2, 18.8)	
2001-2002	1224 (41.1)	93.5 (91.5, 95.5)	0.79	5.9 (4.2, 7.6)		7.5 (6.9, 8.1)	0.42	12.4 (9.8, 15.0)	
2003-2004	1205 (38.6)	93.8 (92.8, 94.8)	ref	6.6 (5.3, 7.9)	0.59	7.2 (6.8, 7.6)	ref	11.4 (9.9, 13.0)	0.38

[a] age-adjusted

TABLE XLVI.
WEIGHTED GEOMETRIC MEAN LIPID ADJUSTED B-HEXACHLOROCYCLOHEXANE, HEXACHLOROBENZENE, HEPTACHLOR EPOXIDE, AND OXYCHLORDANE CONCENTRATION LEVELS AMONG NHANES 1999-2004 PARTICIPANTS, OVERALL AND BY COVARIATES

	β-hexachlorocyclohexane (ng/g lipid)		Hexachlorobenzene (ng/g lipid)		Heptachlor Epoxide (ng/g lipid)		Oxychlordane (ng/g lipid)	
	GM (95% CI)	p-value	GM (95% CI)	p-value	GM (95% CI)	p-value	GM (95% CI)	p-value
Overall	8.6 (7.9, 9.3)		15.9 (15.1, 16.7)		5.9 (5.6, 6.3)		12.4 (11.8, 13.1)	
Age in years, 20-39	4.7 (4.3, 5.2)	<0.0001	15.2 (14.2, 16.3)	0.0001	4.6 (4.3, 4.9)	<0.0001	6.9 (6.5, 7.4)	<0.0001
40-59	9.1 (8.3, 10.1)	<0.0001	15.3 (14.5, 16.2)	<0.0001	5.9 (5.5, 6.4)	<0.0001	13.9 (13.1, 14.8)	<0.0001
60+	22.3 (20.3, 24.6)	ref	18.0 (16.8, 19.4)	ref	9.2 (8.4, 10.2)	ref	28.3 (26.4, 30.3)	ref
Male	7.1 (6.5, 7.7)		15.3 (14.4, 16.2)		5.9 (5.5, 6.4)		11.8 (11.0, 12.6)	
Female	10.3 (9.5, 11.2)	<0.0001	16.4 (15.5, 17.3)	0.005	5.9 (5.6, 6.3)	0.97	13.0 (12.4, 13.8)	0.003
Premenopausal	6.7 (6.0, 7.3)		16.4 (15.5, 17.3)		4.9 (4.6, 5.3)		9.1 (8.6, 9.8)	
Postmenopausal	22.2 (19.8, 25.0)	<0.0001	16.4 (15.2, 17.7)	0.97	8.3 (7.5, 9.1)	<0.0001	24.3 (22.4, 26.5)	<0.0001
Race/ethnicity								
African-American, nH	7.6 (6.7, 8.6)	0.67	15.7 (14.1, 17.5)	0.90	5.7 (5.1, 6.4)	0.46	12.8 (11.4, 14.2)	0.59
White, nH	7.8 (7.1, 8.5)	ref	15.6 (14.6, 16.7)	ref	6.0 (5.6, 6.4)	ref	13.1 (12.4, 13.9)	ref
Hispanic	12.4 (10.7, 14.3)	<0.0001	17.8 (15.5, 20.5)	0.11	5.7 (5.1, 6.3)	0.35	9.3 (8.4, 10.4)	<0.0001
Other	17.9 (12.6, 25.5)	<0.0001	15.3 (13.3, 17.5)	0.75	5.9 (5.0, 6.9)	0.75	10.3 (9.0, 11.9)	0.001
Education, < High school	12.3 (11.0, 13.7)	<0.0001	17.0 (15.8, 18.3)	0.004	6.8 (6.3, 7.4)	0.001	14.9 (13.3, 16.8)	0.004
High school graduate	8.3 (7.3, 9.5)	0.91	16.2 (14.9, 17.7)	0.07	5.9 (5.3, 6.5)	0.67	12.7 (11.7, 13.6)	0.60
Some college	7.1 (6.4, 8.0)	0.02	15.6 (14.5, 16.7)	0.322	5.6 (5.2, 6.0)	0.59	11.0 (10.2, 11.9)	0.03
≥ College graduate	8.4 (7.6, 9.4)	ref	15.0 (14.1, 15.9)	ref	5.7 (5.3, 6.2)	ref	12.3 (11.4, 13.3)	ref
Born in the United States, Yes	7.6 (7.0, 8.2)		15.6 (14.6, 16.6)		6.1 (5.7, 6.5)		13.2 (12.4, 14.0)	
No	18.0 (15.7, 20.7)	<0.0001	17.5 (15.9, 19.3)	0.08	5.1 (4.7, 5.5)	0.002	8.8 (8.0, 9.7)	<0.0001
BMI, kg/m², <25	7.6 (6.7, 8.7)	0.0001	16.4 (15.4, 17.6)	0.23	4.9 (4.6, 5.2)	<0.0001	11.5 (10.7, 12.3)	0.0004
25 to <30	8.5 (7.9, 9.2)	0.01	15.4 (14.5, 16.3)	0.38	5.9 (5.5, 6.3)	<0.0001	12.6 (11.9, 13.4)	0.19
≥30	9.9 (8.9, 11.0)	ref	15.8 (14.8, 16.8)	ref	7.4 (6.8, 8.0)	ref	13.4 (12.4, 14.4)	ref
Triglycerides ≥ 200 mg/dL, Yes	10.3 (9.0, 11.8)		12.8 (11.7, 14.1)		7.3 (6.7, 8.0)		16.1 (14.6, 17.7)	
No	8.2 (7.6, 8.9)	0.001	16.6 (15.8, 17.5)	<0.0001	5.6 (5.3, 6.0)	<0.0001	11.7 (11.1, 12.4)	<0.0001
Total cholesterol ≥ 200 mg/dL, Yes	9.1 (8.3, 9.9)		14.3 (13.5, 15.3)		5.9 (5.5, 6.4)		13.7 (12.9, 14.6)	
No	8.1 (7.3, 9.0)	0.03	17.5 (16.5, 18.6)	<0.0001	6.0 (5.6, 6.3)	0.79	11.3 (10.6, 12.0)	<0.0001
Diabetes	20.4 (17.2, 24.1)		16.5 (15.0, 18.3)		11.0 (9.6, 12.5)		24.3 (21.7, 27.3)	
Non-diabetic	8.0 (7.3, 8.7)	<0.0001	15.8 (15.0, 16.6)	0.25	5.6 (5.3, 6.0)	<0.0001	11.7 (11.1, 12.4)	<0.0001
Hypertension	13.3 (12.2, 14.5)		16.2 (15.2, 17.3)		7.7 (7.1, 8.3)		18.3 (17.1, 19.6)	
Non-hypertensive	6.6 (6.0, 7.2)	<0.0001	15.6 (14.7, 16.6)	0.30	5.1 (4.8, 5.4)	<0.0001	9.8 (9.3, 10.4)	<0.0001

TABLE XLVI (continued).
WEIGHTED GEOMETRIC MEAN LIPID ADJUSTED B-HEXACHLOROCYCLOHEXANE, HEXACHLOROBENZENE, HEPTACHLOR EPOXIDE, AND OXYCHLORDANE CONCENTRATION LEVELS AMONG NHANES 1999-2004 PARTICIPANTS, OVERALL AND BY COVARIATES

	β-hexachlorocyclohexane (ng/g lipid)		Hexachlorobenzene (ng/g lipid)		Heptachlor Epoxide (ng/g lipid)		Oxychlordane (ng/g lipid)	
	GM (95% CI)	p-value	GM (95% CI)	p-value	GM (95% CI)	p-value	GM (95% CI)	p-value
Smoking status, Never	8.6 (7.9, 9.2)	0.002	15.9 (15.0, 16.7)	0.09	5.7 (5.4, 6.1)	0.27	11.5 (10.8, 12.1)	0.72
Former (5+ years)	11.6 (10.5, 12.8)	<0.0001	17.0 (15.8, 18.2)	0.005	7.2 (6.5, 7.9)	<0.0001	17.4 (15.9, 19.0)	<0.0001
Former (<5 years)	7.7 (6.6, 9.0)	0.22	16.2 (14.0, 18.8)	0.28	5.4 (4.8, 6.2)	0.98	10.8 (9.2, 12.6)	0.34
Current (infrequent)	7.6 (6.0, 9.6)	0.49	14.8 (12.9, 17.0)	0.92	5.6 (4.8, 6.5)	0.81	10.2 (8.4, 12.3)	0.18
Current (daily)	6.9 (5.9, 7.9)	ref	14.9 (13.8, 16.2)	ref	5.5 (4.9, 6.1)	ref	11.6 (10.8, 12.5)	ref
Survey year, 1999-2000	7.7 (6.4, 9.1)	0.80	37.3 (35.9, 38.9)	<0.0001	7.6 (7.0, 8.3)	<0.0001	14.6 (13.3, 16.0)	<0.0001
2001-2002	9.9 (9.0, 10.8)	0.01	10.6 (10.3, 10.9)	<0.0001	6.5 (6.0, 7.0)	<0.0001	13.1 (11.9, 14.4)	0.002
2003-2004	7.9 (6.9, 9.0)	ref	15.5 (14.8, 16.3)	ref	4.7 (4.3, 5.3)	ref	10.8 (10.1, 11.5)	ref

TABLE XLVII.
WEIGHTED GEOMETRIC MEAN LIPID ADJUSTED P,P'-DDE, P,P'-DDT, TRANS-NONACHLOR, AND MIREX CONCENTRATION LEVELS AMONG NHANES 1999-2004 PARTICIPANTS, OVERALL AND BY COVARIATES

	p,p'-DDE (ng/g lipid)		p,p'-DDT (ng/g lipid)		Trans-nonachlor (ng/g lipid)		Mirex (ng/g lipid)	
	GM (95% CI)	p-value	GM (95% CI)	p-value	GM (95% CI)	p-value	GM (95% CI)	p-value
Overall	307 (277, 340)		6.9 (6.4, 7.3)		19.1 (17.8, 20.4)		4.6 (4.0, 5.3)	
Age in years, 20-39	177 (158, 198)	<0.0001	6.1 (5.7, 6.6)	<0.0001	10.5 (9.7, 11.4)	<0.0001	4.0 (3.5, 4.5)	<0.0001
40-59	345 (306, 388)	<0.0001	6.7 (6.1, 7.4)	<0.0001	21.5 (19.8, 23.3)	<0.0001	4.7 (4.1, 5.4)	0.004
60+	652 (581, 733)	ref	8.7 (8.1, 9.4)	ref	43.8 (39.9, 48.2)	ref	5.7 (4.6, 7.0)	ref
Male	287 (257, 322)		6.6 (6.1, 7.1)		18.6 (17.0, 20.3)		4.8 (4.2, 5.5)	
Female	326 (291, 365)	0.01	7.1 (6.7, 7.6)	0.01	19.5 (18.2, 20.9)	0.22	4.4 (3.8, 5.1)	0.02
Premenopausal	226 (200, 257)		6.1 (5.6, 6.6)		13.8 (12.8, 14.9)		3.9 (3.5, 4.4)	
Postmenopausal	618 (539, 709)	<0.0001	9.3 (8.6, 10.0)	<0.0001	35.6 (31.9, 39.8)	<0.0001	5.3 (4.3, 6.6)	<0.0001
Race/ethnicity								
African-American, nH	372 (326, 425)	<0.0001	8.4 (7.5, 9.4)	<0.0001	21.7 (19.2, 24.4)	0.15	7.5 (5.6, 10.1)	<0.0001
White, nH	260 (232, 290)	ref	6.0 (5.6, 6.5)	ref	19.7 (18.2, 21.3)	ref	4.5 (3.9, 5.2)	ref
Hispanic	613 (544, 691)	<0.0001	10.2 (9.0, 11.7)	<0.0001	14.2 (12.4, 16.4)	<0.0001	3.7 (3.5, 4.0)	0.03
Other	432 (343, 543)	0.0003	10.9 (8.7, 13.7)	<0.0001	18.6 (15.6, 22.2)	0.55	3.8 (3.3, 4.3)	0.06
Education, < High school	495 (428, 572)	<0.0001	9.4 (8.5, 10.4)	<0.0001	24.1 (21.3, 27.4)	0.001	5.8 (4.5, 7.6)	0.01
High school graduate	281 (240, 328)	0.76	6.5 (5.9, 7.3)	0.90	18.8 (17.0, 20.7)	0.92	4.8 (3.9, 6.0)	0.12
Some college	266 (235, 300)	0.64	6.1 (5.7, 6.6)	0.16	16.8 (15.3, 18.4)	0.05	4.2 (3.8, 4.6)	0.80
≥ College graduate	274 (246, 306)	ref	6.5 (6.1, 6.9)	ref	18.9 (17.3, 20.6)	ref	4.1 (3.7, 4.5)	ref
Born in the United States, Yes	274 (246, 304)		6.2 (5.8, 6.7)		20.0 (18.5, 21.6)		4.8 (4.1, 5.6)	
No	597 (529, 674)	<0.0001	12.1 (10.6, 13.7)	<0.0001	14.5 (13.0, 16.1)	<0.0001	3.6 (3.3, 3.9)	0.001
BMI, kg/m², <25	282 (246, 323)	0.01	6.8 (6.2, 7.4)	0.11	17.4 (16.0, 19.0)	0.004	5.1 (4.4, 5.9)	<0.0001
25 to <30	313 (282, 349)	0.41	6.7 (6.3, 7.1)	0.11	19.7 (18.3, 21.1)	0.54	4.5 (4.0, 5.1)	0.12
≥30	328 (290, 372)	ref	7.2 (6.5, 7.9)	ref	20.3 (18.3, 22.6)	ref	4.2 (3.5, 5.0)	ref
Triglycerides ≥ 200 mg/dL, Yes	327 (280, 384)		6.6 (6.0, 7.3)		25.2 (22.5, 28.2)		4.3 (3.3, 5.5)	
No	302 (272, 335)	0.23	6.9 (6.5, 7.4)	0.24	17.9 (16.7, 19.2)	<0.0001	4.7 (4.1, 5.3)	0.35
Total cholesterol ≥ 200 mg/dL, Yes	313 (280, 350)		6.3 (5.9, 6.8)		21.2 (19.4, 23.1)		4.4 (3.7, 5.3)	
No	300 (267, 337)	0.38	7.5 (6.9, 8.1)	<0.0001	17.1 (15.8, 18.5)	<0.0001	4.8 (4.2, 5.4)	0.24
Diabetes	595 (482, 735)		10.0 (8.7, 11.6)		39.0 (33.7, 45.1)		5.9 (4.7, 7.4)	
Non-diabetic	289 (261, 321)	<0.0001	6.6 (6.2, 7.1)	<0.0001	17.9 (16.7, 19.2)	<0.0001	4.5 (3.9, 5.1)	0.0002
Hypertension	439 (388, 496)		7.9 (7.3, 8.5)		29.4 (26.8, 32.2)		4.9 (4.1, 6.0)	
Non-hypertensive	248 (222, 276)	<0.0001	6.3 (5.9, 6.7)	<0.0001	14.7 (13.8, 15.7)	<0.0001	4.4 (3.9, 4.9)	0.03
Smoking status, Never	314 (283, 348)	0.001	7.4 (6.9, 7.9)	<0.0001	17.5 (16.3, 18.8)	0.70	4.4 (3.9, 5.0)	0.07
Former (5+ years)	377 (334, 426)	<0.0001	7.1 (6.7, 7.6)	0.0008	27.5 (24.6, 30.7)	<0.0001	4.9 (4.2, 5.7)	0.73
Former (<5 years)	292 (242, 353)	0.11	6.3 (5.8, 6.9)	0.18	16.6 (14.1, 19.5)	0.41	3.9 (3.4, 4.5)	0.01
Current (infrequent)	284 (233, 346)	0.27	6.5 (5.6, 7.5)	0.27	14.9 (12.0, 18.4)	0.12	4.2 (3.5, 5.1)	0.25
Current (daily)	247 (208, 293)	ref	5.8 (5.1, 6.6)	ref	17.8 (16.0, 19.7)	ref	5.0 (4.0, 6.2)	ref
Survey year, 1999-2000	334 (263, 425)	0.17	9.2 (8.7, 9.8)	<0.0001	21.3 (18.7, 24.2)	0.01	5.2 (4.6, 5.7)	<0.0001
2001-2002	332 (303, 364)	0.06	7.8 (7.5, 8.1)	<0.0001	20.0 (17.9, 22.3)	0.05	6.0 (4.5, 8.0)	0.0006
2003-2004	269 (220, 329)	ref	5.1 (4.5, 5.8)	ref	17.1 (15.3, 19.1)	ref	3.3 (2.8, 3.8)	ref

TABLE XLVIII.
MULTIVARIABLE ADJUSTED ASSOCIATIONS BETWEEN CATEGORIZED LEVELS OF LIPID ADJUSTED PESTICIDE CONCENTRATIONS AND KIDNEY OUTCOMES AMONG NHANES 1999-2004 PARTICIPANTS

Serum pesticide concentrations (lipid adjusted ng/g)	**Continuous eGFR[a] (mL/minute/1.73 m^2)**	**Low eGFR[a] (eGFR <60 vs. ≥60)**	**Continuous UACR[b] (mg/g) Adjusted for diabetes**	**Albuminuria[b] (UACR ≥ 17/25 males and females mg/g)**
	Mean (95% CI)	**OR (95% CI)**	**GM (95% CI)**	**OR (95% CI)**
β-hexachlorocyclohexane				
Q1 (ref)	92.5 (90.5, 94.4)	1.0 (ref)	8.3 (7.5, 9.1)	1.0 (ref)
Q2	92.4 (91.1, 93.7)	2.66 (0.90, 7.83)	7.4 (6.7, 8.2)	0.72 (0.38, 1.36)
Q3	94.5 (93.4, 95.6)	1.74 (0.71, 4.27)	7.0 (6.5, 7.6)	0.71 (0.43, 1.15)
Q4	93.5 (91.5, 95.5)	1.63 (0.66, 4.00)	7.2 (6.2, 8.3)	0.64 (0.36, 1.14)
p for trend	0.16	0.97	0.05	0.12
Hexachlorobenzene Q1 (ref)	93.4 (91.3, 95.5)	1.0 (ref)	7.5 (7.0, 8.0)	1.0 (ref)
Q2	92.2 (89.9, 94.6)	0.33 (0.14, 0.79)[c]	8.3 (7.2, 9.4)	1.41 (0.82, 2.43)
Q3	93.4 (91.3, 95.5)	0.90 (0.48, 1.67)	7.0 (6.2, 8.0)	0.78 (0.46, 1.35)
Q4	93.8 (91.2, 96.4)	0.96 (0.49, 1.88)	7.2 (6.2, 8.3)	0.91 (0.53, 1.55)
p for trend	0.66	0.73	0.21	0.26
Heptachlor epoxide Q1 (ref)	93.4 (92.1, 94.7)	1.0 (ref)	7.3 (6.9, 7.8)	1.0 (ref)
Q2	93.1 (91.4, 94.8)	3.37 (1.60, 7.12)[c]	7.4 (6.7, 8.2)	1.03 (0.71, 1.48)
Q3	93.6 (92.3, 94.8)	1.97 (1.27, 3.06)[c]	7.5 (7.0, 8.1)	1.22 (0.89, 1.66)
Q4	92.7 (91.0, 94.4)	2.68 (1.63, 4.40)[c]	7.9 (7.0, 8.9)	1.13 (0.82, 1.58)
p for trend	0.76	0.006	0.36	0.28
Oxychlordane Q1 (ref)	92.7 (90.2, 95.1)	1.0 (ref)	7.6 (6.7, 8.7)	1.0 (ref)
Q2	92.6 (90.9, 94.2)	3.58 (0.50, 25.59)	7.3 (6.8, 8.0)	0.82 (0.45, 1.51)
Q3	93.9 (93.1, 94.8)	2.25 (0.35, 14.37)	7.2 (6.7, 7.7)	0.81 (0.46, 1.45)
Q4	93.5 (91.6, 95.4)	3.32 (0.51, 21.67)	8.3 (7.2, 9.7)	0.95 (0.49, 1.86)
p for trend	0.33	0.10	0.78	0.94

[a]Model adjusts for age (continuous), sex (male/female), race (non-Hispanic white, non-Hispanic African-American, Hispanic, or other), education level (less than high school, high school grad, some college or more), serum lipids (continuous), self-reported smoking history (never, 5+ years since last cigarette, <5 years since last cigarette, infrequent current smoker, daily smoker), hypertension status (yes/no), nativity (born in the US, yes/no), and survey cycle; [b]Model adjusts for age (continuous), sex (male/female), race (non-Hispanic white, non-Hispanic African-American, Hispanic, or other), education level (less than high school, high school grad, some college or more), serum lipids (continuous), self-reported smoking history (never, 5+ years since last cigarette, <5 years since last cigarette, infrequent current smoker, daily smoker), hypertension status (yes/no), nativity (born in the US, yes/no), survey cycle, and diabetes status (yes/no); [c]Statistically significant ($p<0.05$)

TABLE XLVIII (continued).
MULTIVARIABLE ADJUSTED ASSOCIATIONS BETWEEN CATEGORIZED LEVELS OF LIPID ADJUSTED PESTICIDE CONCENTRATIONS AND KIDNEY OUTCOMES AMONG NHANES 1999-2004 PARTICIPANTS

Serum pesticide concentrations (lipid adjusted ng/g)	**Continuous eGFR[a] (mL/minute/1.73 m^2)**	**Low eGFR[a] (eGFR <60 vs. ≥60)**	**Continuous UACR[b] (mg/g) Adjusted for diabetes**	**Albuminuria[b] (UACR ≥ 17/25 males and females mg/g)**
	Mean (95% CI)	**OR (95% CI)**	**GM (95% CI)**	**OR (95% CI)**
p,p'-DDT Q1 (ref)	92.8 (91.5, 94.0)	1.0 (ref)	7.6 (7.1, 8.1)	1.0 (ref)
Q2	93.0 (91.4, 94.7)	0.86 (0.47, 1.57)	6.9 (6.3, 7.6)	0.81 (0.51, 1.30)
Q3	94.6 (93.3, 95.9)	0.85 (0.47, 1.54)	7.4 (6.6, 8.3)	1.09 (0.76, 1.55)
Q4	93.6 (90.8, 96.5)	0.87 (0.41, 1.86)	8.2 (6.6, 10.2)	1.13 (0.70, 1.81)
p for trend	0.08	0.62	0.87	0.54
p,p'-DDE Q1 (ref)	91.7 (90.0, 93.5)	1.0 (ref)	7.9 (7.3, 8.6)	1.0 (ref)
Q2	93.6 (92.6, 94.7)	0.81 (0.39, 1.69)	7.2 (6.6, 7.7)	0.62 (0.44, 0.89)[c]
Q3	94.5 (93.0, 96.0)	0.76 (0.39, 1.49)	7.2 (6.6, 7.9)	0.73 (0.48, 1.11)
Q4	94.5 (92.2, 96.8)	0.72 (0.36, 1.43)	7.4 (6.3, 8.6)	0.70 (0.43, 1.14)
p for trend	0.05	0.35	0.32	0.22
***trans*-Nonachlor** Q1 (ref)	91.8 (88.5, 95.2)	1.0 (ref)	7.3 (6.2, 8.7)	1.0 (ref)
Q2	93.1 (91.4, 94.8)	0.59 (0.10, 3.50)	7.2 (6.7, 7.8)	1.09 (0.49, 2.45)
Q3	93.5 (92.6, 94.3)	0.61 (0.13, 2.97)	7.4 (6.9, 7.9)	1.06 (0.44, 2.53)
Q4	94.0 (92.3, 95.8)	0.72 (0.13, 3.93)	8.2 (7.2, 9.3)	1.27 (0.50, 3.22)
p for trend	0.27	0.48	0.29	0.52
Mirex Q1 (ref)	93.0 (91.8, 94.2)	1.0 (ref)	7.5 (7.1, 8.0)	1.0 (ref)
Q2	93.7 (91.9, 95.4)	0.66 (0.37, 1.19)	6.9 (6.0, 7.9)	0.73 (0.49, 1.10)
Q3	93.7 (92.5, 94.9)	1.14 (0.68, 1.93)	7.4 (6.8, 7.9)	0.81 (0.57, 1.13)
Q4	94.7 (92.7, 96.6)	0.87 (0.51, 1.49)	7.7 (6.1, 9.7)	1.03 (0.53, 2.00)
p for trend	0.17	0.94	0.98	0.76
Dieldrin Q1 (ref)	92.4 (90.5, 94.4)	1.0 (ref)	7.7 (6.9, 8.7)	1.0 (ref)
Q2	93.8 (91.9, 95.7)	1.24 (0.61, 2.54)	6.3 (5.6, 7.0)	0.65 (0.30, 1.41)
Q3	94.2 (92.8, 95.5)	1.04 (0.53, 2.05)	7.6 (7.0, 8.4)	1.12 (0.70, 1.79)
Q4	94.9 (93.0, 96.8)	1.14 (0.55, 2.36)	7.6 (6.9, 8.4)	1.02 (0.64, 1.61)
p for trend	0.04	0.89	0.36	0.25

[a]Model adjusts for age (continuous), sex (male/female), race (non-Hispanic white, non-Hispanic African-American, Hispanic, or other), education level (less than high school, high school grad, some college or more), serum lipids (continuous), self-reported smoking history (never, 5+ years

since last cigarette, <5 years since last cigarette, infrequent current smoker, daily smoker), hypertension status (yes/no), nativity (born in the US, yes/no), and survey cycle

[b]Model adjusts for age (continuous), sex (male/female), race (non-Hispanic white, non-Hispanic African-American, Hispanic, or other), education level (less than high school, high school grad, some college or more), serum lipids (continuous), self-reported smoking history (never, 5+ years since last cigarette, <5 years since last cigarette, infrequent current smoker, daily smoker), hypertension status (yes/no), nativity (born in the US, yes/no), survey cycle, and diabetes status (yes/no).

[c]Statistically significant ($p<0.05$);

D. Discussion

In our study, we evaluated the associations between concentrations of multiple persistent organic pollutants with measures of glomerular filtration and urinary albumin excretion in adults. Study participants had relatively healthy kidney function, with population-based estimates indicating only 6% being classified as having low eGFR and 12% with albuminuria. We observed consistent associations with PCB classifications and eGFR that showed two to three mL/minute/1.73 m^2 higher average eGFR values among those in the highest exposure category relative to the lowest exposure category. This held for both the estrogenic and the anti-estrogenic groups. The pooled associations were likely driven by the males in the sample, as we also observed consistent sex differences in these associations, indicating the positive association was among the male subsample and there was no association with PCB classes and eGFR among females. It is unknown if the small increase in eGFR observed in this study has clinical implications for disease manifestation or progression. The small increase in eGFR among males could be due to increased filtration as a result of the higher concentration of analyte in the blood, but the magnitude is not large enough to point toward hyperfiltration. It is possible that this positive association is due to bias introduced by using the CKD-EPI equation to estimate GFR. Equation based GFR estimation is known to be biased particularly for eGFR values greater than 90 ml/min per 1.73 m2, with heterogeneity in the magnitude of the bias among subgroups of age, sex, race, and BMI level (Stevens et al. 2010). Given this, it is possible that the small positive association observed in this study is a result of bias in GFR estimation at higher levels. We cannot definitely say that the positive association is not real, but

alternative explanations for the positive association observed are helpful to understand how to interpret these results, particularly given their discordance with available literature. A prior study that exposed male rats to dioxin and PCBs repeatedly showed that dosing was associated with increased serum creatinine, renal oxidative stress, and renal cytochrome P450 1A1 (CYP1A1) protein expression (Lu et al. 2009). A small study of 40 residents living near an electronic waste facility in China and 15 control residents found a positive correlation between total sum of PCBs and serum creatinine, but the association was not explored using multivariable modeling (Xu et al. 2015). These results from other studies implicate these analytes as being positively associated with serum creatinine, which in turn, would lead to an inverse association with calculated eGFR, which is not consistent with the results of our current study.

Few studies have examined the associations of PCDD, PCDF, and PCB exposures with eGFR or UACR in humans, making it difficult to compare our findings to other populations. A prior study of residents living near a factory in Taiwan that emitted dioxin found that a high dioxin level (polychlorinated dibenzo-p-dioxins and dibenzofurans ≥ 20 pg WHO_{98}-TEQ_{DF}/g lipid measured from serum) was associated with increased odds (OR= 1.76, 95% CI: 1.04-2.99) of having low eGFR (≤ 60 mL/min/1.73m2) or a diagnosis of CKD by a physician (Huang, Wu, et al. 2016). This dioxin level is equivalent to the fourth quartile of TEQ exposure in our study, and we did not observe any association with low eGFR at that exposure level. In a nested case control study of American Indians from central Arizona with diabetes, exposure to non-dioxin-like PCB28, PCB49, and PCB44 was associated with 75%, 64%, and 59% increased risk of ESRD after an average of 27 years of follow-up, respectively (Grice et

al. 2017). Although our study outcomes were quite different than ESRD which can take decades to manifest, we did observe small positive associations with most PCBs categorizations and eGFR. It is unlikely that concentrations of these analytes are associated with better GFR, indicating a need to better understand how these analytes are associated with glomerular hemodynamics across time. Linkage to long-term follow-up data among a cohort with well categorized exposure concentrations may be warranted to better understand the implications of these findings.

In our evaluation of PCDDs, PCDFs, and PCBs associations with UACR, there was a positive association between group 2A anti-estrogenic PCBs and UACR, but no association with total anti-estrogenic or group 2B anti-estrogenic PCBs. A positive association was observed with CYP1A PCBs and UACR. Similar to the findings with eGFR, there was some evidence of effect modification by sex via statistically significant interaction terms, but sex-stratified estimates were not statistically significant or large in magnitude. One very specific study of young adults ages 12 to 30 years old sampled from the 1999-2004 NHANES investigated the associations between select pollutants and UACR > 30 mg/g stratified by diabetes status. This study showed that among young adults with hemoglobin A1c levels less than 5.7% (indicative of normal levels) in individual models concentrations of 1,2,3,6,7,8-hexachlorodibenzo-p-dioxin and PCBs 126, 169, and 156 were associated with increased odds of UACR > 30 mg/g (Everett and Thompson 2016). Further study is needed to better understand if these analytes are associated with UACR among males and non-significant among females.

We did not observe any associations between pesticide concentrations with eGFR other than a small positive trend with dieldrin; however, it should be noted that

dieldrin was not measured across all three survey cycles and may not be representative of our total study sample. Although there was no association with continuous eGFR, we observed positive associations between concentrations of heptachlor epoxide (p for trend 0.006) and oxychlordane (p for trend 0.10) with low eGFR. Observed associations between pesticide concentrations with UACR were not independent of diabetes status. Concentrations of heptachlor epoxide were associated with higher average levels of UACR and higher odds of albuminuria, but after adjustment for diabetes status these associations diminished and were no longer statistically significant. A previous study of the NHANES 1999-2004 cycles showed levels of heptachlor epoxide to be associated with odds of diabetes with UACR >30 mg/g (OR= 1.75, 95% CI 1.05-2.93) (Everett and Thompson 2015). This study did not examine associations with eGFR, nor use sex-specific cut points for UACR categorization.

Interestingly, there was some evidence that suggested positive associations with UACR among males in the highest concentration categories of β-hexachlorocyclohexane, oxychlordane, and trans-nonachlor, but these patterns lacked statistical significance after multivariable adjustment. In a recent study of chronic kidney disease of unknown etiology in Dehli, India, investigators found higher levels of aldrin, β-endosulfan, and α-hexocyclochlorohexane among participants with CKD of unknown etiology relative to those with known etiology and healthy controls (Ghosh et al. 2017). We did not observe any associations between concentrations of DDE or DDT with kidney outcomes in this study. In a prior study using the 1999-2004 NHANES data, analyses restricted to Mexican American participants showed that p,p'-DDT levels above 0.086 ng/g compared to levels less than or equal to 0.086 ng/g were associated

with increased odds of diabetes with concurrent UACR >30 mg/g (OR= 4.42, 95% CI 2.23-8.76), and levels of p,p'-DDE in the fourth quartile relative to the first quartile were associated with higher odds of diabetes with UACR >30 mg/g (OR= 14.95, 95% CI 2.96-75.48) (Everett, Thompson, and Dismuke 2017). The prior study by Everett, Thompson, and Dismuke did not examine eGFR as an outcome nor were any analyses conducted to assess association with measures kidney function outside of the context of comorbid diabetes.

Overall, we did not observe strong associations with most of the exposures under study in this large sample of adults with relatively normal kidney function. A strength of this study is the classification of the concentrations of PCDDs, PCDFs, and PCBs into various indices using biologically plausible risk groups that have been demonstrated to be pertinent to chronic diseases such as cancer and diabetes in the literature (Wolff et al. 1997, Warner et al. 2012, Van den Berg et al. 2006). This included congener-specific groupings assumed to be relevant to potential mechanisms of action through which additive exposures could be working to contribute to kidney disorders. We had objective measures of all of the analytes under study, and laboratory values were available for the calculations of eGFR and UACR. This study is also subject to various limitations. It uses two single, cross-sectional samples to estimate kidney function using multiple parameters, and these measurements may vary over time. There was missing data for various PCB measurements, and we could not use all measured analytes due to inconsistencies in the analytes measured across survey cycles. The cross-sectional study design is useful for exploratory analyses, but prospective study of repeat measurements of kidney function parameters and consistent disease endpoints such as

end stage renal disease is needed. Such studies may benefit from considering other endpoints related to kidney disease, such as cardiovascular events and mortality. We cannot draw conclusions about the temporality of exposures and kidney function. Diabetes and hypertension status are well-known risk factors for chronic kidney disease, however, these parameters may be in the causal pathway between POPs exposure and kidney disease. In our analyses, we compared crude estimates of associations to adjusted estimates and used a forward approach to evaluate hypertension and diabetes related parameters as potential confounders. When we adjusted for diabetes status in the analyses using the NHANES data, some of the previously observed associations with parameters of kidney health were no longer observed. We cannot rule out the possibility that we introduced bias into our estimates when we adjusted for the intermediate diabetes status variable in our models. Future analyses to investigate the mediating role of diabetes in the association of POPs and kidney function may be warranted.

E. Conclusions

In conclusion, we evaluated the association between multiple persistent organic pollutants measured in serum to determine if exposure concentrations are associated with measures of kidney function. We demonstrated that PCB concentrations may be associated with small increases in eGFR, particularly among males, but it is uncertain if these associations are real or due to bias in GFR estimation. We also showed that concentrations of heptachlor epoxide may be associated with increased odds of low eGFR. Most other associations with pesticide concentrations were not independent of diabetes status, indicating that diabetes may play a large role

in the causal pathway connecting these analytes to poor kidney outcomes among adults. Additional investigation into these exposures with longitudinal endpoints is warranted to fully understand their impact on renal health.

VII. CONCLUSIONS

In the previous chapters, the work presented identified associations between endogenous thyroid and pituitary hormones and kidney function. Additionally, we presented associations between persistent organic pollutants, specifically PCBs, DDT and its metabolites, and heptachlor epoxide with measures of kidney function. Considering that many of the pollutants we evaluated are known to impact levels of endogenous hormones, our findings suggest that exploration of the relationships between circulating levels of these chemicals and endogenous hormones with kidney function may provide information about the mechanism of action through which these pollutants exert their effects on the renal system.

In Chapter III, we used data from an ancillary study of the HCHS/SOL cohort and found overall associations with TSH that were more consistent than associations with the peripheral hormones FT4 and T3. In this study we found that circulating levels of TSH were inversely associated with eGFR cross-sectionally and over an average six-year follow up period in a diverse cohort of Hispanic/Latino participants free of diabetes at baseline. Previous epidemiologic studies of TSH and kidney function have provided results ranging from null (Huang, Ding, et al. 2016) to identifying higher serum TSH to be associated with higher odds of low eGFR (<60ml/min/1.73 m^2) (Gopinath et al. 2013, Schultheiss et al. 2017) and incident low eGFR (Zhang et al. 2014). In our study, TSH levels were also positively associated with incident albuminuria. Few studies have used albuminuria as a clinical endpoint in their evaluation of associations with kidney function.

Chapter IV describes our identification of inverse associations between LH and FSH concentrations and eGFR among post-menopausal females cross-sectionally. When we looked at the odds of incident albuminuria and CKD at visit 2 among the post-menopausal females who were not categorized as having albuminuria or CKD at visit 1, we again saw associations with the pituitary hormones. Among females, we observed an inverse association between LH and odds of incident albuminuria, but we did not observe a similar association when we modeled the odds of incident CKD composite. Among the male participants, LH was inversely associated with eGFR at baseline and positively associated with UACR and odds of albuminuria. However, there was no association with LH and any outcome at Visit 2. Also among males, FSH concentration appeared to be positively associated with UACR and odds of albuminuria at baseline; however, the associations with eGFR and UACR among males observed at baseline using cross-sectional data were not observed when we examined hormone associations with levels of eGFR and UACR at visit 2 after the six year follow-up. When we evaluated the associations with free and bound testosterone among males, we observed an inverse association with free testosterone and UACR cross-sectionally, and an inverse association between testosterone and visit 2 eGFR. The results for free testosterone and total testosterone are therefore not completely consistent. The fact that we did not measure, but instead estimated, free testosterone suggests that we might have somewhat more confidence in the total testosterone results, although final interpretation must await future studies. Endogenous androgens are known to negatively regulate LH levels, and we cannot determine if unmeasured androgens are impacting LH levels

measured in this study, driving the associations we observed with kidney function parameters.

Although several review articles have suggested sex-differences in the mechanisms of CKD (Neugarten, Acharya, and Silbiger 2000, Neugarten and Golestaneh 2019, Silbiger and Neugarten 2003), few have actually studied these associations in humans using objectively measured hormones. The secondary analysis of the Diabetes Prevention Program (DPP) Outcome Study, found an inverse association between concentrations of estradiol and eGFR, and a positive association between concentrations of DHEAS with log transformed UACR in the analyses of the male participants (Kim et al. 2019). Among the female participants, estrone was positively associated with eGFR (Kim et al. 2019). We did not observe any of these associations in our baseline analyses, though it should be noted that we did not measure estrone, and our cohort had a healthier profile at baseline relative to those at risk for diabetes that were enrolled in the DPP. A limited number of additional studies have investigated the association between sex hormone levels and eGFR or albuminuria in males, but very few of them have included the pituitary hormones. In a study of 101 men without diabetes aged 18 to 50 years old, investigators compared hormone levels by CKD stage, and found that luteinizing hormone levels were higher in the more advanced CKD stages relative to the less severe and healthy stages (Hylander and Lehtihet 2015). In the Hylander sample, only 23 of the participants had eGFR levels that are representative of those in our study, but the results are consistent with the inverse association between LH and eGFR and the positive association

between LH and UACR that we observed in our cross-sectional analyses of the male participants in our study.

We described our evaluation of pollutant measurements in Chapter V, where we showed that circulating levels of PCBs concentrations may be associated with albuminuria and small increases in UACR. Assessing the associations between PCB subcategories and health outcomes can be difficult since the estrogenic categories are not always consistent but the positive association of antiestrogenic categories of PCBs with albuminuria could support the interpretation of that androgens are harmful to kidney function and estrogens protective. We also showed that concentrations of DDE may be associated with decreased odds of albuminuria and lower levels of UACR over time. The inverse associations observed with DDE and the sum of DDT and its metabolites may be indicative of the antiandrogenic properties of DDE (O'Connor et al. 1999). In Chapter VI, we reevaluated these associations using cross-sectional data from the NHANES. We found that PCB concentrations may be associated with small increases in eGFR, particularly among males, but it is uncertain if these associations are real or due to bias. We also showed that concentrations of heptachlor epoxide may be associated with increased odds of low eGFR. In the NHANES, most other associations with pesticide concentrations were not independent of diabetes status, indicating that diabetes may play a large role in the causal pathway connecting these analytes to poor kidney outcomes among adults in the general population.

Taken together the findings from this group of studies indicate that endogenous hormones are associated with kidney function, and that circulating levels of certain persistent pollutants also impact kidney function. Given that persistent pollutants are

known endocrine disruptors, findings from this group of studies suggest that future work should be undertaken to evaluate the direct effect of the environmental exposures and the indirect effects that may be occurring through hormonal pathways. While many of our findings are novel, particularly those from the HCHS/SOL cohort, there are some limitations worth noting. All of our studies used a urine or blood sample measured at one point in time to determine kidney function, whereas a diagnosis of CKD requires multiple measurements over a short time period. Additionally, our cross-sectional results are subject to reverse causality, particularly among the results with the dichotomous outcomes. Our results may be susceptible to error related to multiple comparisons, but since these analyses were exploratory we did not adjust for multiple comparisons in the results presented. We were able to compare results of the cross-sectional, longitudinal, and incident analyses for three of our four aims, which allowed us to comment on the consistency of associations in each study. Although we did not employ advanced methods to evaluate the pollutant mixtures using still developing epidemiologic methods, we did create summary measures of most of the pollutants to assess the additivity of the associations between multiple pollutants of the same class and the outcomes, in addition to summarizing PCBs by hypothesized mechanism of action. Future analyses are planned to employ advanced analytic techniques to assess associations between true mixtures with the study outcomes, in addition to using multiple imputation techniques to address missing data issues with the pollutant data. Additionally, future analyses should be conducted to investigate the potential mediating role of both hypertension and diabetes in the association of POPs and kidney function. Diabetes and hypertension status are well-known risk factors for chronic kidney

disease, however, these parameters may be intermediate variables in the causal pathway between POPs exposure and kidney disease. In our analyses, we compared crude estimates of associations to adjusted estimates and used a forward approach to evaluate hypertension and diabetes related parameters as potential confounders. We recognize that these parameters may be intermediate variables in the analyses of the associations with POP exposures. Our studies also had numerous strengths worth noting. Three of our four studies used data from a well-characterized cohort of Hispanic/Latino participants, and all of the laboratory data was measured in state of the art laboratories. Very few studies exist that have evaluated associations among endogenous hormones or persistent pollutants with kidney function in a large sample of adults. Furthermore, most studies that have evaluated the associations between persistent pollutants and kidney function have been cross-sectional and have focused on diabetic nephropathy, which is a different disease state than kidney disease without diabetes. The HCHS/SOL ancillary study participants did not have diabetes at baseline, allowing us to understand the associations between our independent variables of interest and kidney function parameters in a relatively healthy sample of participants.

The findings from our group of studies have a number of implications. As stated previously, this group of studies indicate that endogenous hormones are associated with kidney function. Endogenous hormones can be monitored, and levels may be managed using medications. Collaboration with experts in the fields of nephrology and endocrinology may lead to interventions to protect kidney health targeted in this area. This group of studies indicated that circulating levels of certain persistent pollutants also impact kidney function. Although many of the pollutants measured in our study are

banned from current production, they still exist in our environment as a contaminant in our food, water, and land. Furthermore, certain people may be susceptible to high levels of exposure due to working in or living near sources of various industrial processes, such as waste management facilities. A better understanding of exposure sources may help to reduce exposures to susceptible groups. Our results require further validation and reproduction in additional cohorts, but suggest that particular legacy pollutants are involved in the pathology of CKD and that endogenous hormones may play a mechanistic role. Further analyses to evaluate associations between POPs and endogenous hormones should be completed, with mediation analyses to evaluate the mechanism of action with respect to renal health if deemed necessary.

CITED LITERATURE

Abdelouahab, N., D. Mergler, L. Takser, C. Vanier, M. St-Jean, M. Baldwin, P. A. Spear, and H. M. Chan. 2008. "Gender differences in the effects of organochlorines, mercury, and lead on thyroid hormone levels in lakeside communities of Quebec (Canada)." *Environ Res* 107 (3):380-92. doi: 10.1016/j.envres.2008.01.006.

Agarwal, M., V. Selvan, B. I. Freedman, Y. Liu, and L. E. Wagenknecht. 2005. "The relationship between albuminuria and hormone therapy in postmenopausal women." *Am J Kidney Dis* 45 (6):1019-25.

Agency for Toxic Substances and Disease Registry (ATSDR). 2005. Toxicological profile for Hexachlorocyclohexane. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service.

Agency for Toxic Substances and Disease Registry (ATSDR). 2015. Toxicological Profile for Hexachlorobenzene. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service.

Agency for Toxic Substances and Disease Registry (ATSDR). 2019. Toxicological profile for DDT, DDE, DDD (Draft for Public Comment). Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service.

Ahlborg, U. G., L. Lipworth, L. Titus-Ernstoff, C. C. Hsieh, A. Hanberg, J. Baron, D. Trichopoulos, and H. O. Adami. 1995. "Organochlorine compounds in relation to breast cancer, endometrial cancer, and endometriosis: an assessment of the biological and epidemiological evidence." *Crit Rev Toxicol* 25 (6):463-531. doi: 10.3109/10408449509017924.

Ahmed, S. B., B. F. Culleton, M. Tonelli, S. W. Klarenbach, J. M. Macrae, J. Zhang, and B. R. Hemmelgarn. 2008. "Oral estrogen therapy in postmenopausal women is associated with loss of kidney function." *Kidney Int* 74 (3):370-6. doi: 10.1038/ki.2008.205.

Ahmed, S. B., and S. Ramesh. 2016. "Sex hormones in women with kidney disease." *Nephrol Dial Transplant* 31 (11):1787-1795. doi: 10.1093/ndt/gfw084.

Alvarez, L., S. Hernandez, R. Martinez-de-Mena, R. Kolliker-Frers, M. J. Obregon, and D. L. Kleiman de Pisarev. 2005. "The role of type I and type II 5' deiodinases on hexachlorobenzene-induced alteration of the hormonal thyroid status." *Toxicology* 207 (3):349-62. doi: 10.1016/j.tox.2004.10.006.

Arcaro, K. F., L. Yi, R. F. Seegal, D. D. Vakharia, Y. Yang, D. C. Spink, K. Brosch, and J. F. Gierthy. 1999. "2,2',6,6'-Tetrachlorobiphenyl is estrogenic in vitro and in vivo." *J Cell Biochem* 72 (1):94-102.

Asvold, B. O., T. Bjoro, and L. J. Vatten. 2011. "Association of thyroid function with estimated glomerular filtration rate in a population-based study: the HUNT study." *Eur J Endocrinol* 164 (1):101-5. doi: 10.1530/eje-10-0705.

Axmon, A., and A. Rignell-Hydbom. 2006. "Estimations of past male and female serum concentrations of biomarkers of persistent organochlorine pollutants and their impact on fecundability estimates." *Environ Res* 101 (3):387-94. doi: 10.1016/j.envres.2005.10.005.

Bairey Merz, C. N., L. M. Dember, J. R. Ingelfinger, A. Vinson, J. Neugarten, K. L. Sandberg, J. C. Sullivan, C. Maric-Bilkan, T. L. Rankin, P. L. Kimmel, and R. A. Star. 2019. "Sex and the kidneys: current understanding and research opportunities." *Nat Rev Nephrol* 15 (12):776-783. doi: 10.1038/s41581-019-0208-6.

Balash, K. J., M. A. Al-Omar, and B. M. Abdul Latif. 1987. "Effect of chlordane on testicular tissues of Swiss mice." *Bull Environ Contam Toxicol* 39 (3):434-42.

Bastomsky, C. H. 1974. "Effects of a polychlorinated biphenyl mixture (aroclor 1254) and DDT on biliary thyroxine excretion in rats." *Endocrinology* 95 (4):1150-5. doi: 10.1210/endo-95-4-1150.

Belgorosky, A., M. E. Escobar, and M. A. Rivarola. 1987. "Validity of the calculation of non-sex hormone-binding globulin-bound estradiol from total testosterone, total estradiol and sex hormone-binding globulin concentrations in human serum." *J Steroid Biochem* 28 (4):429-32.

Benson, K., E. Yang, N. Dutton, A. Sjodin, P. F. Rosenbaum, and M. Pavuk. 2018. "Polychlorinated biphenyls, indicators of thyroid function and thyroid autoantibodies in the Anniston Community Health Survey I (ACHS-I)." *Chemosphere* 195:156-165. doi: 10.1016/j.chemosphere.2017.12.050.

Beyer, A., and M. Biziuk. 2009. "Environmental fate and global distribution of polychlorinated biphenyls." *Rev Environ Contam Toxicol* 201:137-58. doi: 10.1007/978-1-4419-0032-6_5.

Blanco-Munoz, J., M. Lacasana, C. Aguilar-Garduno, M. Rodriguez-Barranco, S. Bassol, M. E. Cebrian, I. Lopez-Flores, and I. Ruiz-Perez. 2012. "Effect of exposure to p,p'-DDE on male hormone profile in Mexican flower growers." *Occup Environ Med* 69 (1):5-11. doi: 10.1136/oem.2010.059667.

Boas, M., U. Feldt-Rasmussen, N. E. Skakkebaek, and K. M. Main. 2006. "Environmental chemicals and thyroid function." *Eur J Endocrinol* 154 (5):599-611. doi: 10.1530/eje.1.02128.

Borlakoglu, J. T., and C. H. Walker. 1989. "Comparative aspects of congener specific PCB metabolism." *Eur J Drug Metab Pharmacokinet* 14 (2):127-31. doi: 10.1007/bf03190852.

Burch, H. B. 2019. "Drug Effects on the Thyroid." *N Engl J Med* 381 (8):749-761. doi: 10.1056/NEJMra1901214.

Carrero, J. J., M. Hecking, N. C. Chesnaye, and K. J. Jager. 2018. "Sex and gender disparities in the epidemiology and outcomes of chronic kidney disease." *Nat Rev Nephrol* 14 (3):151-164. doi: 10.1038/nrneph.2017.181.

Cassidy, R. A., C. V. Vorhees, D. J. Minnema, and L. Hastings. 1994. "The effects of chlordane exposure during pre- and postnatal periods at environmentally relevant levels on sex steroid-mediated behaviors and functions in the rat." *Toxicol Appl Pharmacol* 126 (2):326-37. doi: 10.1006/taap.1994.1123.

Chainy, G. B. N., and D. K. Sahoo. 2019. "Hormones and oxidative stress: an overview." *Free Radic Res*:1-26. doi: 10.1080/10715762.2019.1702656.

Chavers, B. M., J. Simonson, and A. F. Michael. 1984. "A solid phase fluorescent immunoassay for the measurement of human urinary albumin." *Kidney Int* 25 (3):576-8. doi: 10.1038/ki.1984.57.

Cheek, A. O., K. Kow, J. Chen, and J. A. McLachlan. 1999. "Potential mechanisms of thyroid disruption in humans: interaction of organochlorine compounds with thyroid receptor, transthyretin, and thyroid-binding globulin." *Environ Health Perspect* 107 (4):273-8. doi: 10.1289/ehp.99107273.

Chen, Y. F., A. J. Naftilan, and S. Oparil. 1992. "Androgen-dependent angiotensinogen and renin messenger RNA expression in hypertensive rats." *Hypertension* 19 (5):456-63. doi: 10.1161/01.hyp.19.5.456.

Chonchol, M., G. Lippi, G. Salvagno, G. Zoppini, M. Muggeo, and G. Targher. 2008. "Prevalence of subclinical hypothyroidism in patients with chronic kidney disease." *Clin J Am Soc Nephrol* 3 (5):1296-300. doi: 10.2215/cjn.00800208.

Craig, Z. R., W. Wang, and J. A. Flaws. 2011. "Endocrine-disrupting chemicals in ovarian function: effects on steroidogenesis, metabolism and nuclear receptor signaling." *Reproduction* 142 (5):633-46. doi: 10.1530/rep-11-0136.

Delle, H., J. R. Rocha, R. C. Cavaglieri, J. M. Vieira, Jr., D. M. Malheiros, and I. L. Noronha. 2012. "Antifibrotic effect of tamoxifen in a model of progressive renal disease." *J Am Soc Nephrol* 23 (1):37-48. doi: 10.1681/asn.2011010046.

den Besten, C., M. H. Bennik, I. Bruggeman, P. Schielen, F. Kuper, A. Brouwer, J. H. Koeman, J. G. Vos, and P. J. Van Bladeren. 1993. "The role of oxidative metabolism in hexachlorobenzene-induced porphyria and thyroid hormone homeostasis: a comparison with pentachlorobenzene in a 13-week feeding study." *Toxicol Appl Pharmacol* 119 (2):181-94.

Derose, S. F., M. P. Rutkowski, P. W. Crooks, J. M. Shi, J. Q. Wang, K. Kalantar-Zadeh, C. P. Kovesdy, N. W. Levin, and S. J. Jacobsen. 2013. "Racial differences in estimated GFR decline, ESRD, and mortality in an integrated health system." *Am J Kidney Dis* 62 (2):236-44. doi: 10.1053/j.ajkd.2013.01.019.

Desaulniers, D., G. M. Cooke, K. Leingartner, K. Soumano, J. Cole, J. Yang, M. Wade, and A. Yagminas. 2005. "Effects of postnatal exposure to a mixture of polychlorinated biphenyls, p,p'-dichlorodiphenyltrichloroethane, and p-p'-dichlorodiphenyldichloroethene in prepubertal and adult female Sprague-Dawley rats." *Int J Toxicol* 24 (2):111-27. doi: 10.1080/10915810590936382.

Diamanti-Kandarakis, E., J. P. Bourguignon, L. C. Giudice, R. Hauser, G. S. Prins, A. M. Soto, R. T. Zoeller, and A. C. Gore. 2009. "Endocrine-disrupting chemicals: an Endocrine Society scientific statement." *Endocr Rev* 30 (4):293-342. doi: 10.1210/er.2009-0002.

Donato, F., C. Zani, M. Magoni, U. Gelatti, L. Covolo, G. Orizio, F. Speziani, A. Indelicato, C. Scarcella, R. Bergonzi, and P. Apostoli. 2008. "Polychlorinated biphenyls and thyroid hormone serum concentrations among people living in a highly polluted area: a cross-sectional population-based study." *Environ Res* 108 (3):380-6. doi: 10.1016/j.envres.2008.08.003.

Dunkel, L., T. Raivio, J. Laine, and C. Holmberg. 1997. "Circulating luteinizing hormone receptor inhibitor(s) in boys with chronic renal failure." *Kidney Int* 51 (3):777-84. doi: 10.1038/ki.1997.109.

Dutta, R., A. M. Mondal, V. Arora, T. C. Nag, and N. Das. 2008. "Immunomodulatory effect of DDT (bis[4-chlorophenyl]-1,1,1-trichloroethane) on complement system and macrophages." *Toxicology* 252 (1-3):78-85. doi: 10.1016/j.tox.2008.07.063.

Ellison, K. E., J. R. Ingelfinger, M. Pivor, and V. J. Dzau. 1989. "Androgen regulation of rat renal angiotensinogen messenger RNA expression." *J Clin Invest* 83 (6):1941-5. doi: 10.1172/jci114102.

Everett, C. J., and O. M. Thompson. 2014. "Dioxins, furans and dioxin-like PCBs in human blood: causes or consequences of diabetic nephropathy?" *Environ Res* 132:126-31. doi: 10.1016/j.envres.2014.03.043.

Everett, C. J., and O. M. Thompson. 2015. "Association of DDT and heptachlor epoxide in human blood with diabetic nephropathy." *Rev Environ Health* 30 (2):93-7. doi: 10.1515/reveh-2015-0003.

Everett, C. J., and O. M. Thompson. 2016. "Association of dioxins, furans and dioxin-like PCBs in human blood with nephropathy among US teens and young adults." *Rev Environ Health* 31 (2):195-201. doi: 10.1515/reveh-2015-0031.

Everett, C. J., O. M. Thompson, and C. E. Dismuke. 2017. "Exposure to DDT and diabetic nephropathy among Mexican Americans in the 1999-2004 National Health and Nutrition Examination Survey." *Environ Pollut* 222:132-137. doi: 10.1016/j.envpol.2016.12.069.

Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults., . 2001. "Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III)." *Jama* 285 (19):2486-97. doi: 10.1001/jama.285.19.2486.

Fangstrom, B., M. Athanasiadou, P. Grandjean, P. Weihe, and A. Bergman. 2002. "Hydroxylated PCB metabolites and PCBs in serum from pregnant Faroese women." *Environ Health Perspect* 110 (9):895-9. doi: 10.1289/ehp.110-1240989.

Fisher, J. W., J. Campbell, S. Muralidhara, J. V. Bruckner, D. Ferguson, M. Mumtaz, B. Harmon, J. M. Hedge, K. M. Crofton, H. Kim, and T. L. Almekinder. 2006. "Effect of PCB 126 on hepatic metabolism of thyroxine and perturbations in the hypothalamic-pituitary-thyroid axis in the rat." *Toxicol Sci* 90 (1):87-95. doi: 10.1093/toxsci/kfj069.

Fortepiani, L. A., L. Yanes, H. Zhang, L. C. Racusen, and J. F. Reckelhoff. 2003. "Role of androgens in mediating renal injury in aging SHR." *Hypertension* 42 (5):952-5. doi: 10.1161/01.Hyp.0000099241.53121.7f.

Foster, W. G., J. A. Pentick, A. McMahon, and P. R. Lecavalier. 1993. "Body distribution and endocrine toxicity of hexachlorobenzene (HCB) in the female rat." *J Appl Toxicol* 13 (2):79-83.

Freire, C., R. J. Koifman, P. N. Sarcinelli, A. C. Rosa, R. Clapauch, and S. Koifman. 2014. "Association between serum levels of organochlorine pesticides and sex hormones in adults living in a heavily contaminated area in Brazil." *Int J Hyg Environ Health* 217 (2-3):370-8. doi: 10.1016/j.ijheh.2013.07.012.

Freire, C., R. J. Koifman, P. N. Sarcinelli, A. C. Simoes Rosa, R. Clapauch, and S. Koifman. 2013. "Long-term exposure to organochlorine pesticides and thyroid status in adults in a heavily contaminated area in Brazil." *Environ Res* 127:7-15. doi: 10.1016/j.envres.2013.09.001.

Fung, M. M., S. Poddar, R. Bettencourt, S. K. Jassal, and E. Barrett-Connor. 2011. "A cross-sectional and 10-year prospective study of postmenopausal estrogen therapy and blood pressure, renal function, and albuminuria: the Rancho

Bernardo Study." *Menopause* 18 (6):629-37. doi: 10.1097/gme.0b013e3181fca9c4.

Garber, J. R., R. H. Cobin, H. Gharib, J. V. Hennessey, I. Klein, J. I. Mechanick, R. Pessah-Pollack, P. A. Singer, and K. A. Woeber. 2012. "Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association." *Endocr Pract* 18 (6):988-1028. doi: 10.4158/ep12280.GI.

Ghosh, R., M. Siddarth, N. Singh, V. Tyagi, P. K. Kare, B. D. Banerjee, O. P. Kalra, and A. K. Tripathi. 2017. "Organochlorine pesticide level in patients with chronic kidney disease of unknown etiology and its association with renal function." *Environ Health Prev Med* 22 (1):49. doi: 10.1186/s12199-017-0660-5.

Gierthy, J. F., K. F. Arcaro, and M. Floyd. 1997. "Assessment of PCB estrogenicity in a human breast cancer cell line." *Chemosphere* 34 (5-7):1495-505.

Giwercman, A. H., A. Rignell-Hydbom, G. Toft, L. Rylander, L. Hagmar, C. Lindh, H. S. Pedersen, J. K. Ludwicki, V. Lesovoy, M. Shvets, M. Spano, G. C. Manicardi, D. Bizzaro, E. C. Bonefeld-Jorgensen, and J. P. Bonde. 2006. "Reproductive hormone levels in men exposed to persistent organohalogen pollutants: a study of inuit and three European cohorts." *Environ Health Perspect* 114 (9):1348-53. doi: 10.1289/ehp.8935.

Go, A. S., D. Mozaffarian, V. L. Roger, E. J. Benjamin, J. D. Berry, M. J. Blaha, S. Dai, E. S. Ford, C. S. Fox, S. Franco, H. J. Fullerton, C. Gillespie, S. M. Hailpern, J. A. Heit, V. J. Howard, M. D. Huffman, S. E. Judd, B. M. Kissela, S. J. Kittner, D. T. Lackland, J. H. Lichtman, L. D. Lisabeth, R. H. Mackey, D. J. Magid, G. M. Marcus, A. Marelli, D. B. Matchar, D. K. McGuire, E. R. Mohler, 3rd, C. S. Moy, M. E. Mussolino, R. W. Neumar, G. Nichol, D. K. Pandey, N. P. Paynter, M. J. Reeves, P. D. Sorlie, J. Stein, A. Towfighi, T. N. Turan, S. S. Virani, N. D. Wong, D. Woo, and M. B. Turner. 2014. "Executive summary: heart disease and stroke statistics--2014 update: a report from the American Heart Association." *Circulation* 129 (3):399-410. doi: 10.1161/01.cir.0000442015.53336.12.

Gopinath, B., D. C. Harris, J. R. Wall, A. Kifley, and P. Mitchell. 2013. "Relationship between thyroid dysfunction and chronic kidney disease in community-dwelling older adults." *Maturitas* 75 (2):159-64. doi: 10.1016/j.maturitas.2013.03.009.

Grice, B. A., R. G. Nelson, D. E. Williams, W. C. Knowler, C. Mason, R. L. Hanson, K. M. Bullard, and M. E. Pavkov. 2017. "Associations between persistent organic pollutants, type 2 diabetes, diabetic nephropathy and mortality." *Occup Environ Med* 74 (7):521-527. doi: 10.1136/oemed-2016-103948.

Hagmar, L., E. Wallin, B. Vessby, B. A. Jonsson, A. Bergman, and L. Rylander. 2006. "Intra-individual variations and time trends 1991-2001 in human serum levels of

PCB, DDE and hexachlorobenzene." *Chemosphere* 64 (9):1507-13. doi: 10.1016/j.chemosphere.2005.12.054.

Hallgren, S., and P. O. Darnerud. 2002. "Polybrominated diphenyl ethers (PBDEs), polychlorinated biphenyls (PCBs) and chlorinated paraffins (CPs) in rats-testing interactions and mechanisms for thyroid hormone effects." *Toxicology* 177 (2-3):227-43. doi: 10.1016/s0300-483x(02)00222-6.

Hallgren, S., T. Sinjari, H. Hakansson, and P. O. Darnerud. 2001. "Effects of polybrominated diphenyl ethers (PBDEs) and polychlorinated biphenyls (PCBs) on thyroid hormone and vitamin A levels in rats and mice." *Arch Toxicol* 75 (4):200-8. doi: 10.1007/s002040000208.

Haugen, T. B., T. Tefre, G. Malm, B. A. Jonsson, L. Rylander, L. Hagmar, C. Bjorsvik, T. Henrichsen, T. Saether, Y. Figenschau, and A. Giwercman. 2011. "Differences in serum levels of CB-153 and p,p'-DDE, and reproductive parameters between men living south and north in Norway." *Reprod Toxicol* 32 (3):261-7. doi: 10.1016/j.reprotox.2011.06.072.

Hecking, M., B. A. Bieber, J. Ethier, A. Kautzky-Willer, G. Sunder-Plassmann, M. D. Saemann, S. P. Ramirez, B. W. Gillespie, R. L. Pisoni, B. M. Robinson, and F. K. Port. 2014. "Sex-specific differences in hemodialysis prevalence and practices and the male-to-female mortality rate: the Dialysis Outcomes and Practice Patterns Study (DOPPS)." *PLoS Med* 11 (10):e1001750. doi: 10.1371/journal.pmed.1001750.

Herrick, R. F., M. D. McClean, J. D. Meeker, L. K. Baxter, and G. A. Weymouth. 2004. "An unrecognized source of PCB contamination in schools and other buildings." *Environ Health Perspect* 112 (10):1051-3. doi: 10.1289/ehp.6912.

Hopf, N. B., A. M. Ruder, M. A. Waters, and P. Succop. 2013. "Concentration-dependent half-lives of polychlorinated biphenyl in sera from an occupational cohort." *Chemosphere* 91 (2):172-8. doi: 10.1016/j.chemosphere.2012.12.039.

Huang, C. Y., C. L. Wu, J. S. Wu, J. W. Chang, Y. Y. Cheng, Y. C. Kuo, Y. C. Yang, C. C. Lee, and H. R. Guo. 2016. "Association between Blood Dioxin Level and Chronic Kidney Disease in an Endemic Area of Exposure." *PLoS One* 11 (3):e0150248. doi: 10.1371/journal.pone.0150248.

Huang, X., L. Ding, K. Peng, L. Lin, T. Wang, Z. Zhao, Y. Xu, J. Lu, Y. Chen, W. Wang, Y. Bi, G. Ning, and M. Xu. 2016. "Thyroid hormones associate with risk of incident chronic kidney disease and rapid decline in renal function: a prospective investigation." *J Transl Med* 14 (1):336. doi: 10.1186/s12967-016-1081-8.

Hylander, B., and M. Lehtihet. 2015. "Testosterone and gonadotropins but not SHBG vary with CKD stages in young and middle aged men." *Basic Clin Androl* 25:9. doi: 10.1186/s12610-015-0027-y.

Inker, L. A., C. H. Schmid, H. Tighiouart, J. H. Eckfeldt, H. I. Feldman, T. Greene, J. W. Kusek, J. Manzi, F. Van Lente, Y. L. Zhang, J. Coresh, and A. S. Levey. 2012. "Estimating glomerular filtration rate from serum creatinine and cystatin C." *N Engl J Med* 367 (1):20-9. doi: 10.1056/NEJMoa1114248.

Iseki, K., S. Nakai, T. Shinzato, Y. Nagura, and T. Akiba. 2005. "Increasing gender difference in the incidence of chronic dialysis therapy in Japan." *Ther Apher Dial* 9 (5):407-11. doi: 10.1111/j.1744-9987.2005.00318.x.

Jansen, H. T., P. S. Cooke, J. Porcelli, T. C. Liu, and L. G. Hansen. 1993. "Estrogenic and antiestrogenic actions of PCBs in the female rat: in vitro and in vivo studies." *Reprod Toxicol* 7 (3):237-48.

Ji, H., W. Zheng, S. Menini, C. Pesce, J. Kim, X. Wu, S. E. Mulroney, and K. Sandberg. 2007. "Female protection in progressive renal disease is associated with estradiol attenuation of superoxide production." *Gend Med* 4 (1):56-71. doi: 10.1016/s1550-8579(07)80009-x.

Jones R, Edenfield E, Anderson S, Zhang Y, Sjodin A.,. 2012. "Semi-automated extraction and cleanup method for measuring persistent organic pollutants in human serum." *Organohalogen Comp* (74):97-98.

Kataria, A., L. Trasande, and H. Trachtman. 2015. "The effects of environmental chemicals on renal function." *Nat Rev Nephrol* 11 (10):610-25. doi: 10.1038/nrneph.2015.94.

Khan, M. A., C. A. Lichtensteiger, O. Faroon, M. Mumtaz, D. J. Schaeffer, and L. G. Hansen. 2002. "The hypothalamo-pituitary-thyroid (HPT) axis: a target of nonpersistent ortho-substituted PCB congeners." *Toxicol Sci* 65 (1):52-61.

Kim, C., A. C. Ricardo, E. J. Boyko, C. A. Christophi, M. Temprosa, K. E. Watson, X. Pi-Sunyer, and R. R. Kalyani. 2019. "Sex Hormones and Measures of Kidney Function in the Diabetes Prevention Program Outcomes Study." *J Clin Endocrinol Metab* 104 (4):1171-1180. doi: 10.1210/jc.2018-01495.

Klein, I., and K. Ojamaa. 2001. "Thyroid hormone and the cardiovascular system." *N Engl J Med* 344 (7):501-9. doi: 10.1056/nejm200102153440707.

Klett, C., W. Hellmann, E. Hackenthal, and D. Ganten. 1993. "Modulation of tissue angiotensinogen gene expression by glucocorticoids, estrogens, and androgens in SHR and WKY rats." *Clin Exp Hypertens* 15 (4):683-708.

Knutsen, H. K., H. E. Kvalem, M. Haugen, H. M. Meltzer, A. L. Brantsaeter, J. Alexander, O. Papke, V. H. Liane, G. Becher, and C. Thomsen. 2011. "Sex, BMI and age in addition to dietary intakes influence blood concentrations and congener profiles of dioxins and PCBs." *Mol Nutr Food Res* 55 (5):772-82. doi: 10.1002/mnfr.201000243.

Krishnan, V., and S. Safe. 1993. "Polychlorinated biphenyls (PCBs), dibenzo-p-dioxins (PCDDs), and dibenzofurans (PCDFs) as antiestrogens in MCF-7 human breast cancer cells: quantitative structure-activity relationships." *Toxicol Appl Pharmacol* 120 (1):55-61. doi: 10.1006/taap.1993.1086.

Kutz, F. W., P. H. Wood, and D. P. Bottimore. 1991. "Organochlorine pesticides and polychlorinated biphenyls in human adipose tissue." *Rev Environ Contam Toxicol* 120:1-82.

Lavange, L. M., W. D. Kalsbeek, P. D. Sorlie, L. M. Aviles-Santa, R. C. Kaplan, J. Barnhart, K. Liu, A. Giachello, D. J. Lee, J. Ryan, M. H. Criqui, and J. P. Elder. 2010. "Sample design and cohort selection in the Hispanic Community Health Study/Study of Latinos." *Ann Epidemiol* 20 (8):642-9. doi: 10.1016/j.annepidem.2010.05.006.

Levey, A. S., L. A. Stevens, C. H. Schmid, Y. L. Zhang, A. F. Castro, 3rd, H. I. Feldman, J. W. Kusek, P. Eggers, F. Van Lente, T. Greene, and J. Coresh. 2009. "A new equation to estimate glomerular filtration rate." *Ann Intern Med* 150 (9):604-12.

Lo, J. C., G. M. Chertow, A. S. Go, and C. Y. Hsu. 2005. "Increased prevalence of subclinical and clinical hypothyroidism in persons with chronic kidney disease." *Kidney Int* 67 (3):1047-52. doi: 10.1111/j.1523-1755.2005.00169.x.

Lu, C. F., Y. M. Wang, S. Q. Peng, L. B. Zou, D. H. Tan, G. Liu, Z. Fu, Q. X. Wang, and J. Zhao. 2009. "Combined effects of repeated administration of 2,3,7,8-tetrachlorodibenzo-p-dioxin and polychlorinated biphenyls on kidneys of male rats." *Arch Environ Contam Toxicol* 57 (4):767-76. doi: 10.1007/s00244-009-9323-x.

Lyche, J. L., I. C. Oskam, J. U. Skaare, O. Reksen, T. Sweeney, E. Dahl, W. Farstad, and E. Ropstad. 2004. "Effects of gestational and lactational exposure to low doses of PCBs 126 and 153 on anterior pituitary and gonadal hormones and on puberty in female goats." *Reprod Toxicol* 19 (1):87-95. doi: 10.1016/j.reprotox.2004.05.005.

Malisch, R., and A. Kotz. 2014. "Dioxins and PCBs in feed and food--review from European perspective." *Sci Total Environ* 491-492:2-10. doi: 10.1016/j.scitotenv.2014.03.022.

Mankhey, R. W., F. Bhatti, and C. Maric. 2005. "17beta-Estradiol replacement improves renal function and pathology associated with diabetic nephropathy." *Am J Physiol Renal Physiol* 288 (2):F399-405. doi: 10.1152/ajprenal.00195.2004.

Manning, P. J., W. H. Sutherland, A. R. Allum, S. A. de Jong, and S. D. Jones. 2003. "HRT does not improve urinary albumin excretion in postmenopausal diabetic women." *Diabetes Res Clin Pract* 60 (1):33-9.

Mariani, L. H., and J. S. Berns. 2012. "The renal manifestations of thyroid disease." *J Am Soc Nephrol* 23 (1):22-6. doi: 10.1681/asn.2010070766.

Maric, C., and S. Sullivan. 2008. "Estrogens and the diabetic kidney." *Gend Med* 5 Suppl A:S103-13. doi: 10.1016/j.genm.2008.03.010.

Mathews, H. B., and M. W. Anderson. 1975. "Effect of chlorination on the distribution and excretion of polychlorinated biphenyls." *Drug Metab Dispos* 3 (5):371-80.

Mattix, H. J., C. Y. Hsu, S. Shaykevich, and G. Curhan. 2002. "Use of the albumin/creatinine ratio to detect microalbuminuria: implications of sex and race." *J Am Soc Nephrol* 13 (4):1034-9.

McClellan, W. M., B. B. Newsome, L. A. McClure, G. Howard, N. Volkova, P. Audhya, and D. G. Warnock. 2010. "Poverty and racial disparities in kidney disease: the REGARDS study." *Am J Nephrol* 32 (1):38-46. doi: 10.1159/000313883.

McFarland, V. A., and J. U. Clarke. 1989. "Environmental occurrence, abundance, and potential toxicity of polychlorinated biphenyl congeners: considerations for a congener-specific analysis." *Environ Health Perspect* 81:225-39. doi: 10.1289/ehp.8981225.

Meeker, J. D., L. Altshul, and R. Hauser. 2007. "Serum PCBs, p,p'-DDE and HCB predict thyroid hormone levels in men." *Environ Res* 104 (2):296-304. doi: 10.1016/j.envres.2006.11.007.

Metzger, R., D. Wagner, S. Takahashi, F. Suzuki, K. Lindpaintner, and D. Ganten. 1988. "Tissue renin-angiotensin systems aspects of molecular biology and pharmacology." *Clin Exp Hypertens A* 10 (6):1227-38. doi: 10.1080/07300077.1988.11878913.

Meuwese, C. L., J. Gussekloo, A. J. de Craen, F. W. Dekker, and W. P. den Elzen. 2014. "Thyroid status and renal function in older persons in the general population." *J Clin Endocrinol Metab* 99 (8):2689-96. doi: 10.1210/jc.2013-3778.

Mostafalou, S., and M. Abdollahi. 2013. "Pesticides and human chronic diseases: evidences, mechanisms, and perspectives." *Toxicol Appl Pharmacol* 268 (2):157-77. doi: 10.1016/j.taap.2013.01.025.

Mostafalou, S., and M. Abdollahi. 2017. "Pesticides: an update of human exposure and toxicity." *Arch Toxicol* 91 (2):549-599. doi: 10.1007/s00204-016-1849-x.

Moysich, K. B., P. Mendola, E. F. Schisterman, J. L. Freudenheim, C. B. Ambrosone, J. E. Vena, P. G. Shields, P. Kostyniak, H. Greizerstein, S. Graham, and J. R. Marshall. 1999. "An evaluation of proposed frameworks for grouping polychlorinated biphenyl (PCB) congener data into meaningful analytic units."

Am J Ind Med 35 (3):223-31. doi: 10.1002/(sici)1097-0274(199903)35:3<223::aid-ajim2>3.0.co;2-l.

Ness, D. K., S. L. Schantz, J. Moshtaghian, and L. G. Hansen. 1993. "Effects of perinatal exposure to specific PCB congeners on thyroid hormone concentrations and thyroid histology in the rat." *Toxicol Lett* 68 (3):311-23.

Neugarten, J., A. Acharya, and S. R. Silbiger. 2000. "Effect of gender on the progression of nondiabetic renal disease: a meta-analysis." *J Am Soc Nephrol* 11 (2):319-29.

Neugarten, J., and L. Golestaneh. 2013. "Gender and the prevalence and progression of renal disease." *Adv Chronic Kidney Dis* 20 (5):390-5. doi: 10.1053/j.ackd.2013.05.004.

Neugarten, J., and L. Golestaneh. 2019. "Influence of Sex on the Progression of Chronic Kidney Disease." *Mayo Clin Proc* 94 (7):1339-1356. doi: 10.1016/j.mayocp.2018.12.024.

Nicholas, S. B., K. Kalantar-Zadeh, and K. C. Norris. 2015. "Socioeconomic disparities in chronic kidney disease." *Adv Chronic Kidney Dis* 22 (1):6-15. doi: 10.1053/j.ackd.2014.07.002.

O'Connor, J. C., S. R. Frame, L. G. Davis, and J. C. Cook. 1999. "Detection of the environmental antiandrogen p,p-DDE in CD and long-evans rats using a tier I screening battery and a Hershberger assay." *Toxicol Sci* 51 (1):44-53. doi: 10.1093/toxsci/51.1.44.

Patterson, D. G., Jr., L. Y. Wong, W. E. Turner, S. P. Caudill, E. S. Dipietro, P. C. McClure, T. P. Cash, J. D. Osterloh, J. L. Pirkle, E. J. Sampson, and L. L. Needham. 2009. "Levels in the U.S. population of those persistent organic pollutants (2003-2004) included in the Stockholm Convention or in other long range transboundary air pollution agreements." *Environ Sci Technol* 43 (4):1211-8.

Persky, V., J. Piorkowski, M. Turyk, S. Freels, R. Chatterton, Jr., J. Dimos, H. L. Bradlow, L. K. Chary, V. Burse, T. Unterman, D. Sepkovic, and K. McCann. 2011. "Associations of polychlorinated biphenyl exposure and endogenous hormones with diabetes in post-menopausal women previously employed at a capacitor manufacturing plant." *Environ Res* 111 (6):817-24. doi: 10.1016/j.envres.2011.05.012.

Persky, V., J. Piorkowski, M. Turyk, S. Freels, R. Chatterton, Jr., J. Dimos, H. L. Bradlow, L. K. Chary, V. Burse, T. Unterman, D. W. Sepkovic, and K. McCann. 2012. "Polychlorinated biphenyl exposure, diabetes and endogenous hormones: a cross-sectional study in men previously employed at a capacitor manufacturing plant." *Environ Health* 11:57. doi: 10.1186/1476-069x-11-57.

Persky, V., M. Turyk, H. A. Anderson, L. P. Hanrahan, C. Falk, D. N. Steenport, R. Chatterton, Jr., and S. Freels. 2001. "The effects of PCB exposure and fish consumption on endogenous hormones." *Environ Health Perspect* 109 (12):1275-83.

Phillips, D. L., J. L. Pirkle, V. W. Burse, J. T. Bernert, Jr., L. O. Henderson, and L. L. Needham. 1989. "Chlorinated hydrocarbon levels in human serum: effects of fasting and feeding." *Arch Environ Contam Toxicol* 18 (4):495-500.

Reckelhoff, J. F., and J. P. Granger. 1999. "Role of androgens in mediating hypertension and renal injury." *Clin Exp Pharmacol Physiol* 26 (2):127-31. doi: 10.1046/j.1440-1681.1999.02996.x.

Rhee, C. M. 2016. "The interaction between thyroid and kidney disease: an overview of the evidence." *Curr Opin Endocrinol Diabetes Obes* 23 (5):407-15. doi: 10.1097/med.0000000000000275.

Ricardo, A. C., M. F. Flessner, J. H. Eckfeldt, P. W. Eggers, N. Franceschini, A. S. Go, N. M. Gotman, H. J. Kramer, J. W. Kusek, L. R. Loehr, M. L. Melamed, C. A. Peralta, L. Raij, S. E. Rosas, G. A. Talavera, and J. P. Lash. 2015. "Prevalence and Correlates of CKD in Hispanics/Latinos in the United States." *Clin J Am Soc Nephrol* 10 (10):1757-66. doi: 10.2215/cjn.02020215.

Ricardo, A. C., W. Yang, D. Sha, L. J. Appel, J. Chen, M. Krousel-Wood, A. Manoharan, S. Steigerwalt, J. Wright, M. Rahman, S. E. Rosas, M. Saunders, K. Sharma, M. L. Daviglus, and J. P. Lash. 2019. "Sex-Related Disparities in CKD Progression." *J Am Soc Nephrol* 30 (1):137-146. doi: 10.1681/asn.2018030296.

Richthoff, J., L. Rylander, B. A. Jonsson, H. Akesson, L. Hagmar, P. Nilsson-Ehle, M. Stridsberg, and A. Giwercman. 2003. "Serum levels of 2,2',4,4',5,5'-hexachlorobiphenyl (CB-153) in relation to markers of reproductive function in young males from the general Swedish population." *Environ Health Perspect* 111 (4):409-13. doi: 10.1289/ehp.5767.

Ritter, R., M. Scheringer, M. MacLeod, C. Moeckel, K. C. Jones, and K. Hungerbuhler. 2011. "Intrinsic human elimination half-lives of polychlorinated biphenyls derived from the temporal evolution of cross-sectional biomonitoring data from the United Kingdom." *Environ Health Perspect* 119 (2):225-31. doi: 10.1289/ehp.1002211.

Rogers, J. L., A. R. Mitchell, C. Maric, K. Sandberg, A. Myers, and S. E. Mulroney. 2007. "Effect of sex hormones on renal estrogen and angiotensin type 1 receptors in female and male rats." *Am J Physiol Regul Integr Comp Physiol* 292 (2):R794-9. doi: 10.1152/ajpregu.00424.2006.

Safe, S. H. 1994a. "Dietary and environmental estrogens and antiestrogens and their possible role in human disease." *Environ Sci Pollut Res Int* 1 (1):29-33. doi: 10.1007/bf02986921.

Safe, S. H. 1994b. "Polychlorinated biphenyls (PCBs): environmental impact, biochemical and toxic responses, and implications for risk assessment." *Crit Rev Toxicol* 24 (2):87-149. doi: 10.3109/10408449409049308.

Sandberg, K. 2008. "Mechanisms underlying sex differences in progressive renal disease." *Gend Med* 5 (1):10-23.

Saran, R., B. Robinson, K. C. Abbott, L. Y. Agodoa, J. Ayanian, J. Bragg-Gresham, R. Balkrishnan, J. L. Chen, E. Cope, P. W. Eggers, D. Gillen, D. Gipson, S. M. Hailpern, Y. N. Hall, Y. Han, K. He, W. Herman, M. Heung, D. Hutton, S. J. Jacobsen, K. Kalantar-Zadeh, C. P. Kovesdy, Y. Li, Y. Lu, M. Z. Molnar, H. Morgenstern, B. Nallamothu, D. V. Nguyen, A. M. O'Hare, Y. Obi, B. Plattner, R. Pisoni, F. K. Port, P. Rao, V. Ravel, C. M. Rhee, A. Sakhuja, D. E. Schaubel, D. T. Selewski, J. J. Sim, P. Song, E. Streja, M. Kurella Tamura, F. Tentori, S. White, K. Woodside, R. A. Hirth, and V. Shahinian. 2017. "US Renal Data System 2016 Annual Data Report: Epidemiology of Kidney Disease in the United States." *Am J Kidney Dis* 69 (3s1):A7-a8. doi: 10.1053/j.ajkd.2016.12.004.

Schaefer, F., C. Seidel, R. Mitchell, K. Scharer, and W. R. Robertson. 1991. "Pulsatile immunoreactive and bioactive luteinizing hormone secretion in adolescents with chronic renal failure. The Cooperative Study Group on Pubertal Development in Chronic Renal Failure (CSPCRF)." *Pediatr Nephrol* 5 (4):566-71. doi: 10.1007/bf01453703.

Schultheiss, U. T., N. Daya, M. E. Grams, J. Seufert, M. Steffes, J. Coresh, E. Selvin, and A. Kottgen. 2017. "Thyroid function, reduced kidney function and incident chronic kidney disease in a community-based population: the Atherosclerosis Risk in Communities study." *Nephrol Dial Transplant* 32 (11):1874-1881. doi: 10.1093/ndt/gfw301.

Scollon, E. J., J. A. Carr, and G. P. Cobb. 2004. "The effect of flight, fasting and p,p'-DDT on thyroid hormones and corticosterone in Gambel's white-crowned sparrow, Zonotrichia leucophrys gambelli." *Comp Biochem Physiol C Toxicol Pharmacol* 137 (2):179-89. doi: 10.1016/j.cca.2004.01.004.

Shain, S. A., J. C. Shaeffer, and R. W. Boesel. 1977. "The effect of chronic ingestion of selected pesticides upon rat ventral prostate homeostasis." *Toxicol Appl Pharmacol* 40 (1):115-30.

Siddarth, M., S. K. Datta, M. Mustafa, R. S. Ahmed, B. D. Banerjee, O. P. Kalra, and A. K. Tripathi. 2014. "Increased level of organochlorine pesticides in chronic kidney disease patients of unknown etiology: role of GSTM1/GSTT1 polymorphism." *Chemosphere* 96:174-9. doi: 10.1016/j.chemosphere.2013.10.029.

Siddharth, M., S. K. Datta, S. Bansal, M. Mustafa, B. D. Banerjee, O. P. Kalra, and A. K. Tripathi. 2012. "Study on organochlorine pesticide levels in chronic kidney

disease patients: association with estimated glomerular filtration rate and oxidative stress." *J Biochem Mol Toxicol* 26 (6):241-7. doi: 10.1002/jbt.21416.

Silbiger, S., and J. Neugarten. 2008. "Gender and human chronic renal disease." *Gend Med* 5 Suppl A:S3-s10. doi: 10.1016/j.genm.2008.03.002.

Silbiger, S. R. 2011. "Raging hormones: gender and renal disease." *Kidney Int* 79 (4):382-4. doi: 10.1038/ki.2010.474.

Silbiger, S. R., and J. Neugarten. 1995. "The impact of gender on the progression of chronic renal disease." *Am J Kidney Dis* 25 (4):515-33. doi: 10.1016/0272-6386(95)90119-1.

Silbiger, S. R., and J. Neugarten. 2003. "The role of gender in the progression of renal disease." *Adv Ren Replace Ther* 10 (1):3-14. doi: 10.1053/jarr.2003.50001.

Singer, M. A. 2001. "Of mice and men and elephants: metabolic rate sets glomerular filtration rate." *Am J Kidney Dis* 37 (1):164-178. doi: 10.1016/s0272-6386(01)80073-1.

Sjodin, A., R. S. Jones, S. P. Caudill, L. Y. Wong, W. E. Turner, and A. M. Calafat. 2014. "Polybrominated diphenyl ethers, polychlorinated biphenyls, and persistent pesticides in serum from the national health and nutrition examination survey: 2003-2008." *Environ Sci Technol* 48 (1):753-60. doi: 10.1021/es4037836.

Sjodin, A., R. S. Jones, C. R. Lapeza, J. F. Focant, E. E. McGahee, 3rd, and D. G. Patterson, Jr. 2004. "Semiautomated high-throughput extraction and cleanup method for the measurement of polybrominated diphenyl ethers, polybrominated biphenyls, and polychlorinated biphenyls in human serum." *Anal Chem* 76 (7):1921-7. doi: 10.1021/ac030381+.

Sonne, C., H. Wolkers, P. S. Leifsson, B. M. Jenssen, E. Fuglei, O. Ahlstrom, R. Dietz, M. Kirkegaard, D. C. Muir, and E. Jorgensen. 2008. "Organochlorine-induced histopathology in kidney and liver tissue from Arctic fox (Vulpes lagopus)." *Chemosphere* 71 (7):1214-24. doi: 10.1016/j.chemosphere.2007.12.028.

Sorlie, P. D., L. M. Aviles-Santa, S. Wassertheil-Smoller, R. C. Kaplan, M. L. Daviglus, A. L. Giachello, N. Schneiderman, L. Raij, G. Talavera, M. Allison, L. Lavange, L. E. Chambless, and G. Heiss. 2010. "Design and implementation of the Hispanic Community Health Study/Study of Latinos." *Ann Epidemiol* 20 (8):629-41. doi: 10.1016/j.annepidem.2010.03.015.

Stevens, L. A., C. H. Schmid, T. Greene, Y. L. Zhang, G. J. Beck, M. Froissart, L. L. Hamm, J. B. Lewis, M. Mauer, G. J. Navis, M. W. Steffes, P. W. Eggers, J. Coresh, and A. S. Levey. 2010. "Comparative performance of the CKD Epidemiology Collaboration (CKD-EPI) and the Modification of Diet in Renal Disease (MDRD) Study equations for estimating GFR levels above 60

mL/min/1.73 m2." *Am J Kidney Dis* 56 (3):486-95. doi: 10.1053/j.ajkd.2010.03.026.

Su, K., X. Lv, H. Song, X. Luo, and C. Chen. 2015. "PCB77 Inducing Renal Tubular Cell Apoptosis." *Ultrastruct Pathol* 39 (3):192-7. doi: 10.3109/01913123.2014.973130.

Szekacs, B., Z. Vajo, S. Varbiro, R. Kakucs, L. Vaslaki, N. Acs, I. Mucsi, and E. A. Brinton. 2000. "Postmenopausal hormone replacement improves proteinuria and impaired creatinine clearance in type 2 diabetes mellitus and hypertension." *Bjog* 107 (8):1017-21.

Tanaka, R., H. Tsutsui, S. Kobuchi, T. Sugiura, M. Yamagata, M. Ohkita, M. Takaoka, T. Yukimura, and Y. Matsumura. 2012. "Protective effect of 17beta-estradiol on ischemic acute kidney injury through the renal sympathetic nervous system." *Eur J Pharmacol* 683 (1-3):270-5. doi: 10.1016/j.ejphar.2012.02.044.

Tee, P. G., A. M. Sweeney, E. Symanski, J. C. Gardiner, D. M. Gasior, and S. L. Schantz. 2003. "A longitudinal examination of factors related to changes in serum polychlorinated biphenyl levels." *Environ Health Perspect* 111 (5):702-7. doi: 10.1289/ehp.5866.

Turyk, M. E., H. A. Anderson, S. Freels, R. Chatterton, Jr., L. L. Needham, D. G. Patterson, Jr., D. N. Steenport, L. Knobeloch, P. Imm, and V. W. Persky. 2006. "Associations of organochlorines with endogenous hormones in male Great Lakes fish consumers and nonconsumers." *Environ Res* 102 (3):299-307. doi: 10.1016/j.envres.2006.01.009.

Turyk, M. E., H. A. Anderson, and V. W. Persky. 2007. "Relationships of thyroid hormones with polychlorinated biphenyls, dioxins, furans, and DDE in adults." *Environ Health Perspect* 115 (8):1197-203. doi: 10.1289/ehp.10179.

Van den Berg, M., L. S. Birnbaum, M. Denison, M. De Vito, W. Farland, M. Feeley, H. Fiedler, H. Hakansson, A. Hanberg, L. Haws, M. Rose, S. Safe, D. Schrenk, C. Tohyama, A. Tritscher, J. Tuomisto, M. Tysklind, N. Walker, and R. E. Peterson. 2006. "The 2005 World Health Organization reevaluation of human and Mammalian toxic equivalency factors for dioxins and dioxin-like compounds." *Toxicol Sci* 93 (2):223-41. doi: 10.1093/toxsci/kfl055.

van Hoek, I., and S. Daminet. 2009. "Interactions between thyroid and kidney function in pathological conditions of these organ systems: a review." *Gen Comp Endocrinol* 160 (3):205-15. doi: 10.1016/j.ygcen.2008.12.008.

Vargas, F., J. M. Moreno, I. Rodriguez-Gomez, R. Wangensteen, A. Osuna, M. Alvarez-Guerra, and J. Garcia-Estan. 2006. "Vascular and renal function in experimental thyroid disorders." *Eur J Endocrinol* 154 (2):197-212. doi: 10.1530/eje.1.02093.

Vermeulen, A., L. Verdonck, and J. M. Kaufman. 1999. "A critical evaluation of simple methods for the estimation of free testosterone in serum." *J Clin Endocrinol Metab* 84 (10):3666-72. doi: 10.1210/jcem.84.10.6079.

Warner, J., J. R. Osuch, W. Karmaus, J. R. Landgraf, B. Taffe, M. O'Keefe, D. Mikucki, and P. Haan. 2012. "Common classification schemes for PCB congeners and the gene expression of CYP17, CYP19, ESR1 and ESR2." *Sci Total Environ* 414:81-9. doi: 10.1016/j.scitotenv.2011.10.044.

Whitehead, S. A., and S. Rice. 2006. "Endocrine-disrupting chemicals as modulators of sex steroid synthesis." *Best Pract Res Clin Endocrinol Metab* 20 (1):45-61. doi: 10.1016/j.beem.2005.09.003.

Wolff, M. S., D. Camann, M. Gammon, and S. D. Stellman. 1997. "Proposed PCB congener groupings for epidemiological studies." *Environ Health Perspect* 105 (1):13-4. doi: 10.1289/ehp.9710513.

Xu, P., X. Lou, G. Ding, H. Shen, L. Wu, Z. Chen, J. Han, and X. Wang. 2015. "Effects of PCBs and PBDEs on thyroid hormone, lymphocyte proliferation, hematology and kidney injury markers in residents of an e-waste dismantling area in Zhejiang, China." *Sci Total Environ* 536:215-222. doi: 10.1016/j.scitotenv.2015.07.025.

Yanes, L. L., J. C. Sartori-Valinotti, and J. F. Reckelhoff. 2008. "Sex steroids and renal disease: lessons from animal studies." *Hypertension* 51 (4):976-81. doi: 10.1161/hypertensionaha.107.105767.

Yi, S., E. Selvin, S. Rohrmann, S. Basaria, A. Menke, N. Rifai, E. Guallar, E. A. Platz, and B. Astor. 2009. "Endogenous sex steroid hormones and measures of chronic kidney disease (CKD) in a nationally representative sample of men." *Clin Endocrinol (Oxf)* 71 (2):246-52. doi: 10.1111/j.1365-2265.2008.03455.x.

Zhang, Q. L., and D. Rothenbacher. 2008. "Prevalence of chronic kidney disease in population-based studies: systematic review." *BMC Public Health* 8:117. doi: 10.1186/1471-2458-8-117.

Zhang, Y., Y. Chang, S. Ryu, J. Cho, W. Y. Lee, E. J. Rhee, M. J. Kwon, R. Pastor-Barriuso, S. Rampal, W. K. Han, H. Shin, and E. Guallar. 2014. "Thyroid hormone levels and incident chronic kidney disease in euthyroid individuals: the Kangbuk Samsung Health Study." *Int J Epidemiol* 43 (5):1624-32. doi: 10.1093/ije/dyu126.

Zimmerman, M. A., D. D. Hutson, E. H. Trimmer, S. N. Kashyap, J. L. Duong, B. Murphy, E. M. Grissom, J. M. Daniel, and S. H. Lindsey. 2017. "Long- but not short-term estradiol treatment induces renal damage in midlife ovariectomized Long-Evans rats." *Am J Physiol Renal Physiol* 312 (2):F305-f311. doi: 10.1152/ajprenal.00411.2016.

Zimmerman, R. S., J. Ryan, B. S. Edwards, G. Klee, D. Zimmerman, N. Scott, and J. C. Burnett, Jr. 1988. "Cardiorenal endocrine dynamics during volume expansion in hypothyroid dogs." *Am J Physiol* 255 (1 Pt 2):R61-6. doi: 10.1152/ajpregu.1988.255.1.R61.

APPENDICES

APPENDIX A.
IRB APPROVAL FOR STUDY

Approval Notice
Amendment – Expedited Review
UIC Amendment # 12

May 28, 2019

Victoria W. Persky, MD, MPH
Epidemiology and Biostatistics
Phone: (312) 996-4783 / Fax: (312) 996-0064

RE: **Protocol # 2015-0908**
"Persistent Organic Pollutants, Endogenous Hormones and Diabetes in Latinos"

Dear Dr. Persky:

Your application was reviewed and approved on May 28, 2019. The amendment to your research may now be implemented.

Please note the following information about your approved amendment:

Amendment Approval Date: May 28, 2019
Amendment:

Summary: UIC Amendment #12, dated May 16, 2019 and received May 17, 2019, is an investigator-initiated amendment which involves the following changes to the protocol:

1. The inclusion of two additional secondary aims to the protocol. Secondary aim 2: Investigate the interaction effects between diabetes-related single nucleotide polymorphisms (SNPs) and POPs on diabetes, prediabetes, insulin resistance, and β-cell dysfunction. Secondary aim 3: Investigate the effects of POPs and hormones on other relevant health outcomes included in the SOL study, including kidney function, hypertension, cardiovascular disease, etc.
2. The removal the postmenopausal eligibility criteria for females. Based on measured hormone levels (FSH, LH and estradiol) and questionnaire responsesmenopausal (n=221) and post-menopausal (n=834). Thus, 70% are now classified as post-menopausal. This will slightly reduce the power for the hormone data analyses, but will not affect the

APPENDIX A (continued).

sample size for POPs and diabetes analyses. Initial application (version 5, 5/16/2019), was included in the submission.

Research Protocol(s):

a) Persistent Organic Pollutants, Endogenous Hormones and Diabetes in Latinos, Version 8, 5-16-19.

Please be sure to:

→ Use your research protocol number (2015-0908) on any documents or correspondence with the IRB concerning your research protocol.

→ Review and comply with the policies of the UIC Human Subjects Protection Program (HSPP) and the guidance ***Investigator Responsibilities***.

Please note that the IRB has the right to ask further questions, seek additional information, or monitor the conduct of your research and the consent process.

Please be aware that if the scope of work in the grant/project changes, the protocol must be amended and approved by the UIC IRB before the initiation of the change.

We wish you the best as you conduct your research. If you have any questions or need further help, please contact the OPRS at (312) 996-1711 or me at (312) 413-0241. Please send any correspondence about this protocol to OPRS via OPRS Live.

Sincerely,
Ibraheem Oguntade
IRB Coordinator, IRB 3
Office for the Protection of Research Subjects

cc: Ronald C. Hershow, Epidemiology and Biostatistics, M/C 923

UNIVERSITY OF ILLINOIS AT CHICAGO
Office for the Protection of Research Subjects
201 AOB (MC 672)
1737 West Polk Street
Chicago, Illinois 60612
Phone (312) 996-1711

APPENDIX B.
IRB APPROVAL FOR STUDY

Notice of Determination
Activity Does Not Represent Human Subjects Research

December 19, 2019

20191397-129084-1

Jessica Madrigal, MS
Epidemiology and Biostatistics
Phone: (708) 254-1198

RE: **Protocol # 2019-1397**
"Concentrations of Multiple Persistant Organic Pollutants and Measures of Kidney Health in Adults: Cross-sectional findings from the 1999-2004 National Health and Nutrition Examination Survey"

Sponsor: None

Dear Jessica Madrigal:

The UIC Office for the Protection of Research Subjects received your Determination application and has determined that this activity **DOES NOT meet the definition of human subject research** as defined by 45 CFR 46.102(e)/ 21 CFR 50.3(g) and 21 CFR 56.102(e).

Specifically, this study will use data from adult participants in the NHANES 1999-2004 cycles. NHANES data will be downloaded from the NCHS NHANES website. These data are publicly available and do not contain any identifying information.

You may conduct your activity without further submission to the IRB.

Please note:

- If this activity is used in conjunction with any other research involving human subjects, prospective IRB approval or a Claim of Exemption is required.
- If this activity is altered in such a manner that may result in the activity representing human subject research, a NEW Determination application must be submitted.

cc: Ronald C. Hershow

APPENDIX B (continued).

Mary Ellen Turyk

UNIVERSITY OF ILLINOIS AT CHICAGO
Office for the Protection of Research Subjects

201 AOB (MC 672)
1737 West Polk Street
Chicago, Illinois 60612

Phone (312) 996-1711

VITA

NAME

Jessica M. Madrigal

EDUCATION

University of Illinois at Chicago
School of Public Health, Chicago, IL
PhD in Epidemiology (Anticipated February 2020)
Doctoral Committee: Victoria Persky, MD (chair),
Martha Daviglus, MD, PhD, Mary Turyk, PhD, James Lash, MD,
Robert Sargis, MD, PhD, and Sally Freels, PhD
Dissertation: Relationships among Exposure to Environmental
Pollutants, Endogenous Hormones, and Kidney Disease Risk

University of Illinois at Chicago
College of Applied Health Sciences, Chicago, IL
MS in Disability and Human Development 2010
Thesis Chair: James H. Rimmer, PhD
Thesis Title: Establishing play area design guidelines for children
of all abilities using the Delphi method

University of Illinois at Chicago
College of Liberal Arts and Sciences, Chicago, IL
BA in Anthropology with highest distinction 2007
Minor in Biological Sciences

HONORS AND AWARDS

Chancellor's Student Service Award 2019
University of Illinois at Chicago

Kidney STARS Program Award ($1,500) 2018
American Society of Nephrology

Rodney P. Musselman Travel Award ($1,000) 2017, 2019
UIC School of Public Health

Graduate Student Council Travel Award ($275) 2016, 2018
UIC Graduate Student Council

Graduate Student Presenter Award ($200) 2016-2019
UIC Graduate College

Sustainability Fee Project Award ($6,300) 2016
UIC Office of Sustainability

Best Research Poster Award, University of Chicago Diabetes Day ($100) 2016

Dr. Arthur Steinhaus Award 2013
Illinois Association for Health, Physical Recreation & Dance (IAHPERD)

RESEARCH EXPERIENCE & PROFESSIONAL DEVELOPMENT

Graduate Research Assistant 2019-present
Office of Community Engaged Research and Implementation Science (OCERIS)
University of Illinois Cancer Center

Graduate Research Assistant 2017-2019
ChicAgo Center for Health and EnvironmenT (CACHET)
Community Engagement Core (CEC) (P30ES027792)
Division of Epidemiology and Biostatistics
School of Public Health, University of Illinois at Chicago

Graduate Research Assistant 2017-present
Persistent Organic Pollutants, Endogenous Hormones and Diabetes in Latinos: Hispanic Community Health Study/Study of Latinos Ancillary Study (R01ES025159)
Division of Epidemiology and Biostatistics
School of Public Health, University of Illinois at Chicago

Graduate Research Assistant 2017
Understanding the Relationship between Psychological Well-Being and Well-Woman Visit and Preventive Care Use in Midlife African-American Women (R36AG054652)
Division of Community Health Sciences
School of Public Health, University of Illinois at Chicago

Graduate Research Assistant 2016-2018
The Relationship of Manganese Exposure with Pulmonary Function and School Performance Study (SPH Seed Funding)
Division of Epidemiology and Biostatistics
School of Public Health, University of Illinois at Chicago

Graduate Research Assistant 2015-2017
Jose Oberholzer Lab
Division of Transplantation
Islet and Pancreas Transplant Program
College of Medicine, University of Illinois at Chicago

Occupational and Environmental Epidemiology Predoc Fellowship 2015-present
National Institute for Occupational Safety and Health (NIOSH)
T42 training program (T42OH008672)
Division of Epidemiology and Biostatistics
School of Public Health, University of Illinois at Chicago

Research Specialist in Public Health 2014-2015
Institute for Health Research and Policy, School of Public Health
University of Illinois at Chicago

ADA Technical Assistance Specialist 2012-2014
Institute on Disability and Human Development,
Department of Disability and Human Development
University of Illinois at Chicago

Research Specialist in Disability and Health Promotion 2009-2012
Institute on Disability and Human Development,
Department of Disability and Human Development
University of Illinois at Chicago

Graduate Research Assistant 2008-2009
Institute on Disability and Human Development,
Department of Disability and Human Development
University of Illinois at Chicago

MEMBERSHIP IN PROFESSIONAL ORGANIZATIONS

International Society for Environmental Epidemiology, Member	2018-
American Society of Nephrology, Member	2018-
Graduate Student Council Representative (School of Public Health)	2016-2018
Society for Epidemiologic Research, Member	2016-
Cook County Dept. of Public Health Community Health Advisory Council, Community Representative	2015-2017
American Society on Aging, Member	2014-2015
Illinois Governor's Task Force, Co-Chair, Enhanced PE Promotion Committee	2012-2013
NuStep Inclusive Fitness Advisory Board Member	2011-2013
American College of Sports Medicine, Certified Personal Trainer®	2010-2018
American Public Health Association, Disability Section Member	2009-2014
Chicago Mayor's Fitness Council, Member	2008-2012

SERVICE

Abstract Reviewer

Society for Epidemiologic Research	2018-2019
American Public Health Association	2012-2015

TEACHING EXPERIENCE

Guest Lectures

"*Epidemiologic Methods for Surveillance and Survey Data Analysis"* 2019
EPID 594: Applied Epidemiologic Methods
University of Illinois at Chicago

(Graduate audience)
"*Environmental Public Health Surveillance"* 2019
EPID 536: Methods in Environmental Epidemiology
University of Illinois at Chicago
(Graduate audience)

"*Understanding the Health of Illinois' Workforce:* 2017
2013-2015 Behavioral Risk Factor Surveillance System Findings"
Targeted Research Training (NIOSH-funded T42)
University of Illinois at Chicago
(Graduate/faculty audience)

"Introduction to Planning Clinical Research Projects" 2016
Diabetes Training Program (NIH-funded R25)
University of Illinois at Chicago
(Undergraduate audience)

Teaching Assistant
EPID 594: *Applied Epidemiologic Methods* 2016-2017
"Survey Data Analysis Methods"
"Causal Diagrams"
University of Illinois at Chicago
(Graduate audience; total enrollment =25; semesters=2)

PUBLICATIONS

Peer-Reviewed Articles *(View my bibliography with this URL: https://www.ncbi.nlm.nih.gov/myncbi/1tQHfuzisvvQh/bibliography/public/)*

Madrigal JM, Stempinski-Metoyer K, McManus AE, Zimmerman L, Patel A. The family planning quotient and reproductive life index (FPQ/RepLI) tool: a solution for family planning, reproductive life planning and contraception counseling. Reprod Health.2019 Aug 19;16(1):125. doi: 10.1186/s12978-019-0787-5. PubMed PMID: 31426800; PubMed Central PMCID: PMC6700782.

Lee J, **Madrigal JM**, Patel A. Follow-Up Rates And Contraceptive Choices After Medical Abortion In Adolescents At Cook County Hospital. J Pediatr Adolesc Gynecol. 2019 Apr 10;. doi: 10.1016/j.jpag.2019.04.006. [Epub ahead of print] PubMed PMID: 30980940.

Madrigal JM, Atluri M, Radeke E, Patel A. Looking Through the Lens of a Family Planner to Prioritize Reproductive Health Among Women With Cancer. Journal of Oncology Practice. 2019 Feb;15(2):e141-e152. doi: 10.1200/JOP.18.00429. Epub 2018 Dec 17. PubMed PMID: 30763204.

Cannon R, **Madrigal JM**, Feldman E, Stempinski-Metoyer K, Holloway L, Patel A. Contraceptive needs among newly incarcerated women in a county jail in the United States. Int J Prison

Health. 2018 Dec 17;14(4):244-253. doi: 10.1108/IJPH-08-2017-0036. PubMed PMID: 30468113.

Madrigal JM, Persky V, Pappalardo A, Argos M. Association of heavy metals with measures of pulmonary function in children and youth: Results from the National Health and Nutrition Examination Survey (NHANES). Environ Int. 2018 Dec;121(Pt 1):871-878. doi: 10.1016/j.envint.2018.09.045. Epub 2018 Oct 18. PubMed PMID: 30343186; PubMed Central PMCID: PMC6277046.

Gokhale P, **Madrigal JM**, Aparicio J, Shim JY, Patel A. Demographic and Other Characteristics, and Rates of Sexually Transmitted Infections among Adolescents Who Underwent Multiple Abortions in 1 Year. J Pediatr Adolesc Gynecol. 2018 Dec;31(6):610-613. doi: 10.1016/j.jpag.2018.07.011. Epub 2018 Aug 3. PubMed PMID: 30081083.

Henderson V, **Madrigal JM**, Handler A. A mixed methods study: Midlife African American women's knowledge, beliefs, and barriers to well-woman visit, flu vaccine, and mammogram use. J Women Aging. 2018 Nov 22:1-22. doi: 10.1080/08952841.2018.1549433. [Epub ahead of print] PubMed PMID: 30466373.

Madrigal JM, Ricardo AC, Persky V, Turyk M. Associations between blood cadmium concentration and kidney function in the U.S. population: Impact of sex, diabetes and hypertension. Environ Res. 2018 Nov 6;169:180-188. doi: 10.1016/j.envres.2018.11.009. [Epub ahead of print] PubMed PMID: 30466011.

Zimmerman LP, **Madrigal JM**, Jordan LM, Patel A. The Association Between Multiple Abortions Within 1 Year and Previous Postabortal Desired Contraception at an Urban, Public Hospital. *J Womens Health (Larchmt)*. 2018 Nov 3. doi: 10.1089/jwh.2018.6944. [Epub ahead of print] PubMed PMID: 30394817.

Shim JY, **Madrigal JM**, Aparicio J, Patel A. Beyond Routine Abortion Practice: Identifying Adolescents and Young Adults at risk for Anemia. *J Pediatr Adolesc Gynecol*. 2018 Jun 18. pii: S1083-3188(18)30243-2. doi: 10.1016/j.jpag.2018.06.002. [Epub ahead of print] PubMed PMID: 29929018.

Suarez Mora A, **Madrigal JM**, Jordan L, Patel A. Effectiveness of an Educational Intervention to Increase Human Papillomavirus Knowledge in High-Risk Minority Women. J Low Genit Tract Dis. 2018 Oct;22(4):288-294. doi: 10.1097/LGT.0000000000000386. PubMed PMID: 29570136.

Madrigal JM, Monson RS, Hatipoglu B, Oberholzer J, Kondos GT, Varady KA, Danielson KK. Coronary artery calcium may stabilize following islet cell transplantation in patients with type 1 diabetes. *Clinical Transplantation*. 2017 Oct;31(10). doi: 10.1111/ctr.13059. Epub 2017 Aug 19. PubMed PMID: 28748581; PubMed Central PMCID: PMC5633499.

Muramatsu N, **Madrigal J**, Berbaum ML, Henderson VA, Jurivich DA, Zanoni J, Marquez DX, Cruz Madrid K. Co-learning with home care aides and their clients: collaboratively increasing individual and organizational capacities. *Gerontology and Geriatrics Education*. 2015;36(3):261-77. doi: 10.1080/02701960.2015.1015121. Epub 2015 Feb 11. PubMed PMID: 25671492; PubMed Central PMCID: PMC4715832.

Other Articles

Madrigal, J. (2014) The ADA @ 24: An Accessibility Refresh. *The Journal on Active Aging*, 13(5), 38-41.

Madrigal, J. (2011) Accessible Design: What adoption of the revised ADA Standards means for the active-aging industry. *The Journal on Active Aging*, 10(1), 52-55.

Madrigal, J**.** (2010). Exercise is for EveryBody. *Children & Youth with Special Health Care Needs Magazine*, The Official Publication of the Kansas Department of Health & Environment. Topeka, KS.

CONFERENCE PRESENTATIONS AND PUBLISHED ABSTRACTS

(Madrigal, JM = presenter; *Other* = co-author presenter)

Madrigal, JM., Turyk, M., Ricardo, A., Sargis, R., Kaplan, R., Freels, S., Persky, V., Lash, J., Daviglus, M. November 2019. *Association between Endogenous Sex Hormones and Kidney Function: Cross-sectional Findings from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL).* American Society of Nephrology Kidney Week, Washington, DC. (poster)

Madrigal, JM., Persky, V., Sargis, R., Turyk, M. August 2019. *Multiple Pesticide Exposures and Measures of Sex Steroid Hormones in Adult Males: Cross-sectional findings from the 1999-2004 NHANES.* Annual Meeting of the International Society for Environmental Epidemiology 2019, Utrecht, Netherlands. (poster)

Cavens, A., **Madrigal, JM.**, & Patel, A. June 2018. *Appropriateness of Venous Thromboembolism Prophylaxis Risk Assessment and Prophylaxis among Gynecologic Surgical Patients at John H. Stroger Hospital of Cook County.* Northwestern University Feinberg School of Medicine Thirty-Ninth Annual Residents' and Fellows' Research Seminar. Chicago, IL. (oral)

Madrigal JM., Johnson, C., Patel, A. June 2019. *Social Support and Risk Factors for Cardiovascular Disease Among Women Accessing Care in an Urban Public Health Care System.* Society for Epidemiology Research Annual Meeting, Minneapolis, MN. (poster)

Shim JY., **Madrigal JM**., Williams A, Patel A. April 2019. *Acceptance of Expedited Partner Therapy Among Adolescents in an Urban Reproductive Health Clinic*. 33nd Annual Clinical and Research Meeting of the North American Society for Pediatric and Adolescent Gynecology, New Orleans, LA. (poster)

Madrigal, JM., Cedillo, E., Ricardo, A., Appel L., Anderson, C., Deo, R., Hamm, L., Sha, D., Hsu, J., Zenk, S., Saunders, M., Persky, V., Lash, JP., on behalf of the CRIC Investigators. March 2019. *Associations of Food Environment with Bone Mineral Disorders in the Chronic Renal Insufficiency Cohort (CRIC) Study*. University of Illinois at Chicago, Department of Medicine Scholarly Activities Day, Chicago, IL. (poster)

Betman, S., **Madrigal, JM.**, Stempinski-Metoyer, K., Rao, R., Patel, A. March 2019. *Assessment of Contraception and Fertility Knowledge Among Female Oncology Patients of Child Bearing Age and Their Providers.* 36th Rush University Forum for Research and Clinical Investigation, Chicago, IL. (poster)

Madrigal, JM., Cedillo, E., Ricardo, A., Appel L., Anderson, C., Deo, R., Hamm, L., Sha, D., Hsu, J., Zenk, S., Saunders, M., Persky, V., Lash, JP., on behalf of the CRIC Investigators. October 2018. *Associations of Food Environment with Bone Mineral Disorders in the Chronic Renal Insufficiency Cohort (CRIC) Study*. American Society of Nephrology Kidney Week, San Diego, CA. (poster)

Stempinski-Metoyer, K., **Madrigal JM.,** Adam, M., Patel, A. October 2018. *Utility of the Comfort, Assurance, Language Model (CALM) as a non-pharmacological intervention for pain relief during IUD insertion.* 2018 North American Forum on Family Planning (Forum), New Orleans, LA. (poster)

Madrigal, JM., Ricardo, A., Persky, V., Turyk, M. August 2018. *Cadmium and Kidney Function in the U.S. Population: Impact of Sex, Diabetes and Hypertension.* Joint Annual Meeting of the International Society of Exposure Science and the International Society for Environmental Epidemiology 2018, Ottawa, Canada. (poster)

Madrigal, JM., Persky, V., Pappallardo, A., Argos, M. August 2018. *Association of heavy metals with measures of pulmonary function in youth: Findings from the 2011-2012 National Health and Nutrition Examination Survey (NHANES)*. Joint Annual Meeting of the International Society of Exposure Science and the International Society for Environmental Epidemiology 2018, Ottawa, Canada. (oral)

Madrigal JM., Williams, P., Patel, A. June 2018. *Utility of Peer Educators to Conduct Sexually Transmitted Disease Surveillance among Young Women Seeking Care in an Urban Public Healthcare System.* Society for Epidemiology Research Annual Meeting, Baltimore, MD. (poster)

Madrigal JM., Johnson, C., Patel, A. June 2018. *The Role of Cardiovascular Risk Factor Surveillance in Women's Healthcare Settings: Incorporating Preventative Care into Reproductive Health Services.* Society for Epidemiology Research Annual Meeting, Baltimore, MD. (poster)

Sobecki-Rausch, J., Cavens, A., **Madrigal, JM.**, & Patel, A. June 2018. *Ectopic pregnancy in a high-risk population.* Northwestern University Feinberg School of Medicine Thirty-Eighth Annual Residents' and Fellows' Research Seminar. Chicago, IL. (oral – 2nd place award winner)

Madrigal JM., Stempinski-Metoyer, K., Patel, A. April 2018. *Exploring the impact of post-abortion contraceptive counseling on contraceptive uptake in a vulnerable population at an*

urban public hospital in Illinois. 42nd Annual Meeting of the National Abortion Federation, Seattle, WA. (poster)

Madrigal JM., Stempinski-Metoyer, K., Aparicio, J., Patel, A. April 2018. *Assessment of Contraception Use, Knowledge, and Interest among Women Seeking Abortion at an Urban Public Hospital.* 42nd Annual Meeting of the National Abortion Federation, Seattle, WA. (poster)

Madrigal JM., Henry-Reid, L., Patel, A. April 2018. *Uptake of HPV Vaccination in High-Risk Vulnerable Women: Intersection of Reproductive Health and Preventative Care.* ASCCP Annual Meeting, Las Vegas, NV. (oral)

Madrigal JM., Henry-Reid, L., Patel, A. April 2018. *A Community Based Assessment of HPV Vaccination Prevalence in High-Risk Women in Chicago.* ASCCP Annual Meeting, Las Vegas, NV. (poster)

Madrigal, JM., Persky, V., Pappallardo, A., Argos, M. April 2018. *Association of heavy metals with measures of pulmonary function in youth: Findings from the 2011-2012 National Health and Nutrition Examination Survey (NHANES)*. University of Illinois at Chicago School of Public Health 13th Annual Research and Practice Awards Day, Chicago, IL. (poster)

Madrigal, JM., Stempinski-Metoyer, K., Adam, M., Holloway, L., Patel, A., Feldman, E. April 2018. *Incorporating health promotion into healthcare visits provided to incarcerated women within an urban county jail*. Northwestern University 14th Annual Lewis Landsberg Research Day, Chicago, IL. (poster)

Shim, J., **Madrigal, JM.**, Patel, A. April 2018. *Beyond Routine Abortion Practice: Identifying Adolescents at Risk of Anemia.* North American Society for Pediatric and Adolescent Gynecology, 32nd Annual Clinical and Research Meeting, West Palm Beach, FL. (oral)

Gokhale, P., **Madrigal, JM.**, Shim, J., Patel, A. April 2018. *Demographics and Rates of Sexually Transmitted Infections in Adolescents Undergoing Multiple Abortions in One Year.* North American Society for Pediatric and Adolescent Gynecology, 32nd Annual Clinical and Research Meeting, West Palm Beach, FL. (poster)

Lee, J., **Madrigal, JM.**, Patel, A. April 2018. *Factors Associated with Follow-Up Rates After Medical Abortion iIn Adolescents at Cook County Hospital.* North American Society for Pediatric and Adolescent Gynecology, 32nd Annual Clinical and Research Meeting, West Palm Beach, FL. (poster)

Johnson, C., **Madrigal, JM.**, Aparicio, J., Stempinski-Metoyer, K., Patel, A. March 2018. *Long-acting reversible contraception knowledge, attitudes, and practice patterns among healthcare providers attending top tier methods training in Chicago.* 35th Rush University Forum for Research and Clinical Investigation, Chicago, IL. (poster)

Madrigal JM., Forst, L. March 2018. *Understanding the Health Promotion Needs of Illinois' Workforce: 2013-2015 Behavioral Risk Factor Surveillance System Findings.* Illinois Occupational and Environmental Health and Safety Education and Research Center Regional Research Symposium, Chicago, IL. (poster)

Henderson, V., **Madrigal, JM.**, Handler, A. November 2017. A*ssessing the Relationship between Psychological Well-Being and Well-Woman Visit and Preventive Care Use in Midlife African-American Women*. American Public Health Association's 2017 Annual Meeting and Expo, Atlanta, GA. (poster)

Madrigal JM., Atluri, M., Adam, M., Jordan, L., Radeke, E., Patel, A. November 2017. *Utilization of a family planning and reproductive life tool to prioritize reproductive health among women with diagnosed cancer.* Oncofertility Conference, Chicago, IL. (poster)

Madrigal JM., Forst, L. June 2017. *Understanding the Health Promotion Needs of Illinois' Workforce: 2013-2015 Behavioral Risk Factor Surveillance System Findings.* Work, Stress, and Health Conference, Minneapolis, MN. (poster)

Suarez Mora, A., **Madrigal, JM.**, Jordan, L. & Patel, A. June 2017. *Knowledge of the human papillomavirus, cervical cancer, and vaccination in a high-risk population.* Oral session presented at the Northwestern University Feinberg School of Medicine Thirty-Seventh Annual Residents' and Fellows' Research Seminar. Chicago, IL.

Williams, A., **Madrigal, JM.**, Fischlowitz, A., Williams, P., & Patel, A. June 2017. *Acceptance of expedited partner therapy among young women in an urban reproductive health clinic.* Oral session presented at the Northwestern University Feinberg School of Medicine Thirty-Seventh Annual Residents' and Fellows' Research Seminar. Chicago, IL.

Madrigal JM., Monson R.S., Oberholzer J., Danielson K.K.. November 2016. *Stabilization of coronary artery calcium following islet cell transplant in patients with type 1 diabetes*. University of Illinois at Chicago College of Medicine 2016 Research Forum, Chicago, IL. (poster)

Madrigal JM., Persky V., Forst, L. September 2016. *Understanding risky health behaviors in Illinois workers: Findings from the 2013 Behavioral Risk Factor Surveillance System (BRFSS) using the industry and occupation module.* Epidemiology in Occupational Health Conference, Barcelona, Spain. (oral) Occupational and Environmental Medicine Sep 2016, 73 (Suppl 1) A63.

Madrigal JM., Monson R.S., Oberholzer J., Danielson K.K. June 2016. *Stabilization of coronary artery calcium (CAC) following islet cell transplant in patients with type 1 diabetes*. American Diabetes Association Annual Meeting, New Orleans, LA. (oral) Diabetes 2016; 65(suppl 1): A47.

Madrigal JM., Monson R.S., Oberholzer J., Danielson K.K.. May 2016. *Stabilization of coronary artery calcium following islet cell transplant in patients with type 1 diabetes*. Chicago Diabetes Day, Chicago, IL. (poster)

Madrigal JM., Monson R.S., Oberholzer J., Danielson K.K.. April 2016. *Stabilization of coronary artery calcium following islet cell transplant in patients with type 1 diabetes*. University of Illinois at Chicago School of Public Health Research and Practice Awards Day, Chicago, IL. (poster)

Jurivich, D.A., Cruz Madrid, K., **Madrigal, J.**, & Muramatsu, N. 2015. *Partnering with Caregivers to Enhance Minority Older Adult Research Participation*. American Geriatrics Society 2015 Annual Meeting. National Harbor, MD. (poster)

Muramatsu, N. & **Madrigal, J**. 2015. Symposium: Caregivers' Quality of Life and Care Coordination for the Benefit of Older Adults, *Health Promotion in Home Care: Co-Learning in Practice, Research and Policy.* American Society on Aging, Aging in America Conference. Chicago, IL.

Madrigal, J. 2013. Active Living Workshop: *Creating an Academic Advantage through Enhanced PE and Physical Activity*. 2013 Change Institute: Building & Sustaining Healthier Communities. Rosemont, IL.

Yamaki, K., Rimmer, J., Davis-Lowry, B., **Madrigal, J.**, Buscaj, E., Spassiani, N., & Zisko, L., 2011. *Availability of obesity data on adolescents with disabilities in state health surveillance programs.* Oral session presented at the 139th annual meeting of the American Public Health Association. Washington, DC.

Madrigal, J. 2011. *Improving Health Behaviors of Individuals with ID/DD and Their Support Providers: NCPAD's 14-Week Program to a Healthier You.* Oral session presented at the Annual Convention of The Arc of Illinois & The Autism Program. Lisle, IL.

Madrigal, J., Eisenberg, Y. 2010. *Empowering Community Change: Strategies to create healthy communities for people with disabilities through interactive online mapping*. 138th annual meeting of the American Public Health Association. Denver, CO. (poster)

Madrigal, J. 2010. *Empowering Community Change: Strategies to Facilitate Participation of All Athletes.* Oral Session presented at the 2010 Developing Amazing Leaders Conference, Colorado Springs, CO.

Madrigal, J. & Lullo, C. 2009. *Creating a Welcoming and Accessible Environment for a Diverse Population*. Oral Session presented at the Club Industry Fitness Conference. Chicago, IL.