Journal of Hazardous Materials 424 (2022) 127381

Contents lists available at ScienceDirect

Journal of Hazardous Materials

journal homepage: www.elsevier.com/locate/jhazmat

Health risk assessment of exposure to organochlorine pesticides in the general population in Seoul, Korea over 12 years: A cross-sectional epidemiological study

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ARTICLE INFO

Editor: Dr. S Nan

Keywords:
Organochlorine pesticide
Temporal trend
Cholesterol
Uric acid
Korea

ABSTRACT

This study evaluated the 12-year trends in serum levels of 28 organochlorine pesticides (OCPs) in 880 adults living in Seoul, Korea. The OCP levels decreased from 2006 to 2017, and p,p′-dichlorodiphenyldichloroethylene was a predominant compound. OCP levels were higher in females than in males, and showed positive associations with BMI and age. The OCP concentrations had inverted U-shaped associations with low-density lipoprotein cholesterol and total cholesterol. Concentrations of *β*-hexachlorocyclohexane were significantly higher in patients with hypertension than in participants that were normotensive. OCP levels showed positive associations with uric acid, creatinine, and thyroid-stimulating hormone, but negative associations with free thyroxine. Participants with diabetes had significantly higher OCP levels than those without it. Principal component analysis suggested possible differences in disease manifestation depending on the composition of OCPs. These results suggest that OCPs might disturb renal transport and thyroid homeostasis. To our knowledge, the inverted U-shaped associations of heptachlor epoxide and endosulfan with cholesterol, the epidemiological associations of *trans*-nonachlor and endosulfan with thyroid hormones, and the association of *p,p*′-DDE with hyperuricemia have not been previously reported in general population. This is the first long-term study to show trends of 28 OCPs in serum and associations with various health indicators in Korea.

1. Introduction

Organochlorine pesticides (OCPs) are synthetic chemicals that have been widely used to control insects that are agricultural pests or disease vectors. As a result, OCPs have reached diverse environments and have bioaccumulated throughout the food chain (Kim, 2020; Maisano et al., 2016). The World Health Organization (WHO) estimated that every year about 800,000 people contract diseases as a result of pesticide exposure (World Health Organization (WHO), 2018). Due to their bioaccumulative, persistent, and toxic properties, many OCPs are registered with the Stockholm Convention on Persistent Organic Pollutants (POPs), and their use has been prohibited since the 1970 s in developed countries (Gómez-Ramírez et al., 2019; Kutz et al., 1991). However, OCPs are legally used for malaria control, and some underdeveloped or developing countries continue to use OCPs due to their low cost and high efficiency as pesticides (Angulo Lucena et al., 2007; Khuman et al., 2020). OCPs can be transported long distances by atmospheric circulation and ocean currents (Li et al., 2007; Zhou et al., 2014).

Humans are mainly exposed to OCPs by ingestion of contaminated food (Dirtu and Covaci, 2010; Moon et al., 2009). Human exposure to low-dose OCPs has been emerging as a new risk factor for the increasing prevalence of metabolic syndrome, which is a cluster of several chronic medical conditions such as dyslipidemia, insulin resistance, obesity, and hypertension (Lee et al., 2014; Park et al., 2010). In an experimental animal study, severe dysregulation of lipid homeostasis has been identified in rats that had been fed salmon oil contaminated with OCPs (Ruzzin et al., 2010). Hexachlorobenzene (HCB), *β*-hexachlorocyclohexane (HCH), and DDE have been associated with hypertension risk (Arrebola et al., 2015; Lind et al., 2014). Uric acid, a metabolite of purine nucleotides, is used as a risk factor for metabolic syndrome (Shankar et al., 2006; Hayden and Tyagi, 2004); uric acid accumulation can cause gout (Heinig and Johnson, 2006). Creatinine is

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https://doi.org/10.1016/j.jhazmat.2021.127381
Received 21 July 2021; Received in revised form 25 September 2021; Accepted 27 September 2021
Available online 30 September 2021

a metabolite produced in the process of protein metabolism, mainly measured to evaluate the glomerular filtration rate (Perrone et al., 1992). Serum concentrations of γ-HCH and o,p'-DDE has been associated with increase in hyperuricemia risk (Arrebola et al., 2019). Toxicological studies using animal models have demonstrated the mechanism by which OCP induces changes in the thyroid system by reducing free thyroxine (fT4) levels (Cheek et al., 1999; Gerlienke Schuur et al., 1998; van Raaij et al., 1993). In in-vivo cell-tracking experiments, OCPs were associated with decreased insulin secretion and diabetes (Lee et al., 2017).

Recently, the prevalence of metabolic dysfunction such as obesity, hypertension, dyslipidemia, insulin resistance, and type 2 diabetes in developed countries has been increasing (Park et al., 2010), and it is a serious public health problem affected by environmental factors. However, most previous studies on the associations between OCP exposure and health effects have used animal models or toxicological assessments (Cheek et al., 1999; Gerlienke Schuur et al., 1998; Lee et al., 2017; Ruzzin et al., 2010; van Raaij et al., 1993), or have mainly reported exposure assessments for specific occupational or patient groups (Ellsworth et al., 2018; Holt et al., 2017; Louis et al., 2006; Siddharth et al., 2012; Soliman et al., 1997). Moreover, epidemiological studies of the general population have shown inconsist associations between human exposure to OCPs and the occurrence of metabolic dysfunctions (Hayden et al., 2004; Lee et al., 2011a; Serdar et al., 2014; Takser et al., 2005). Research on changes in cholesterol level and low-dose OCP exposure is limited (Lee et al., 2011b), and levels of thyroid hormones and OCP exposure have shown inconsistent associations (Chevrier et al., 2008; Bloom et al., 2003; Kim et al., 2013). In addition, few studies have confirmed a significant association between OCP exposure and serum concentrations of uric acid or creatinine in the general population. Thus, the potential impacts of long-term exposure to OCPs in the general population remain controversial.

In Korea, OCPs were continuously monitored from 1999 to 2017 in nationwide air, soil, water, and sediment samples collected from Korean POP monitoring networks, and dichlorodiphenyltrichloroethane (DDT), HCB, and pentachlorobenzene (PeCB) were mainly detected in air and soil (Kim and Yoon, 2014; Natlonal institute of environmental research NIER, 2017). Endosulfan was detected nationwide in air, soil, water, and sediment in 2015, and was mainly detected at high concentrations in air (Kim et al., 2020). In addition, OCPs were detected in 26 types of seafood, and DDT (< 0.04–37 ng/g) and HCB (< 0.004–1.0 ng/g) were detected at high concentrations (Moon et al., 2009), which were higher than those in the United States (DDT: < 5 ng/g) (Nowell et al., 2009) and France (DDT: 0.15–2.20 ng/g, HCB: 0.10–0.80 ng/g) (Thomas et al., 2012). Moreover, DDT has recently been detected in eggs, and this has become a serious concern in Korea (https://en.yna.co.kr/). Although the production and use of OCPs have been prohibited, they are still detected in environmental matrices and food (Natlonal institute of environmental research NIER, 2017). Therefore, individuals can be exposed to OCPs by various routes, including dietary intake, dermal absorption, and inhalation (Lee et al., 2007). Despite the possibility of human exposure to OCPs, few studies have confirmed long-term human exposure to OCPs in Korea. Therefore, associations between the changes in OCP levels in the environment over time and the temporal trends of human exposure to OCPs in Korea could not be evaluated. In addition, studies on long-term human exposure to OCPs and their health effect assessment have been limited.

According to Korean National Health Insurance Service data, the prevalence of metabolic syndrome increased by 1.68% from 2009 to 2013 (Lee et al., 2018). Previous studies conducted using Seoul citizens investigated the associations between the exposure to POPs including polychlorinated dibenzodioxins and dibenzofurans (Seo et al., 2020) in the human body and clinical factors, but did not correlate health effects with human exposure to these compounds. Therefore, to understand the causes of health effects that were not explained in previous studies, the exposure to OCPs should be assessed as a potential risk factor in Seoul citizens, and associations with clinical factors should be identified.

In this study, we measured concentrations of 28 OCPs in human serum collected from 880 Seoul citizens between 2006 and 2017 to assess human exposure to OCPs, trends over time, and possible health effects associated with OCP exposure. In addition, the present study aims to expand current knowledge of potential metabolic disrupting effects of OCPs by investigating the associations between human exposure to OCP and hypertension, lipid homeostasis, hyperuricemia, thyroid homeostasis, and type-2 diabetes. To the best of our knowledge, it is the first long-term study to confirm trends of 28 OCPs in serum and associations with various clinical indicators in Korea, and it is the only study with statistical power to assess the association between OCP exposure and homeostasis of uric acid and creatinine in the general population.

2. Materials and methods

2.1. Sample collection

Serum samples were collected as stratified random samples in March or April from residents who participated in the Health Assessment Study of Seoul Citizens (Seoul Resource Recovery Facility (SRRF), 2017) conducted annually in Seoul since 2000. To ensure representativeness of the sample, the study was conducted on participants who had lived in the Gangnam, Nowon, or Yangcheon district in Seoul for ≥ 5 y, and had participated in this project every year. Participants were recruited by sex and age group, and questionnaire surveys and health examinations for the study were conducted. However, due to the mobile nature of city dwellers, the participants in the project varied among year. In addition, the ratios of subjects by sex and age were not constant every year because all serum samples were collected from volunteers. To minimize the variability of these samples, the participants who had lived in the region for < 5 y were excluded, and the participants who participated in the project every year were recruited as a priority.

For each participant, blood collection, questionnaire survey, and health examinations were performed on the same date, a questionnaire was completed before blood collection, then a health examination was performed. For an accurate health examination, participants maintained an empty stomach and did not take any medications for 12 h prior to the examination. From 2006 to 2017, a total of 880 participants (215 males, 665 females) underwent health examinations to confirm the associations between exposure to OCPs and health effects. Their ages ranged from the 20–80 s (20 s: 32, 30 s: 77, 40 s: 189, 50 s: 350, and ≥ 60 s: 232; Table S1 in the Supplementary Information). Serum samples were collected and stored according to the 'Korean Standard Operational Procedure for POPs' (MOE, 2008). After the blood had been collected, the serum was immediately separated by centrifugation. The samples were stored in polypropylene tubes at temperatures <–20 °C in a light-blocked freezer.

Each participant completed a questionnaire with information about age, sex, and daily lifestyle, then underwent a health examination. The health examinations measured blood pressure, height, weight, body mass index (BMI), serum levels of cholesterol (low-density lipoprotein (LDL), high-density lipoprotein (HDL), total cholesterol (TC), and triglyceride), blood pressure, uric acid, creatinine, hypothyroidism, thyroid hormones (fT4, thyroid-stimulating hormone (TSH)), and blood glucose as a test for diabetes (Table S2). In Korea, the degree of obesity of patients in health examinations follows the Asia-Pacific BMI classification (Lim et al., 2017), so obesity was diagnosed based on this standard in present study as well. The participants were categorized into age groups (20 s, 30 s, 40 s, 50 s, and ≥ 60 s) and BMI groups (underweight (BMI [kg/m^2] < 18.5), normal-weight (18.5 ≤ BMI < 22.9), overweight (23 ≤ BMI < 24.9), obese (25 ≤ BMI < 29.9), and highly obese (30 ≤ BMI)). Hypertension was diagnosed if the blood pressure at rest was consistently > 140/90 mmHg. Renal impairment or renal failure was diagnosed if creatinine values exceeded 1.4 mg/dL for males and 1.0 mg/dL for females. Hyperuricemia was diagnosed if serum uric acid level was ≥ 6 mg/dL in females or ≥ 7 mg/dL in males, or if the subjects had been diagnosed with gout, or if subjects had been prescribed pharmacological treatment to lower uric acid levels. Diabetes was diagnosed according to blood glucose level: < 100 mg/dL, normal; 100–126 mg/dL, impaired glucose tolerance; ≥ 126 mg/dL, diabetes. To minimize the variability of clinical factors, only clinical factors that had been measured using consistent standards over time were used in the present study. Health checkups were performed at the Occupational Health Center of Yonsei University College of Medicine, which conducted the health impact assessment (Seoul Resource Recovery Facility (SRRF), 2017).

2.2. Chemicals and standards

An isotope dilution method was used to analyze OCPs in samples. Isotope labeled OCPs (ES-5465-A, Cambridge Isotope Labs, USA) were used as internal standards, and other non-isotope labeled 4,4′-dichlorobiphenyl and 2,3′,4′,5-tetrachlorobiphenyl (EC-5350, Cambridge Isotope Labs, USA) were used as recovery standards. Native standards (ES-5464-A, Cambridge Isotope Labs, USA) were also used (Table S3). Formic acid (99%; Merck, Germany) was used as the reagent. Hexane, methanol, deionized water, and dichloromethane (J.T Baker Co., USA) were used for extraction and clean up.

2.3. Instrumental analysis

Measurements of OCPs followed the procedure used in the U.S. National Health and Nutrition Examination Survey (NHANES) (Serdar et al., 2014) (Fig. S1). Serum (2 mL) was weighed and spiked with internal standards and mixed; then 2 mL of formic acid and 1 mL of deionized water were added. A solid-phase extraction vacuum manifold (Supelco Inc., USA) was used for extraction and clean up. A Sep-Pak C_{18} solid-phase extraction cartridge (500 mg, 6 cc; Waters Corporation, USA) was conditioned with 12 mL of methanol and 12 mL of deionized water, then each sample was loaded into the cartridge then eluted with 16 mL of hexane. The filtrate was loaded onto a combined Sep-Pak Plus silica (500 mg, 6 cc; Waters Corporation, USA) and florisil cartridge (Waters Corporation, USA) that had been conditioned with 12 mL of a dichloromethane/hexane (1:1, v/v) mixture and 12 mL of hexane. OCPs were eluted with 12 mL of a dichloromethane/hexane (1:1, v/v) mixture. The eluted extract was concentrated by drying under nitrogen gas, and the recovery standard mixture was added.

Gas chromatography-high resolution mass spectrometry (GC-HRMS) measurements were conducted using a JMS-800D instrument (JEOL, Japan) equipped with a 6890 N gas chromatograph (Agilent Technologies, USA). A 60 m × 0.25 mm × 0.25 μm DB-5MS capillary column (Agilent Technologies, USA) was used. Ionization was performed in the electron impact mode, the source temperature was 280 °C, and ionization energy was 38 eV. The data were collected in single-ion monitoring (SIM) mode with a resolution $> 10{,}000$.

2.4. Quality assurance/quality control

Internal and recovery standards were spiked into the samples before extraction and GC-HRMS analysis, respectively. The average internal standard recoveries were 78–97% (Table S4). A procedural blank sample (i.e., distilled water) was extracted in each batch. Solvent blanks (i.e., hexane) were analyzed to check contamination from the laboratory procedures. OCPs were below the limit of detection (LOD), which was defined as three times the signal-to-noise ratio, in both the hexane and water blank samples, for each compound (Table S4). The calibration curve for the individual target compounds had a coefficient of determination $r^2 > 0.99$. To check the precision, seven homogenized samples spiked with the native standard mixture (5 ng/mL) were analyzed. The samples were pretreated and analyzed; the relative standard deviation was 6.36%.

2.5. Statistical analysis

As following the Environmental Protection Agency (EPA) method, OCP levels below the LOD were reported as zero and treated as non-detectable (ND) (Mocking et al., 2012; United States Environmental Protection Agency (US EPA), 1991). Values below LOD could also be calculated as 0.5·LOD, but this procedure can overestimate concentrations of OCP when they are very low (Barghi et al., 2016). The detection rates of compounds ranged from 99.5% of participants for *p,p′*-DDE to 22% for δ-HCH. One or more OCPs were detected in all participants. OCPs with nonpolar and lipophilic properties are related to the lipids in tissues, and thus OCP concentrations are generally expressed per weight of total lipids rather than per volume or per whole weight (Bernert et al., 2007). Total lipids (Son et al., 2010) were calculated as

$$\text{Total lipids}(\text{mg/dL}) = 2.27 \times \text{total cholesterol} + \text{triglycerides} + 62.3.$$

A simulation study reported that the OCP concentrations adjusted by wet-weight concentrations of triglycerides and total cholesterol had less bias than those adjusted by lipid-standardized concentrations; therefore, triglycerides and total cholesterol were included in the model as covariates, and the adjusted wet weight concentration was used (Schisterman et al., 2005). However, the adjustment of serum lipid levels can induce over-adjustment because OCP may interfere with lipid metabolism (Lee et al., 2011). If OCP concentrations were not adjusted by triglycerides and total cholesterol, a strong association between lipids and OCPs was shown, but the adjusted data were applied as a conservative analysis in this study. In addition, analyses were conducted for the quartiles of individual OCP. More than 75% of the measurements that exceeded the detection limit were included, and participants with concentrations below the detection limit were placed in the lowest quartile data for each compound.

Nonparametric statistics were used in this study, because a Kolmogorov-Smirnov test of normality of data showed a skewed distribution. Factors that have potential to influence the outcome were selected as potential confounders (Lee et al., 2017, 2013). The OCPs, thyroid hormone, uric acid, and creatinine levels were adjusted for potential confounders such as age, sex, total lipids calculated by the equation, and BMI, and cholesterol levels were adjusted for age, sex, and BMI. These adjusted data were provided in SPSS linear model procedures to examine the temporal trends of OCPs and the associations with various clinical factors (hypertension, thyroid hormone, uric acid, creatinine, hyperuricemia, cholesterol, and diabetes). Multivariable regression was performed to analyze the associations between OCP levels and age, sex, cholesterol, BMI, thyroid hormone, uric acid, and creatinine levels; adjusted data were used for the models. As a result of normality verification using Kolmogorov-Smirnov test, the concentrations of all OCPs adjusted for sex, age, body mass index, and lipids showed normal distributions. OCP levels were classified by quartiles to represent the change in clinical indicators (cholesterol, uric acid, creatinine, and thyroid hormones) according to OCP levels.

Spearman's rank correlation coefficients were used to measure correlations between variables. This statistical test was used to identify the associations between OCP levels and participants' age, BMI, cholesterol, thyroid hormone, creatinine, or uric acid levels. The Kruskal-Wallis test was used to identify significant differences among more than two groups categorized by age, year, cholesterol, BMI, thyroid hormone, uric acid, and creatinine levels. The Mann-Whitney *U* test was conducted to compare the OCP levels between participants with and without hypertension, or hyperuricemia, or diabetes and to confirm the significant differences among the groups of variables (age, sex, BMI, and year). Principal components analysis (PCA) was performed to confirm the major factors involved in patterns of dominant compounds and clinical indicators. PCA analyzes a multivariable structure that has a large number of correlated variables to combine them into a reduced number of independent factors. The results of the PCA were used to explain the variance and the most important information about original data.

Among the principal components that had eigenvalues > 1, those with the three highest eigenvalues were selected for data interpretation; they explained 66% of the total data variance. Prior to PCA, the clinical indicators and OCP levels were normalized by dividing individual concentrations by the sum of the value of that variable to compare only distributions and profiles, excluding the concept of concentrations or numerical values (Seo et al., 2020, 2018). Statistical analysis was conducted using IBM SPSS Statistics version 20 (IBM Corp., Armonk, NY, USA). The significance level was set at 0.05.

3. Results and discussion

3.1. Levels and profile distributions of OCPs

The total composition of OCPs consisted of 69% *p,p′*-DDE, 7% HCB, 5% *β*-HCH, and 4% *p,p′*-DDT; each of the other compounds accounted for < 2% (Table 1; Fig. S2). The predominance of *p,p′*-DDE (arithmetic mean: 533 ng/g lipid, range: ND to 5942 ng/g lipid) is a result of degradation of DDT to *p,p′*-DDE, which is more persistent than the parent compound (estimated half-life in the human body > 7 y) (Axmon and Rignell-Hydbom, 2006). In nationwide monitoring of POPs conducted annually by the Korean Ministry of Environment, DDT has been continuously detected in air, soil, and sediment (Natlonal institute of environmental research NIER, 2017), and high DDT concentrations were recently detected in Korean foods (https://en.yna.co.kr/). Even though production and use of DDT were phased out several decades ago, it has been detected in various environmental matrices due to long-range atmospheric transport of OCPs (Li et al., 2007) and their bioaccumulation in the aquatic ecosystem by the food web (Kim, 2020). Furthermore, DDT is an intermediate and manufacturing impurity in the production of dicofol (Roberts et al., 2007). In addition, OCPs are legally used for malaria control, and some developing countries continue to use DDT due to its low cost and high efficiency (Kang and Chang, 2011). Therefore, OCPs used in neighboring countries could influence the human exposure by imported livestock feed and intake of imported food products (Angulo Lucena et al., 2007). These results suggest that Korean citizens might have been exposed to DDT and DDE until recently.

LOD: limit of detection.

HCB levels averaged 56 ng/g lipid (range: ND to 2235 ng/g lipid). HCB was used as a fungicide and is also formed as a by-product or impurity during production of chemicals and pesticides (Jung et al., 1997). It is also released during incineration and combustion, and atmospheric levels were 2–10 times higher than those of other OCPs in Korea (MOE, 2011). HCB was banned in the US in 1984 (Kang and Chang, 2011) and designated as a prohibited substance in Korea in the early 2000 s (Ministry of Environment MOE, 2019). HCB is a persistent compound with an environmental half-life exceeding 9 years (Barber et al., 2005).

β-HCH levels averaged 40 ng/g lipid (range: ND to 322 ng/g lipid). HCH was used as a broad-spectrum insecticide and was registered with the Stockholm Convention in 2009 (Kang and Chang, 2011). In Korea, HCH was designated as a prohibited substance for use and production in 2011 (Ministry of Environment MOE, 2019). However, HCH may be formed as by-products in the manufacturing process of other chlorinated compounds (Jung et al., 1997). *β*-HCH has a half-life > 7 y in the human body, whereas the half-life of its isomer *γ*-HCH is only 20 h (Kang and Chang, 2011). The significant serum concentrations of HCB and *β*-HCH demonstrate the continuous exposure of Koreans to these OCPs and the persistence of these chemicals in the human body.

OCP concentrations were significantly and positively correlated with each other, including HCH, HCB, heptachlor, heptachlor epoxide, dieldrin, endosulfan, oxychlordane, chlordane, nonachlor, DDE, dichlorodiphenyldichloroethane (DDD), and DDT (Table S5). In Korea, various OCPs were used to improve crop yields from 1946 to the 1990 s, and the usage of OCPs including endrin, aldrin, heptachlor, dieldrin, HCHs, and DDT in Korea was estimated to be over 3560 tons (Kim et al., 2005). People might be exposed to OCPs through the intake of foods imported from other countries where these pesticides are still in use (Zhang et al., 2014; Zhou et al., 2012). In addition, some OCPs including DDT, *β*-HCH, and HCB are generated as impurities or by-products in the manufacturing process of chlorinated compounds (Jung et al., 1997; Roberts et al., 2007). The associations between these OCPs point to common sources, e.g. food.

OCP exposures can vary considerably among countries due to differences in the timing of regulations, current and historical use of OCPs, and dietary intake. We compared our results to previous studies of other countries (Table S6). In Korea (this study), arithmetic mean levels of major OCPs were several times higher than the levels in the U.S. (Woodruff et al., 2011), France (Saoudi et al., 2014), and Italy (Amodio et al., 2012), and similar to levels in Japan (Itoh et al., 2009). In contrast, the mean concentrations in China (Xu et al., 2009) and Mexico (Waliszewski et al., 2012) were several times higher than our results. In general, the serum OCPs are related to the agreements for restrictions on use and the regulation of production. Although their use has been prohibited since the 1970 s and 1980 s in developed countries (Kutz et al., 1991), some OCPs are still used in underdeveloped or developing countries in Africa, Latin America, and Asia (Angulo Lucena et al., 2007). Therefore, people in developed countries might have been exposed to relatively lower amounts of OCPs than those in underdeveloped or developing countries.

3.2. Temporal trends in OCP exposure

Individual OCP levels were monitored over time (Fig. 1, Table S7). To evaluate trends, we considered four groups of compounds: (1) "parent" OCPs (HCB, heptachlor, aldrin, endrin, dieldrin, *cis*-chlordane, *trans*-chlordane, *p,p′*-DDT, *o,p′*-DDT, and Mirex); (2) "metabolites" of parent OCPs (*p,p′*-DDE, *cis*-heptachlor epoxide, *trans*-heptachlor epoxide, oxychlordane, *cis*-nonachlor, *trans*-nonachlor, *o,p′*-DDD, *p,p′*-DDD, and *o,p′*-DDE); (3) "newly regulated" OCPs, most which have recently been listed as POPs under the Stockholm Convention in 2009 and 2011 (The Stockholm Convention (SC), 2019) (pentachlorobenzene, *α*-HCH, *β*-HCH, *γ*-HCH, endosulfan I, endosulfan II, endosulfan III, and kepone); and (4) "unregulated" OCPs (*δ*-HCH).

Temporal trends varied among compound groups and compounds (Fig. 1). The annual trends of the mean concentrations of OCP compounds are shown in Fig. S3. Serum concentrations gradually decreased from 2006 to 2017 for many of the parent compounds, including HCB, heptachlor, aldrin, dieldrin, and *p,p′*-DDT, and differences from 2006 to 2017 were statistically significant (Kruskal–Wallis test, $p < 0.05$). In contrast, levels of endrin, *trans*-chlordane, *cis*-chlordane, *o,p′*-DDT, and Mirex, did not change significantly over time. For the metabolites, trends were similar to the parent compounds, and most metabolite levels decreased significantly during the study period ($p < 0.05$). However, *trans*-heptachlor epoxide, *o,p′*-DDE, and *o,p′*-DDD did not change significantly. For the newly regulated OCPs, levels of some compounds, including PeCB, *β*-HCH and kepone, showed gradual decreases after 2010 and statistically significant declines; this date coincides with listings in the Stockholm Convention in 2009 (The Stockholm Convention (SC), 2019), however, *α*-HCH, *γ*-HCH, endosulfan I, endosulfan II, and endosulfan III did not show significant changes. The unregulated OCP, *δ*-HCH, was found at low concentrations, and the levels did not change significantly. Overall, serum concentrations of OCPs in the study population either remained similar or decreased over the 12-y study period. These decreasing trends indicate an increase in the amount of OCPs being decomposed, metabolized, and excreted, rather than a decrease in the amount of OCPs accumulated and stored in human body. The decrease rates of each OCP over 12 years are the results of the persistence, metabolic degradation, and continuous exposure to each compound. HCB (30%), *β*-HCH (30%), *p,p′*-DDE (20%), and *trans*-nonachlor (23%) were detected at high concentrations and showed significant decrease rates, whereas OCPs that undergo rapid clearance or were a low levels generally did not show significant decreases in concentration

Table 1
Mean and median (in parentheses) OCP levels (ng/g lipid) in human serum collected from Korean citizens by age (20 s, 30 s, 40 s, 50 s, and ≥ 60 s), sex, body mass index (BMI). BMI (kg/m^2) was classified into five groups; underweight (BMI < 18.5), normal (18.5 ≤ BMI < 23), overweight (23 ≤ BMI < 25), obesity (25 ≤ BMI < 30), and high obesity (30 ≤ BMI).

Mean (median) Range	All samples	Age (years)					Sex		BMI (kg/m2)				
		20 s	30 s	40 s	50 s	≥ 60 s	Male	Female	Under weight	Normal	Overweight	Obesity	High obesity
N (%)	880 (100%)	32 (4%)	77 (9%)	189 (21%)	350 (40%)	232 (26%)	215 (24%)	665 (76%)	65 (7%)	317 (36%)	201 (23%)	206 (23%)	91 (10%)
PeCB	5.47 (4.23)	1.12 (0.00)	2.16 (0.00)	2.70 (0.00)	5.08 (0.00)	10.0 (0.00)	3.62 (0.00)	6.44 (0.00)	1.55 (0.00)	4.58 (0.00)	7.62 (0.00)	6.57 (0.00)	10.8 (0.00)
	<LOD-415	<LOD-35.9	<LOD-46.1	<LOD-148	<LOD-365	<LOD-415	<LOD-317	<LOD-415	<LOD-21.7	<LOD-415	<LOD-317	<LOD-365	<LOD-146
α-HCH	1.24 (0.51)	2.26 (1.14)	0.97 (0.00)	1.04 (0.00)	1.24 (0.41)	1.34 (0.99)	1.18 (0.37)	1.29 (0.70)	1.56 (1.66)	1.44 (0.74)	1.04 (0.38)	1.31 (0.69)	1.30 (0.30)
	<LOD-16.2	<LOD-16.2	<LOD-7.85	<LOD-9.11	<LOD-14.1	<LOD-12.9	<LOD-16.2	<LOD-16.1	<LOD-5.12	<LOD-16.2	<LOD-7.72	<LOD-12.9	<LOD-7.85
β-HCH	40.4 (30.7)	21.5 (17.8)	20.2 (0.00)	32.7(24.2)	39.9 (33.0)	56.8 (44.4)	33.2 (24.6)	42.5 (33.1)	32.0 (24.1)	37.3 (29.6)	39.9 (32.4)	47.1 (37.7)	71.1 (71.9)
	<LOD-322	5.48–131	4.69–69.7	<LOD-185	<LOD-154	<LOD-322	0.06–132	<LOD-322	7.71–115	<LOD-161	<LOD-226	<LOD-322	5.48–185
γ-HCH	1.82 (1.11)	1.56 (0.90)	1.34 (0.00)	2.05 (0.77)	1.88 (1.22)	1.72 (1.22)	1.28 (0.50)	1.84 (1.21)	1.51 (1.41)	2.10 (1.43)	1.96 (1.30)	1.86 (1.13)	1.94 (1.97)
	<LOD-73.7	<LOD-10.2	<LOD-6.24	<LOD-73.7	<LOD-26.4	<LOD-14.8	<LOD-10.2	<LOD-73.7	<LOD-5.66	<LOD-73.7	<LOD-20.7	<LOD-14.8	<LOD-8.23
δ-HCH	0.17 (0.00)	0.09 (0.00)	0.09 (0.00)	0.16 (0.00)	0.18 (0.00)	0.22 (0.00)	0.15 (0.00)	0.19 (0.00)	0.26 (0.00)	0.19 (0.00)	0.29 (0.00)	0.11 (0.00)	0.11 (0.00)
	<LOD-4.63	<LOD-1.40	<LOD-1.91	<LOD-4.57	<LOD-4.03	<LOD-4.63	<LOD-4.63	<LOD-4.55	<LOD-1.91	<LOD-4.03	<LOD-4.63	<LOD-3.48	<LOD-1.12
HCB	55.7 (43.3)	61.7 (0.00)	95.9 (0.00)	75.3 (0.00)	67.4 (0.00)	7.99 (0.00)	15.9 (0.00)	29.7 (13.1)	12.6 (0.00)	68.5 (0.00)	89.4 (0.00)	42.2 (0.00)	9.58 (0.00)
	<LOD-2235	<LOD-425	<LOD-997	<LOD-902	<LOD-2235	<LOD-367	<LOD-386	<LOD-2237	<LOD-176	<LOD-997	<LOD-2235	<LOD-1108	<LOD-194
Heptachlor	2.73 (0.00)	6.75 (0.00)	2.21 (0.00)	1.87 (0.00)	2.93 (0.00)	2.75 (0.00)	3.04 (0.00)	2.80 (0.00)	6,19 (1.34)	2.85 (0.00)	3.17 (0.00)	2.78 (0.00)	3.53 (0.00)
	<LOD-66.9	<LOD-40.5	<LOD-34	<LOD-38.7	<LOD-67.0	<LOD-66.0	<LOD-67.0	<LOD-39.3	<LOD-34.0	<LOD-39.8	<LOD-67.0	<LOD-40.5	<LOD-32.3
c-Heptachlor Epoxide	9.16 (5.98)	3.38 (2.36)	4.99 (0.00)	7.64 (4.66)	9.20 (6.44)	12.5 (9.33)	7.33 (5.42)	8.21 (5.80)	5.42 (3.58)	7.07 (5.35)	9.17 (7.11)	12.5 (9.25)	19.3 (12.)
	<LOD-134	<LOD-14.6	<LOD-22.1	<LOD-70.1	<LOD-66.2	<LOD-134	<LOD-26.2	<LOD-88.2	1.90–25.0	<LOD-64.7	<LOD-66.2	<LOD-88.2	<LOD-134
t-Heptachlor Epoxide	4.26 (1.54)	7.87 (3.19)	3.70 (0.00)	3.90 (0.93)	3.79 (1.35)	4.97 (2.77)	3.86 (0.00)	4.66 (2.14)	8.06 (5.80)	4.49 (1.91)	5.02 (2.57)	4.79 (0.91)	3.38 (2.30)
	<LOD-95.5	<LOD-57.8	<LOD-41.2	<LOD-51.8	<LOD-52.0	<LOD-95.5	<LOD-95.5	<LOD-57.8	<LOD-39.1	<LOD-57.8	<LOD-51.8	<LOD-95.5	<LOD-18.1
Aldrin	3.09 (0.00)	2.66 (0.00)	2.23 (0.00)	3.10 (0.00)	2.75 (0.00)	3.95 (0.00)	2.40 (0.00)	3.43 (0.00)	4.16 (0.64)	2.88 (0.00)	4.11 (0.00)	3.68 (0.00)	2.93 (0.00)
	<LOD-102	<LOD-34.7	<LOD-50.2	<LOD-83.6	<LOD-102	<LOD-56.0	<LOD-49.7	<LOD-102	<LOD-11.9	<LOD-50.2	<LOD-102	<LOD-56.0	<LOD-28.3
Dieldrin	3.89 (3.06)	3.00 (2.40)	2.88 (0.00)	3.43 (2.36)	3.99 (3.26)	4.55 (3.93)	3.69 (3.20)	3.43 (2.80)	2.83 (2.70)	3.48 (2.76)	4.58 (4.09)	4.76 (3.94)	5.04 (4.26)
	<LOD-26.1	<LOD-9.75	<LOD-12.4	<LOD-18.7	<LOD-23.0	<LOD-56.0	<LOD-20.6	<LOD-19.7	<LOD-8.86	<LOD-23.0)	<LOD-19.7	<LOD-26.1	<LOD-16.3
Endrin	1.77 (0.00)	1.64 (0.00)	1.72 (0.00)	1.63 (0.00)	1.92 (0.00)	1.70 (0.00)	1.60 (0.00)	1.92 (0.00)	2.90 (0.00)	1.96 (0.23)	2.18 (0.00)	1.73 (0.00)	1.16 (0.00)
	<LOD-34.1	<LOD-13.1	<LOD-25.0	<LOD-20.9	<LOD-34.1	<LOD-26.1	<LOD-2605	<LOD-34.1	<LOD-25.0	<LOD-34.1	<LOD-31.8	<LOD-16.9	<LOD-9.10
EndosulfanI	3.17 (1.90)	3.01 (1.70)	2.81 (0.00)	3.06 (1.76)	3.53 (2.03)	2.84 (2.03)	2.38 (1.50)	2.99 (1.84)	3.37 (1.95)	3.36 (2.13)	3.68 (2.18)	3.19 (2.23)	3.38 (2.12)
	<LOD-51.2	<LOD-17.7	<LOD-15.2	<LOD-17.7	<LOD-51.2	<LOD-15.2	<LOD-16.3	<LOD-51.2	<LOD-9.70	<LOD-44.2	<LOD-51.2	<LOD-17.4	<LOD-14.1
EndosulfanII	6.87 (3.02)	8.36 (3.97)	4.15 (0.00)	6.74 (2.63)	6.95 (2.84)	7.53 (5.01)	5.59 (2.05)	6.71 (3.12)	2.85 (1.09)	6.97 (3.36)	8.65 (5.25)	7.06 (2.44)	8.43 (4.41)
	<LOD-97.1	<LOD-39.5	<LOD-46.8	<LOD-97.1	<LOD-85.2	<LOD-76.8	<LOD-63.1	<LOD-76.8	<LOD-12.6	<LOD-85.2	<LOD-76.8	<LOD-53.1	<LOD-97.1
EndosulfanIII	3.05 (0.00)	2.90 (0.19)	1.46 (0.00)	2.01 (0.00)	3.09 (0.00)	4.40 (0.00)	2.78 (0.00)	3.37 (0.00)	1.07 (0.00)	3.00 (0.00)	3.92 (0.00)	3.37 (0.00)	3.14 (0.00)
	<LOD-242	<LOD-20.3	<LOD-22.1	<LOD-47.1	<LOD-242	<LOD-189	<LOD-40.7	<LOD-242	<LOD-4.77	<LOD-47.1	<LOD-242	<LOD-189	<LOD-20.7
Oxychlordane	11.5 (8.19)	6.70 (3.12)	6.53 (0.00)	8.00 (5.13)	11.4 (8.44)	16.7 (13.6)	11.2 (7.55)	11.0 (8.07)	11.9 (7.26)	11.2 (9.21)	12.6 (8.85)	13.3 (9.97)	14.6 (11.5)
	<LOD-142	<LOD-39.5	<LOD-52.3	<LOD-48.1	<LOD-142	<LOD-75.0	<LOD-75.0	<LOD-142	2.50–52.3	<LOD-51.5	<LOD-142	<LOD-75.0	<LOD-50.5
t-Chlordane	1.23 (0.31)	1.14 (0.00)	0.60 (0.00)	0.73 (0.23)	1.73 (0.37)	1.10 (0.49)	0.90 (0.21)	1.37 (0.32)	1.36 (0.60)	1.14 (0.36)	2.15 (0.49)	0.98 (0.35)	1.09 (0.35)
	<LOD-216	<LOD-8.02	<LOD-11.3	<LOD-7.64	<LOD-216	<LOD-11.4	<LOD-11.4	<LOD-216	<LOD-6.37	<LOD-11.3	<LOD-216	<LOD-11.4	<LOD-5.57
c-Chlordane	1.82 (0.29)	1.73 (0.13)	0.65 (0.00)	0.82 (0.20)	3.04 (0.29)	1.20 (0.46)	1.14 (0.33)	2.12 (0.32)	1.97 (0.69)	1.18 (0.33)	4.44 (0.33)	1.20 (0.48)	1.11 (0.65)
	<LOD-629	<LOD-17.9	<LOD-7.76	<LOD-12.8	<LOD-629	<LOD-14.4	<LOD-14.4	<LOD-629	<LOD-7.67	<LOD-17.8	<LOD-629	<LOD-12.9	<LOD-6.30
t-Nonachlor	20.4 (13.7)	9.97 (4.75)	9.40 (0.00)	15.6 (8.99)	20.1 (13.6)	29.8 (24.6)	22.0 (12.9)	18.6 (12.7)	22.5 (22.4)	20.0 (14.1)	22.0 (17.2)	25.0 (16.7)	25.7 (20.0)
	<LOD-256	<LOD-52.7	<LOD-64.6	<LOD-256	<LOD-179	<LOD-149	<LOD-149	<LOD-256	<LOD-64.6	<LOD-179	<LOD-256	<LOD-173	<LOD-76.0
c-Nonachlor	4.12 (2.22)	1.79 (0.45)	2.24 (0.00)	3.21 (1.44)	4.43 (2.59)	5.34 (4.07)	4.36 (2.48)	3.91 (2.02)	2.25 (1.48)	3.93 (2.17)	5.02 (2.97)	4.75 (2.78)	5.85 (3.97)
	<LOD-111	<LOD-18.0	<LOD-24.8	<LOD-31.8	<LOD-111	<LOD-38.3	<LOD-38.3	<LOD-111	<LOD-6.50	<LOD-48.1	<LOD-111	<LOD-31.8	<LOD-20.4
Kepone	4.71 (0.00)	18.2 (0.00)	1.31 (0.00)	2.45 (0.00)	5.66 (0.00)	4.39 (0.00)	4.29 (0.00)	5.19 (0.00)	0.07 (0.00)	5.29 (0.00)	7.68 (0.00)	3.78 (0.00)	1.58 (0.00)
	<LOD-386	<LOD-275	<LOD-77.8	<LOD-222	<LOD-386	<LOD-341	<LOD-386	<LOD-341	<LOD-0.54	<LOD-274	<LOD-386	<LOD-341	<LOD-64.8
o,p′-DDE	4.22 (2.13)	2.99 (0.00)	1.29 (0.00)	2.25 (0.00)	7.98 (0.00)	1.31 (0.00)	1.37 (0.00)	5.39 (0.00)	1.52 (0.00)	2.46 (0.00)	9.20 (0.00)	1.66 (0.00)	15.8 (0.00)
	<LOD-1360	<LOD-31.6	<LOD-14.4	<LOD-71.1	<LOD-1360	<LOD-31.2	<LOD-31.6	<LOD-1360	<LOD-9.65	<LOD-205	<LOD-1359	<LOD-71.1	<LOD-576
p,p′-DDE	533 (373)	216 (197)	247 (0.00)	448 (278)	548 (403)	720 (610)	464 (348)	472 (358)	569 (334)	528 (356)	547 (401)	612 (424)	754–533
	<LOD-5943	50.5–741	42.3–1201	<LOD-5943	<LOD-4390	8.69–3129	8.69–3129	<LOD-5943	166–1382	<LOD-4390	<LOD-4175	16.2–5943	<LOD-4892
o,p′-DDD	1.33 (0.17)	0.85 (0.49)	0.68 (0.00)	0.53 (0.00)	2.10 (0.15)	1.09 (0.60)	0.84 (0.27)	1.52 (0.16)	0.34 (0.00)	0.86 (0.34)	3.17 (0.34)	0.97 (0.37)	0.78 (0.00)
	<LOD-460	<LOD-5.33	<LOD-11.4	<LOD-5.15	<LOD-460	<LOD-9.11	<LOD-11.4	<LOD-460	<LOD-1.71	<LOD-5.98	<LOD-460	<LOD-11.4	<LOD-5.63
p,p′-DDD	2.81 (1.99)	1.35 (1.07)	1.70 (0.00)	2.16 (1.57)	3.44 (2.08)	2.96 (2.80)	2.53 (2.00)	2.75 (1.89)	2.28 (1.73)	2.52 (2.01)	3.99 (2.10)	2.72 (2.42)	2.61 (2.32)
	<LOD-294	<LOD-5.57	<LOD-8.19	<LOD-22.8	<LOD-294	<LOD-17.7	<LOD-17.7	<LOD-294	<LOD-6.81	<LOD-22.8	<LOD-294	<LOD-11.8	<LOD-8.21
o,p′-DDT	13 (6.66)	9.29 (2.25)	7.25 (0.00)	14.3 (3.21)	14.1 (8.03)	13.0 (8.95)	10.9 (6.15)	12.1 (7.29)	12.3 (10.2)	13.4 (6.42)	18.2 (7.61)	10.9 (7.60)	12.3 (8.44)
	<LOD-678)	<LOD-41.8	<LOD-49.8	<LOD-678	<LOD-325	<LOD-89.5	<LOD-178	<LOD-325	<LOD-35.5	<LOD-296	<LOD-678	<LOD-80.3	<LOD-54.4
p,p′-DDT	32.6 (26.3)	12.8 (8.17)	16.9 (0.00)	31.7 (24.0)	35.2 (27.4)	38.6 (32.7)	29.7 (26.4)	29.8 (24.3)	31.4 (18.3)	30.9 (24.9)	37.4 (30.28)	37.9 (28.8)	37.59 (27.24)
	<LOD-263	<LOD-90.4	<LOD-67.1	<LOD-196	<LOD-263	<LOD-163	<LOD-104	<LOD-263	<LOD-97.4	<LOD-202	<LOD-262	<LOD-250	<LOD-140
Mirex	4.24 (0.00)	2.76 (0.00)	4.86 (0.00)	3.96 (0.00)	4.40 (0.00)	4.22 (0.00)	4.28 (0.00)	3.70 (0.00)	4.88 (0.00)	4.37 (0.00)	4.63 (0.00)	5.27 (0.00)	4.35 (0.00)
	<LOD-96.2	<LOD-30.2	<LOD-54.4	<LOD-76.8	<LOD-96.2	<LOD-65.2	<LOD-50.4	<LOD-96.2	<LOD-17.5	<LOD-60.4	<LOD-76.8	<LOD-96.2	<LOD-33.3

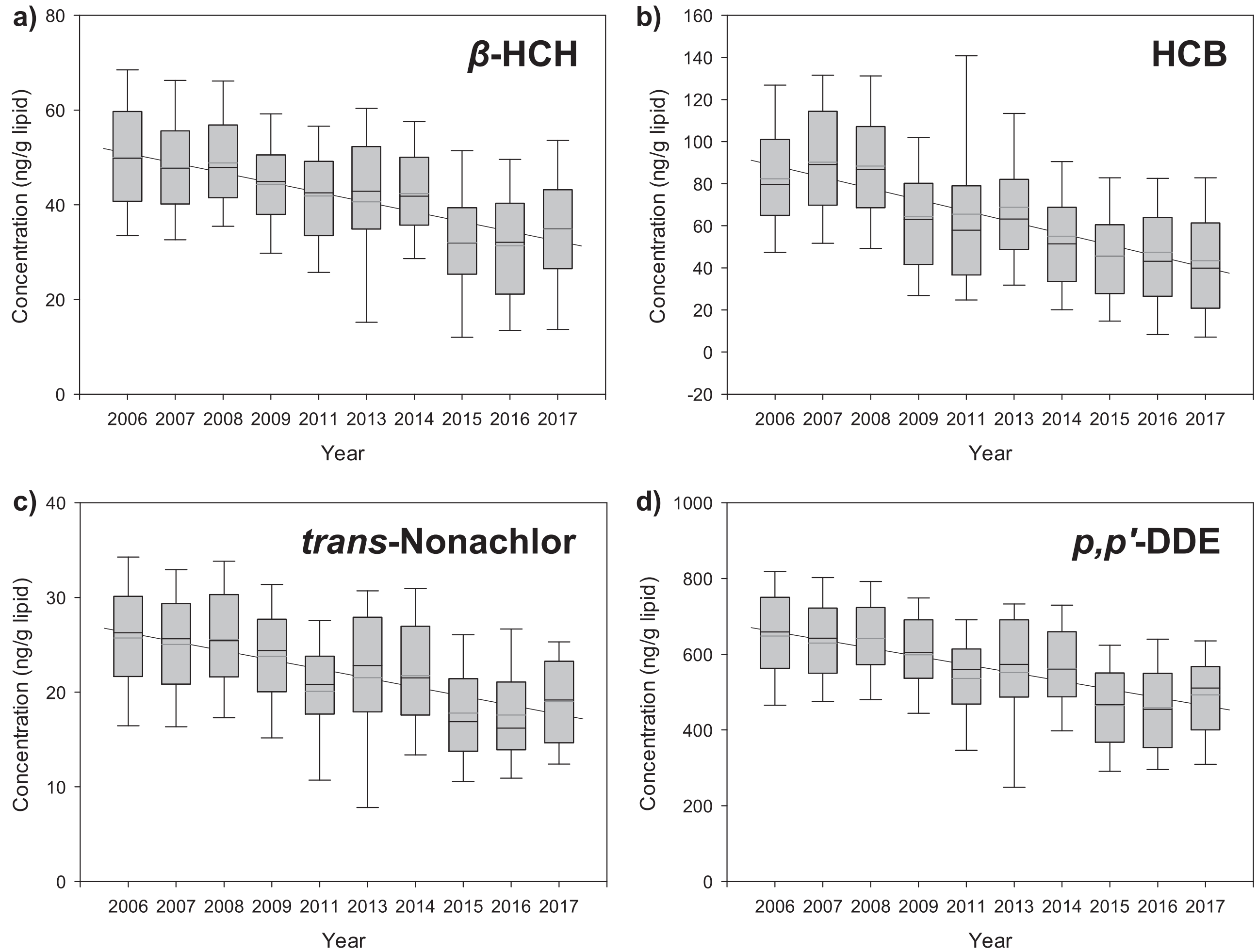

Fig. 1. Trends in the adjusted OCP concentrations in serum (ng/g lipid) collected from Korean citizens from 2006 to 2017. The trend line is fitted to the average. (a) *β*-HCH, (b) HCB, (c) *trans*-nonachlor, and (d) *p,p′*-DDE. Adjusted variables included sex, age, BMI, and lipids. Box plots show 25th, 50th, and 75th percentiles, and the gray line in the box represents the mean values. Error bars below and above boxes indicate the 10th and 90th percentiles, and the linear trend lines are shown.

over time.

The ratios of metabolites were usually higher than those of parent compounds. DDT comprised only 8% of the total level of DDT, DDE and DDD. Chlordane comprised only 8% of the total level of chlordane, oxychlordane and nonachlor, Heptachlor was only 17% of the total level of heptachlor plus heptachlor epoxide. However, HCB comprised 91% of the total level of HCB and its metabolite, PeCB. The ratios of parent compounds and their metabolites could be affected by the half-lives and continuous exposure to each compound; this is the reason that DDT with a long half-life (~ 7 y) (Axmon and Rignell-Hydbom, 2006) can remain in a human body long after exposure to DDT ceases. In contrast, oxychlordane (half-life: 21–88 d) (Blaylock, 2005) and nonachlor (half-life: 10–50 d) (Dearth and Hites, 1991), which are metabolites of chlordane, were detected at high concentrations despite having relatively short half-lives; this result suggests that exposure to chlordane is continuing. In addition, heptachlor epoxide (half-life: 4 y) (Agency for Toxic Substances and Disease Registry ATSDR, 2007), a metabolite of heptachlor (half-life: 3.5 d) (Agency for Toxic Substances and Disease Registry ATSDR, 2007), might persist after being produced, whereas HCB (half-life: 9 y) (Barber et al., 2005) might not be metabolized and may persist in a human body due to its long half-life.

The variables (e.g., dietary intake, occupation, characteristics of living space, life-style) that affect human exposure to OCPs differ among individuals, and these variables affect serum concentration of OCPs. Long-term trends in serum levels of OCP can be explained by several factors, one of which is changes in production and use, which are influenced by international and national regulation. The parent OCPs were produced and increasingly used as pesticides from the 1950 s through the 1990 s (Kutz et al., 1991), but then agreements restricting their use and production were established due to reported toxicity (Abdollahi et al., 2004). The newly regulated compounds were more-recently designated as regulated substances due to the recognition of their properties as POPs, i.e., PeCB, *α*-HCH, *β*-HCH, *γ*-HCH and kepone in 2011, and endosulfan I, endosulfan II, and endosulfan III in 2015 in Korea (Ministry of Environment MOE, 2019).

National emission-source management and emission-reduction strategies also affect the levels of OCPs in the environment and humans. Since 1999, the Korean Ministry of Environment has been conducting an annual national survey of residual levels in air, soil, surface water, sediment, and biota, and emissions by source (Natlonal institute of environmental research NIER, 2017). Based on the survey results, the Ministry of Environment designated the 'Persistent Organic Pollutants Management Method' and established POPs-containing waste treatment and management and measures to reduce emissions and has managed emission sources to reduce emissions (Natlonal institute of environmental research NIER, 2017). In fact, national emission regulations have led to a decrease of POP levels in the human body for 20 y (Seo et al., 2020). Other factors that may explain trends include lags and environmental reservoirs in the food web, particularly in the aquatic environment, and the storage and slow clearance from the human body. Trends of the metabolites suggest declining exposure to the parent compounds.

Considering our measurements along with regulations and use trends, we estimate that OCP exposure in Korea increased from the 1950 s to the late 1990 s, reached a plateau in the early 2000 s, and then decreased starting in the early or mid-2000 s. The Korean Ministry of Environment reported that DDT and HCB levels decreased significantly in air, soil, and sediment from 1999 to 2017, and that PeCB in air decreased gradually from 2013 to 2017 (Natlonal institute of environmental research NIER, 2017). OCP trends in marine sediments from Korea show similar patterns with the trends in the present study: an increase until the mid-2000 s, followed by a plateau or decrease (Choi et al., 2011; Meng et al., 2017). Therefore, this result suggests that the long-term decreasing trend in human serum samples is a result of emission source management and emission reduction policies, and national regulation of production and use of OCPs.

Our data suggest that serum levels of OCP in Korea started to decline later than in Europe and North American, but earlier than in other Asian countries. In North America (Hinck et al., 2009; Schade and Heinzow, 1998) and Europe (Jaraczewska et al., 2006; Polder et al., 2008), OCP levels showed downward trends beginning in the 1970 s or 1980 s until a plateau was reached in the late 1990 s or early 2000 s; these trends are a result of an earlier introduction of regulations than in Asian countries. However, in China (Qiu et al., 2009), India (Sharma et al., 2014), and Egypt (Barakat et al., 2012), OCP levels increased continuously through the 1990 s until the mid- and late-2000 s. Considering the low cost and high efficiency of pesticides, these countries likely continued to use OCPs or introduced regulations much later than in the rest of the world.

3.3. Association of OCP exposure with sex, age, and BMI

3.3.1. Sex

Concentrations of most OCPs were higher in females (arithmetic mean concentrations of Σ_{28} OCPs: 689 ng/g lipid, median concentrations of Σ_{28} OCPs: 581 ng/g lipid) than in males (arithmetic mean concentrations of Σ_{28} OCPs: 646 ng/g lipid, median concentrations of Σ_{28} OCPs: 529 ng/g lipid) (Table 1), and these differences were statistically significant for β-HCH ($p < 0.001$), γ-HCH ($p = 0.003$), HCB ($p = 0.016$), and endosulfan I ($p = 0.029$). However, differences between females and males were not significant for the other OCP compounds. The specific reasons for these differences are unknown, however, previous studies with similar findings suggested that this result might be due to the differences in dietary habits, metabolism, specific activities, and human OCP contamination of gender dimensions (Ben Hassine et al., 2014; Dirtu et al., 2006; Porta et al., 2012). However, in some other previous study, the OCP levels were higher in males than in females; the difference was presumed to be a result of females excreting OCP by menstruation, breastfeeding, and childbirth (Kang et al., 2008).

Serum concentrations of OCPs in females were low in their 20 s and 30 s, but increased with age (Fig. 2). Serum levels did not differ significantly between females in their 20 s and females in their 30 s, but were statistically significant ($p < 0.05$) between these groups and females in age groups > 30 y. This trend may be due to differences in daily intake and lifestyle and may be affected by active menstruation, breastfeeding, and childbirth in females in their 20 s and 30 s (Jiang and Li, 2020). In fact, OCPs have been detected in breast milk (Araki et al., 2018) and fetal cord blood (Müller et al., 2017), and OCPs in maternal body are tranlocated to breast milk and fetus. These results suggest that OCPs can

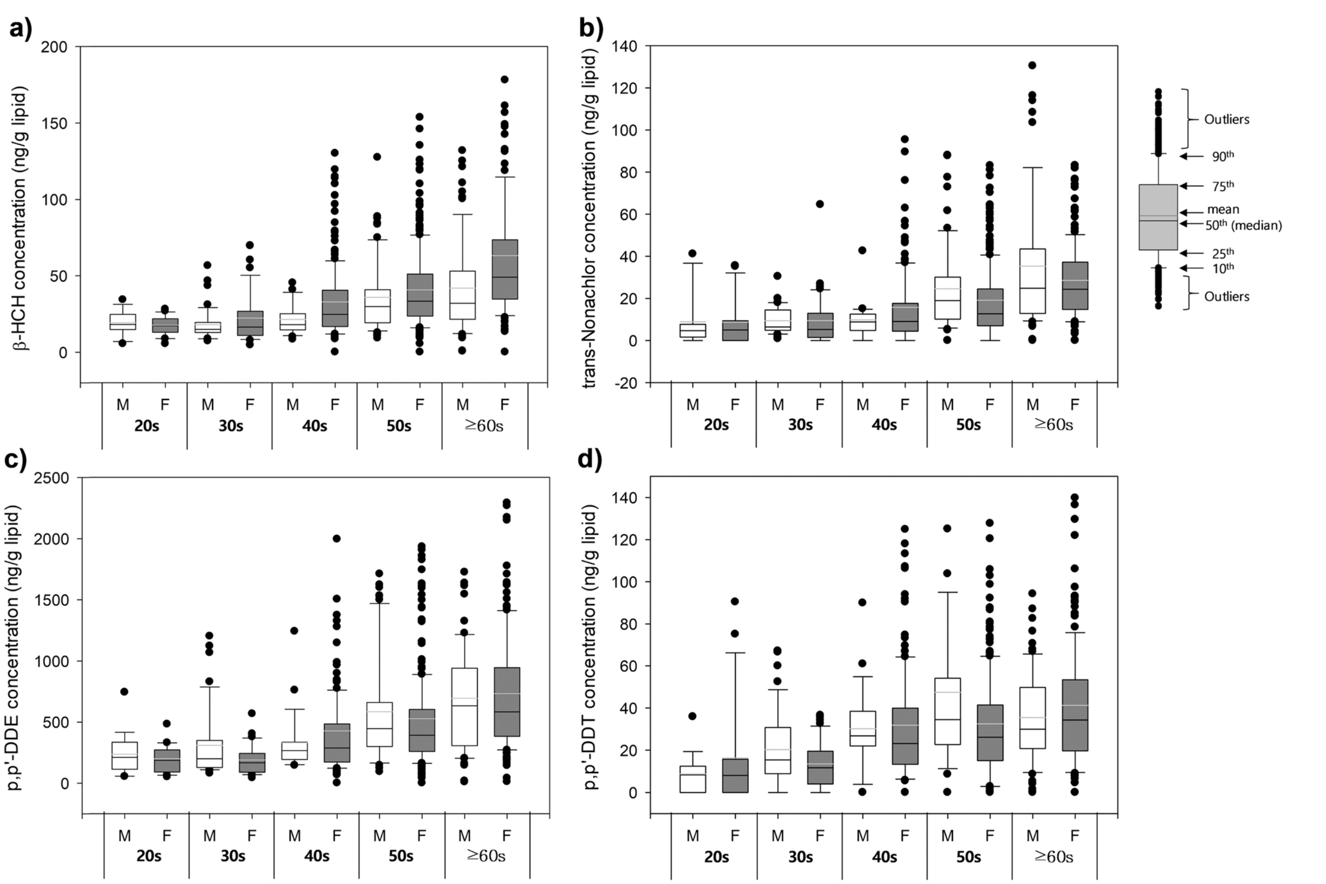

Fig. 2. Total OCP concentrations in serum (ng/g lipid; n = 880) by sex (M; male; n = 215, F; female; n = 665) and age category (20 s; n = 32, 30 s; n = 77, 40 s; n = 189, 50 s; n = 350, and ≥ 60 s; n = 232); (a) β-HCH, (b) *trans*-nonachlor, (c) *p,p*′-DDE, and (d) *p,p*′-DDT. Box plots show 25th, 50th, and 75th percentiles, and the gray line in the box represents the mean values. Error bars below and above boxes indicate 10th and 90th percentiles, respectively. Outliers are presented as individual points.

be transferred to the fetus thereby lowering the body burden of females during childbirth and breastfeeding.

3.3.2. Age

OCP levels adjusted for potential confounders were significantly and positively correlated with age (Table 1). As examples, PeCB ($r = 0.111$, $p = 0.009$), β-HCH ($r = 0.434$, $p < 0.001$), HCB ($r = 0.106$, $p = 0.006$), *cis*-heptachlor epoxide ($r = 0.364$, $p < 0.001$), dieldrin ($r = 0.216$, $p = 0.001$), oxychlordane ($r = 0.320$, $p < 0.001$), *trans*-nonachlor ($r = 0.302$, $p < 0.001$), *cis*-nonachlor ($r = 0.177$, $p < 0.001$), *p,p′*-DDE ($r = 0.267$, $p < 0.001$), and *p,p′*-DDT ($r = 0.184$, $p < 0.001$).

The participants were categorized into five age groups (20 s, 30 s, 40 s, 50 s, and ≥ 60 s) to evaluate the relationship between age and OCP exposure levels (Table 1, Fig. 2). Levels of PeCB, α-HCH, β-HCH, δ-HCH, HCB, *trans*-heptachlor epoxide, *cis*-heptachlor epoxide, aldrin, dieldrin, oxychlordane, *trans*-nonachlor, *cis*-nonachlor, *cis*-chlordane, *trans*-chlordane, kepone, *p,p′*-DDT, *o,p′*-DDT, *p,p′*-DDD, *o,p′*-DDD, and *p,p′*-DDE differed significantly among the age groups ($p < 0.05$). Total OCP levels increased significantly ($p < 0.01$) with participant age, with arithmetic means of 413, 447, 681, 815, and 963 ng/g lipid for age groups of 20 s, 30 s, 40 s, 50 s, and ≥ 60 s, respectively.

Several OCPs did not vary by age group, including γ-HCH, heptachlor, endrin, endosulfan, *o,p′*-DDE and Mirex. This lack of difference may be due to rapid clearance and low concentrations of these compounds, e.g., the half-life is 20 h for γ-HCH (Kang and Chang, 2011), 40 d for heptachlor (Agency for Toxic Substances and Disease Registry ATSDR, 2007), 266 d for endrin (National Center for Biotechnology Information NCBI, 2005a), about 40 d for endosulfan (Agency for Toxic Substances and Disease Registry ATSDR, 2013), 17–37 h for *o,p′*-DDE (Agency for Toxic Substances and Disease Registry ATSDR, 2002), and 20–30 d for Mirex (National Center for Biotechnology Information NCBI, 2005b), whereas many of the other OCPs have half-lives of several years. The lower serum levels of these compounds may increase analytical uncertainties, and thereby reduce the ability to detect trends and statistically significant associations.

Previous studies have also reported that OCP levels increase with the subject's age (Petrik et al., 2006; Thomas et al., 2017). Likely reasons for this trend include long exposure periods, deterioration of metabolic capacity, and different lifestyles (e.g., daily food intake, occupation, cooking method, frequency of use of the products containing OCPs, childbirth, breastfeeding, menstruation, major living spaces according to the participant's occupation and life style e.g., outdoor, indoor at home, office, kitchen).

3.3.3. BMI

After adjustment for potential confounders, OCPs such as β-HCH ($p < 0.001$), *cis*-heptachlor epoxide ($p < 0.001$), dieldrin ($p < 0.001$), oxychlordane ($p = 0.042$), *p,p′*-DDT ($p = 0.020$), and *p,p′*-DDE ($p = 0.006$), had significant positive associations with BMI (Table 1, Fig. S4). The participants were divided into five groups: underweight, normal-weight, overweight, obese, and highly obese. The arithmetic mean levels of β-HCH, *cis*-heptachlor epoxide, dieldrin, endosulfan II, endosulfan III, and *cis*-nonachlor differed significantly ($p < 0.05$) among the groups. In addition, the arithmetic mean of HCB concentrations was significantly higher in the highly obese group than in the normal group, and the *o,p′*-DDD level was significantly higher in the obese groups than in the underweight group. The arithmetic mean concentrations of δ-HCH, oxychlordane, *trans*-nonachlor, and *p,p′*-DDT were significantly higher in the obese groups than in the normal-weight group.

OCP concentrations have been shown to be positively correlated with BMI (Ben Hassine et al., 2014); the trend may relate to dietary intake (Ogden et al., 2004). Further, lipids in the body retain OCPs, and obese people may have metabolic differences that result in further accumulation (Ogden et al., 2004). The possibility that exposure to low dose of OCPs can cause obesity has also been reported (Lee et al., 2011). Levels of methanobacteriales in the gut are known to be related to higher waist circumference and body weight, and levels of methanobacteriales were positively correlated to serum OCP levels (Lee et al., 2011), so human exposure to OCPs might have influenced methanobacteriales in the gut, which are related to BMI.

3.4. Implications of clinical indicators

3.4.1. Multivariable analysis

The associations among OCPs and clinical indicators (uric acid, thyroid hormone, and cholesterol) were evaluated by PCA (Fig. 3). The three main PCs accounted for 66% (PC1: 25%, PC2: 23%, and PC3: 18%) of the variations in the model (Fig. 3a). A loading plot provided information on the contributions of clinical indicators and each major compound to the sample separation. A score plot (Fig. 3b) suggested six groups: Groups I and II contained the major OCP compounds, e.g., *p,p′*-DDE with the highest levels and β-HCH with high detection rates, respectively; Group III contained TC; Group IV contained uric acid; and Groups V and VI included thyroid hormones (fT4 and TSH). The loading plot indicated that TC was linked to *p,p′*-DDE, *p,p′*-DDT, and β-HCH, and uric acid was related to *p,p′*-DDE. TSH was linked to *trans*-nonachlor and *p,p′*-DDT, whereas fT4 was related to β-HCH.

This difference in OCP profiles based on the clinical indicators suggests that each OCP is associated with different disease manifestations. Previous studies have also reported strong associations between TC and *p,p′*-DDE and β-HCH (Ben Hassine et al., 2014; Lee et al., 2011), and *p,p′*-DDE and *cis*-nonachlor have been significantly associated with thyroid hormones (Takser et al., 2005). The current data suggest that these results indicate an association of OCPs with clinical indicators, and that different OCP compounds may affect different clinical indicators; this possibility is further explored below.

3.4.2. Cholesterol

α-HCH, β-HCH, γ-HCH, δ-HCH, HCB, *trans*-heptachlor epoxide, *cis*-heptachlor epoxide, dieldrin, oxychlordane, endosulfan I, endosulfan II, *trans*-nonachlor, *cis*-nonachlor, *p,p′*-DDT, *o,p′*-DDT, and *p,p′*-DDE had positive associations with TC ($p < 0.05$). LDL cholesterol was positively correlated with α-HCH, β-HCH, γ-HCH, δ-HCH, *trans*-heptachlor epoxide, *cis*-heptachlor epoxide, *trans*-nonachlor, endrin, endosulfan II, kepone, *o,p′*-DDT, and *p,p′*-DDE ($p < 0.05$). Triglycerides were correlated with γ-HCH, *trans*-heptachlor epoxide, and endrin ($p < 0.05$), whereas HDL cholesterol was negatively correlated with *p,p′*-DDT ($p < 0.05$) (Table S8).

The levels of the cholesterol species showed increasing quartiles of OCP levels (Fig. 4, Table S9). The associations of OCP levels with levels of TC and LDL cholesterol followed inverted U-shapes, which represent an association that is positive at low exposure levels, then decreases and eventually become negative as exposure level increases. α-HCH, β-HCH, γ-HCH, δ-HCH, HCB, *trans*-heptachlor epoxide, *cis*-heptachlor epoxide, dieldrin, oxychlordane, endosulfan I, endosulfan II, *trans*-nonachlor, *cis*-nonachlor, *p,p′*-DDT, *o,p′*-DDT, and *p,p′*-DDE had inverted U-shape associations with TC. LDL cholesterol had inverted U-shape associations with α-HCH, β-HCH, γ-HCH, δ-HCH, *trans*-heptachlor epoxide, *cis*-heptachlor epoxide, *trans*-nonachlor, endrin, endosulfan II, kepone, *o,p′*-DDT, and *p,p′*-DDE. Triglyceride had a positive correlation with all OCPs except δ-HCH, heptachlor, aldrine, dieldrine, *o,p′*-DDT, mirex, whereas HDL cholesterol had a negative correlation with all OCPs except β-HCH, *trans*-heptachlor epoxide, endrin, endosulfan II, *o,p′*-DDT, and mirex (Table S8).

A previous study also showed inverted U-shape associations between DDE, oxychlordane, or *trans*-nonanchlor and cholesterol (Lee et al., 2011). In the animal model study, rats showed severe dysregulation of lipid homeostasis when fed salmon oil contaminated with POPs, including DDT, HCB, and HCH (Ruzzin et al., 2010). The exposure of the rats to OCPs was associated with strong inhibition of Lpin1 and Insulin-induced gene 1, which are the regulators of fat production and synthesis of cholesterol and triglycerides (Ruzzin et al., 2010). In

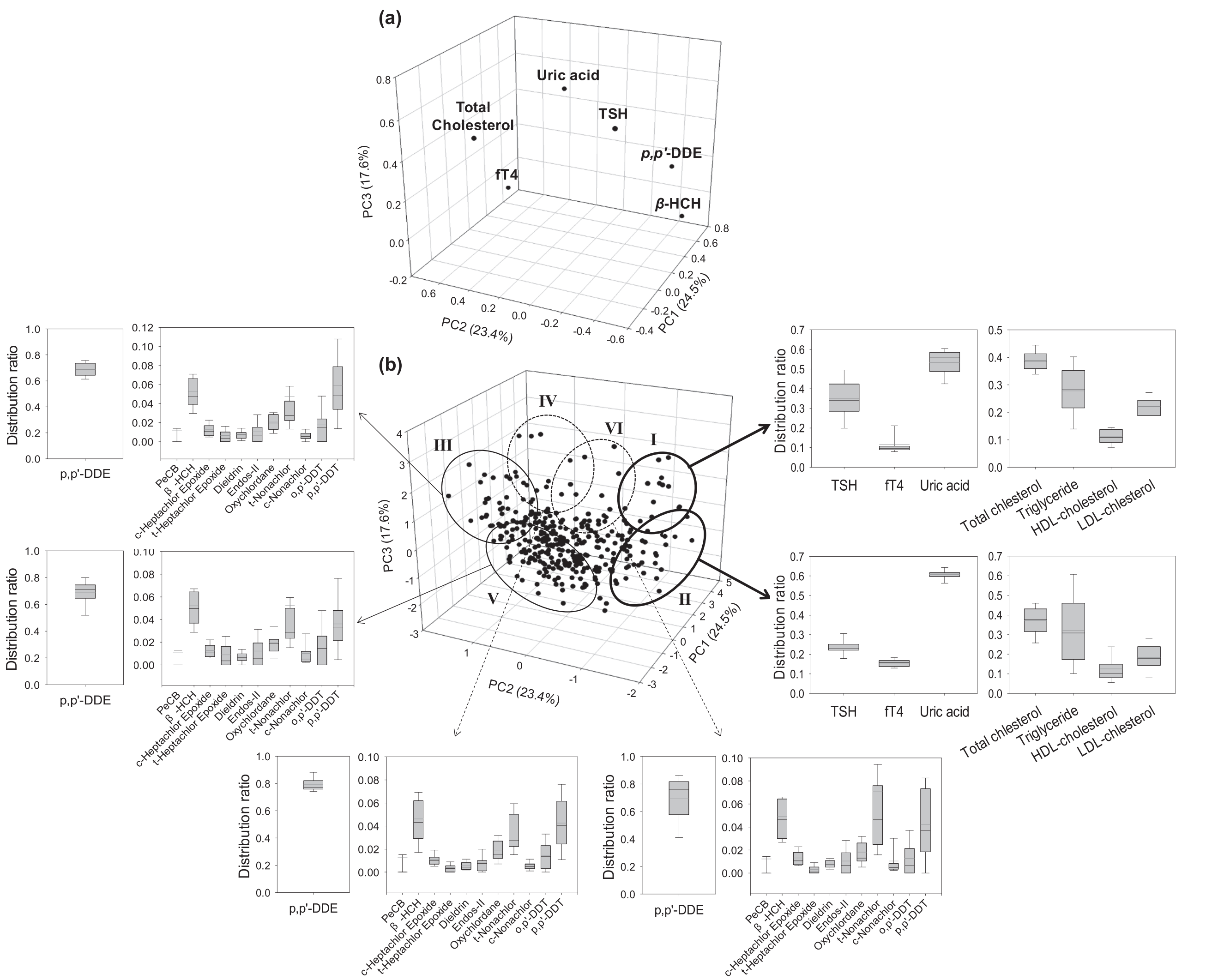

Fig. 3. (a) Loading plot for OCP compounds (β-HCH and p,p'-DDE) and clinical indicators (cholesterol, uric acid, thyroid hormone). Among all OCP compounds and clinical indicators, the major factors were presented. (b) Score plot for factors. Box plots show 25th, 50th, and 75th percentiles, and the gray line in the box represents the mean values. Error bars below and above boxes indicate 10th and 90th percentiles, respectively.

addition, the exposure to OCPs was associated with increase in expression of sterol regulatory element-binding protein 1c, which is a major factor in the lipid production process, and also in expression of the target gene, fatty acid synthase (Ruzzin et al., 2010).

In experiments with cultured cells, low doses of OCPs caused elevated expression of peroxisome proliferator-activated receptor γ, increased glycerol-3-phosphate dehydrogenase activity and adipocyte differentiation, whereas relatively high doses did not affect adipocyte proliferation (Arsenescu et al., 2008). General population exposure to POPs, including OCPs has been significantly associated with impairment of lipid metabolism (Arrebola et al., 2014; Lee et al., 2011). These results suggest that exposure to POPs may affect the expression of genes involved in the regulation of lipid homeostasis. In addition, low concentrations of OCPs, which can act like hormones in the human body, might increase adipocyte differentiation and enzyme activity, whereas the proliferative effect on adipocytes might be stopped by the toxic effects of OCPs at high concentrations; these observations suggest that OCPs might disrupt endocrine function in the body.

3.4.3. Hypertension

Hypertension was diagnosed in 141 participants. After adjustment for potential confounders, only β-HCH levels were significantly higher in individuals with hypertension (49 ± 35 ng/g lipid) than in those without it (41 ± 38 ng/g lipid); $p = 0.013$ (Fig. S5). A previous epidemiological study reported significant associations of hypertension risk with HCB and β-HCH levels in individuals with BMI ≥ 26.3 kg/m^3 (Arrebola et al., 2015), and that p,p'-DDE had increased blood pressure and was associated with onset of hypertension (Lind et al., 2014). The present study also showed a significant association between hypertension and β-HCH, but neither for p,p'-DDE nor HCB.

OCPs are anti-androgen compounds that act on the androgen receptor (Freire et al., 2014). High OCP levels have been shown to be inversely proportional to testosterone levels (Akishita et al., 2010; Blanco-Muñoz et al., 2012; Xu et al., 2013). Low testosterone levels can increase blood pressure and have been associated with hypertension (Akishita et al., 2010; Svartberg et al., 2004). In addition, female sex hormone has been shown to prevent cardiovascular disease (Masi et al., 2006), and 2-hydroxyestradiol, an estradiol metabolite, is a potent inhibitor of vascular smooth muscle cell proliferation; compounds that have anti-androgenic potential can interact with this mechanism (Masi et al., 2006). Therefore, these results suggest that the anti-androgenic effects of β-HCH may have caused increase in blood pressure, and this increase can lead to hypertension.

3.4.4. Uric acid and creatinine

Serum OCP concentrations were classified into quartiles to identify

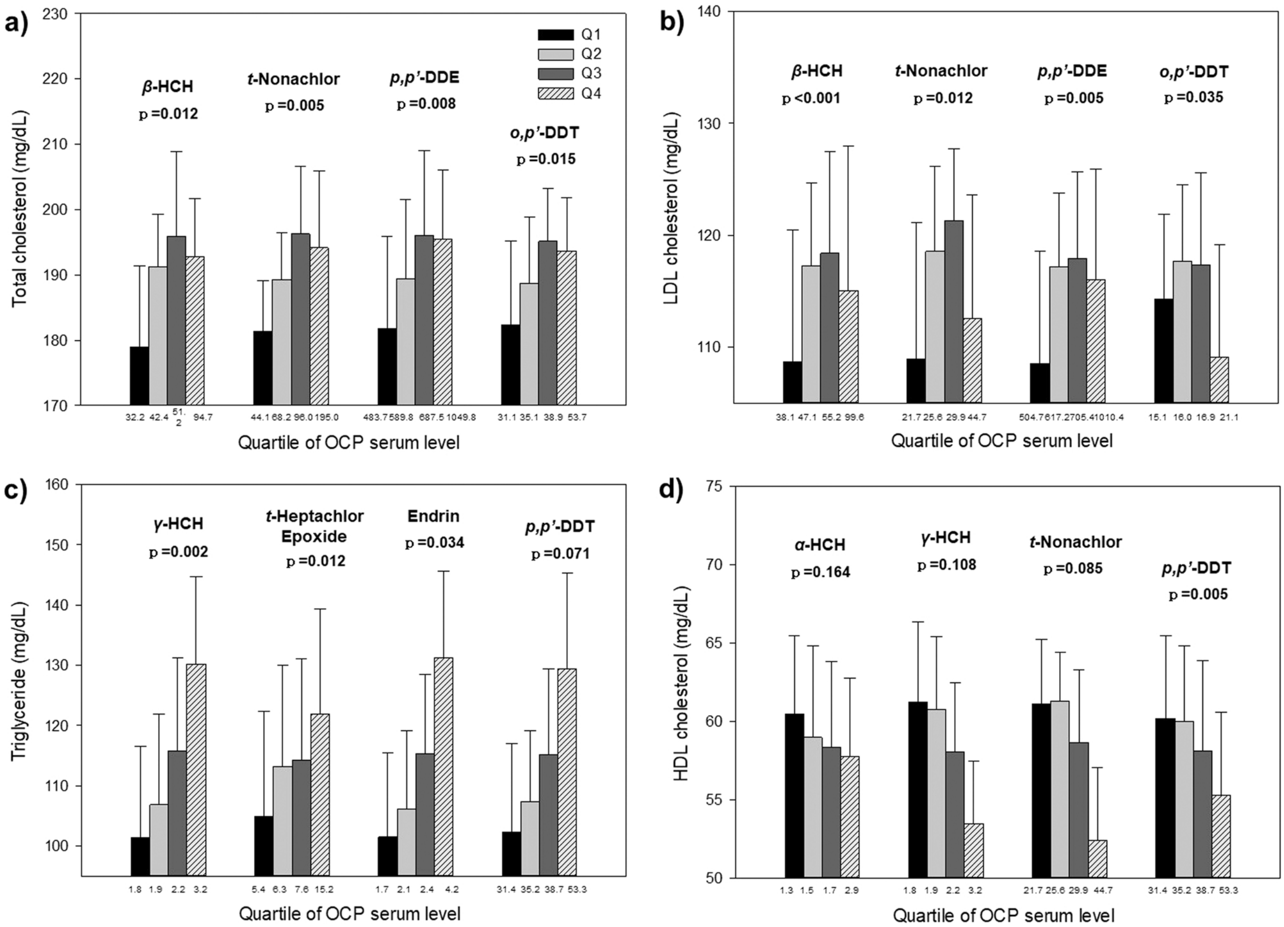

Fig. 4. Adjusted mean lipid levels (mg/dL) by quartile of OCP concentration (ng/g lipid); a) total cholesterol, b) low-density lipoprotein (LDL) cholesterol, c) triglycerides, and d) high-density lipoprotein (HDL) cholesterol. Error bar shows standard deviation. Adjusted variables were sex, age, BMI, and lipids. Among the OCPs, only major compounds or those have with meaningful associations with cholesterol are shown in the figure. OCP levels in each quartile are shown below the bar; p values for trends are shown above the bar.

the association between uric acid and OCP, then the levels of uric acid in each quartile were compared (Fig. 5). Uric acid levels adjusted for potential confounders increased from the lowest to the highest quartile for *cis*-heptachlor epoxide ($p < 0.001$), *cis*-nonachlor ($p = 0.037$), *p,p*′-DDE ($p < 0.001$), and *p,p*′-DDT ($p = 0.001$), and concentrations of these OCP compounds were significantly correlated with uric acid levels (Table 2). In addition, 56 participants who fell in the high-risk group were diagnosed with hyperuricemia, and the serum levels of *β*-HCH ($p = 0.001$), *trans*-nonachlor ($p = 0.018$), *o,p*′-DDE ($p = 0.009$), and *p,p*′-DDE ($p = 0.001$) were significantly higher in these participants than in

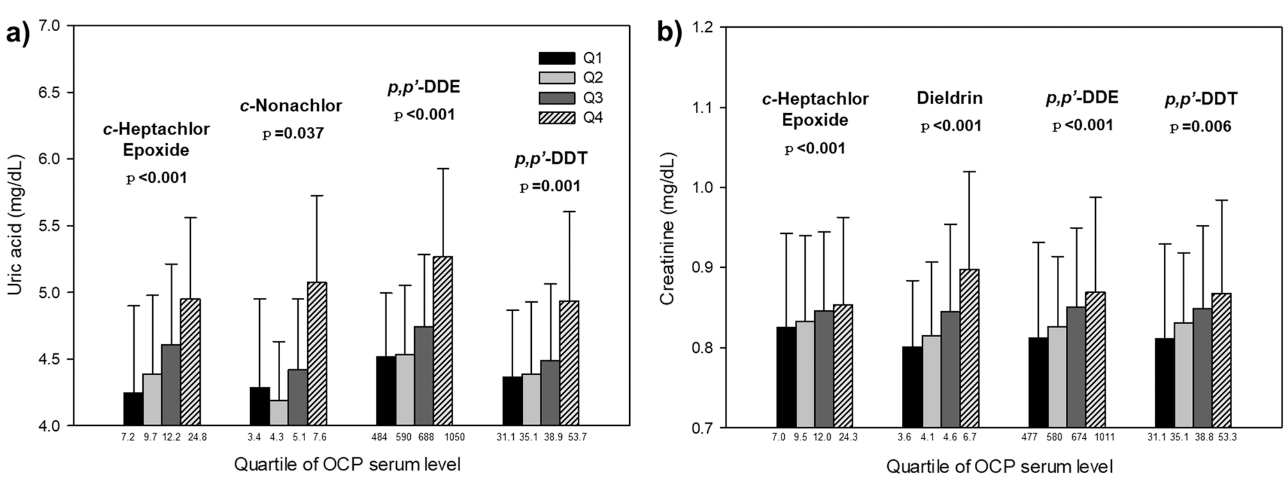

Fig. 5. Adjusted means of (a) uric acid (mg/dL) and (b) creatinine (mg/dL) with increasing quartile of OCP serum concentrations (ng/g lipid). Adjusted variables were sex, age, BMI, and lipids. Among the OCPs, only major compounds or those that have meaningful associations with uric acid were shown in the figure. Error bar shows standard deviation, and *p*-value of each compound is indicated above the bar. OCP level of each quartile group is shown below the bar.

Table 2
Multivariate regression models of uric acid (mg/dL), creatinine (mg/dL), free thyroxine (mg/dL), and thyroid stimulating hormone (mg/dL) levels with OCP concentrations (ng/g lipid).

	Uric acid				Creatinine				Free thyroxine				Thyroid stimulating hormone			
	beta	95% CI		p-value	beta	95% CI		p-value	beta	95% CI		p-value	beta	95% CI		p-value
		lower	upper			lower	upper			lower	upper			lower	upper	
PeCB	-0.035	-0.004	0.001	0.311	-0.047	-0.001	0.000	0.224	0.026	0.000	0.001	0.552	0.074	0.000	0.007	0.082
α-HCH	0.039	-0.019	0.072	0.251	**-0.090**	-0.008	-0.001	0.002	0.011	-0.008	0.010	0.792	0.007	-0.051	0.061	0.863
β-HCH	0.036	-0.002	0.007	0.376	-0.012	-0.002	0.002	0.701	**-0.107**	-0.001	0.000	0.023	0.069	-0.001	0.007	0.140
γ-HCH	-0.041	-0.040	0.010	0.233	0.018	-0.003	0.004	0.637	-0.022	-0.006	0.004	0.605	0.025	-0.022	0.041	0.554
δ-HCH	-0.026	-0.237	0.105	0.488	-0.052	-0.033	0.002	0.075	-0.051	-0.056	0.013	0.232	0.023	-0.163	0.284	0.593
HCB	0.069	0.000	0.009	0.085	0.048	0.000	0.001	0.212	**-0.156**	-0.008	0.001	<0.001	0.030	-0.001	0.002	0.493
Heptachlor	0.031	-0.007	0.017	0.440	-0.032	-0.002	0.001	0.274	-0.019	-0.003	0.002	0.654	0.023	-0.010	0.018	0.583
c-Heptachlor Epoxide	**0.185**	0.003	0.027	<0.001	**0.149**	0.001	0.003	<0.001	-0.045	-0.004	0.001	0.342	0.053	-0.005	0.020	0.251
t-Heptachlor Epoxide	0.030	-0.006	0.015	0.382	-0.051	-0.002	0.000	0.081	-0.038	-0.003	0.001	0.373	0.002	-0.012	0.013	0.958
Aldrin	-0.001	-0.010	0.009	0.977	-0.055	-0.002	0.000	0.059	-0.027	0.002	0.001	0.525	-0.005	-0.013	0.011	0.903
Dieldrin	0.016	-0.028	0.042	0.691	**0.195**	0.005	0.012	<0.001	0.005	-0.006	0.007	0.916	0.010	-0.033	0.041	0.813
Endrin	-0.020	-0.035	0.019	0.563	**-0.085**	-0.007	-0.001	0.003	**-0.092**	-0.011	-0.001	0.030	-0.037	-0.048	0.018	0.376
Endosulfan I	0.071	-0.008	0.048	0.090	-0.034	-0.004	0.002	0.384	**-0.127**	-0.011	-0.002	0.003	0.079	-0.002	0.055	0.063
Endosulfan II	0.015	-0.002	0.015	0.082	-0.007	-0.001	0.001	0.851	**-0.098**	-0.004	0.000	0.021	0.047	-0.005	0.018	0.273
Endosulfan III	-0.039	-0.011	0.004	0.335	0.052	0.000	0.002	0.083	0.058	0.000	0.002	0.193	-0.047	-0.013	0.004	0.270
Oxychlordane	0.016	-0.007	0.010	0.689	0.031	-0.001	0.001	0.421	-0.025	-0.002	0.001	0.575	-0.006	-0.011	0.010	0.892
t-Chlordane	-0.027	-0.015	0.006	0.430	-0.056	-0.002	0.000	0.053	0.017	-0.002	0.002	0.689	0.027	-0.008	0.017	0.520
c-Chlordane	0.027	-0.002	0.006	0.431	-0.070	-0.002	0.000	0.069	0.026	0.000	0.001	0.536	0.029	-0.003	0.006	0.493
t-Nonachlor	0.064	0.000	0.008	0.073	0.074	0.000	0.001	0.056	-0.016	-0.001	0.001	0.723	**0.139**	0.003	0.014	0.002
c-Nonachlor	**0.072**	-0.001	0.030	0.037	-0.020	-0.002	0.001	0.610	-0.067	-0.005	0.001	0.122	0.021	-0.013	0.022	0.630
Kepone	0.054	-0.001	0.006	0.114	-0.022	-0.001	0.001	0.564	0.011	-0.001	0.001	0.792	0.069	-0.001	0.008	0.105
o.p'-DDE	-0.013	-0.002	0.001	0.360	-0.052	-0.002	0.000	0.052	-0.033	-0.002	0.001	0.432	0.024	-0.001	0.003	0.569
p,p'-DDE	**0.151**	0.000	0.001	<0.001	**0.132**	0.001	0.003	<0.001	-0.006	-0.001	0.001	0.894	0.003	-0.001	0.002	0.941
o,p'-DDD	-0.025	-0.007	0.003	0.464	-0.065	-0.001	0.000	0.092	0.033	-0.001	0.001	0.439	-0.032	-0.008	0.004	0.443
p,p'-DDD	0.039	-0.003	0.013	0.248	-0.042	-0.001	0.000	0.224	0.036	-0.001	0.002	0.884	-0.025	-0.012	0.007	0.558
o,p'-DDT	-0.017	-0.003	0.002	0.627	-0.048	-0.001	0.000	0.215	-0.028	-0.002	0.000	0.094	0.013	-0.005	0.007	0.766
p,p'-DDT	**0.118**	-0.002	0.008	0.001	**0.084**	0.000	0.001	0.029	-0.040	-0.001	0.000	0.369	0.057	-0.001	0.007	0.194
Mirex	0.041	-0.005	0.015	0.304	**0.104**	0.000	0.003	0.007	0.032	-0.001	0.002	0.455	0.011	-0.009	0.012	0.800

CI: confidence interval. Models were adjusted for sex, age, body mass index, and lipids. Statistically significant values ($p < 0.05$) were shown in bold. Data showed normal distributions.

participants who had normal uric acid levels.

Concentrations of *cis*-heptachlor expoxide ($p < 0.001$), dieldrin ($p < 0.001$), *p,p′*-DDE ($p < 0.001$), *p,p′*-DDT ($p = 0.029$), and mirex ($p = 0.007$) showed significant positive linear associations with levels of creatinine. Previous toxicological studies using biomarkers (i.e., insulin-like growth factor 1 in muscle, cytochrome P4501A in liver tissues, and glutathione S-transferase gene) confirmed that creatinine levels in fish increased when they were exposed to *p,p′*-DDE and heptachlor (El Megid et al., 2020), and that γ-HCH and *p,p′*-DDT levels showed significant associations with serum creatinine levels of patients with chronic kidney disease (Siddarth et al., 2014). As a result, serum concentrations of *cis*-heptachlor epoxide, *p,p′*-DDE, and *p,p′*-DDT showed strong positive linear associations with serum concentrations of both uric acid and creatinine. In particular, *p,p′*-DDE was significantly associated with hyperuricemia and with elevated levels of uric acid and creatinine.

Previous epidemiological studies reported that hyperuricemia or gout can develop in people who are exposed to high concentrations of OCPs (Lee et al., 2013), and serum concentrations of γ-HCH and *o,p′*-DDE have been associated with an increased risk of hyperuricemia (Arrebola et al., 2019). Several mechanisms for these associations have been suggested.

(1) Some POPs may affect uric acid homeostasis by destroying antioxidant enzymes and the production of intermediates of reactive oxygen (Panaretakis et al., 2001), and chronic exposure of OCP may cause induction of alternative pathways to the glutathione detoxification route, and this alternative pathways have been reported to lead to an increase in oxidative stress (Francisco et al., 2016). (2) The associations may be a result of chronic nephrotoxicity as a result of interaction of serum OCPs with anion transporters involved in excretion by the kidneys (Kataria et al., 2015). (3) The association between OCPs and uric acid may be a result of disruption of the renal excretory system that maintains whole-body homeostasis by excreting metabolic waste products into the urine. Excretion of uric acid and substances such as OCPs is controlled by renal transport systems (Eraly et al., 2008), and therefore the association may be a result of competition for kidney transporters during the process of excretion of OCPs and uric acid (Eraly et al., 2008). Thus, as OCP level increases, the excretion of urate may decrease, so it may accumulate in the blood. Increased uric acid can lead to deposition of uric acid in joints, which causes gout and other diseases (Heinig and Johnson, 2006). These results suggest that exposure to OCPs may interfere with uric acid and creatinine homeostasis and kidney function.

3.4.5. *Thyroid function*

OCP levels were classified by quartiles to represent the change in thyroid hormone levels according to OCP levels (Fig. 6, Table 2). OCP and thyroid hormone levels were adjusted for age, sex, BMI, and lipids. Levels of fT4 were significantly negatively correlated with levels of β-HCH ($p = 0.023$), HCB ($p < 0.001$), endrin ($p = 0.030$), endosulfan I ($p = 0.003$), and endosulfan II ($p = 0.021$) (Fig. 6a), whereas levels of TSH were significantly positively correlated with *trans*-nonachlor ($p = 0.002$) (Fig. 6b). As a result, fT4 and TSH showed opposite tendencies with levels of certain OCP compounds.

A previous study reported an association between exposure to HCB and decreased fT4, and suggested that changes in thyroid parameters can be induced by reducing levels of T3 and thyroxine-binding globulin (Dallaire et al., 2009). Toxicological studies using animal models have demonstrated that OCP induces changes in the thyroid system by reducing fT4 levels (Cheek et al., 1999; Gerlienke Schuur et al., 1998; van Raaij et al., 1993), and have reported that OCP exposure increased TSH levels and reduced fT4 levels, thereby disturbing the thyroid system (Cheek et al., 1999; De Pisarev et al., 1990; van Raaij et al., 1993). In addition, a negative association between HCB and fT4 but a positive association between β-HCH and TSH has been reported, as in the present study (Dallaire et al., 2009). Significant inverse associations of have been reported for HCB and *p,p′*-DDE with fT4 levels but not for TSH levels (Maervoet et al., 2007). In rats that had been treated with HCB, the fT4 and thyroxine hormone (T4) levels decreased, whereas changes in TSH level were not consistent; the activation of hepatic UDP-GT enzymes following T4 glucuronidation and biliary excretion was the mechanism of consequent hypothyroidism in rats (Alvarez et al., 2005; van Raaij et al., 1993).

One possible explanation for the decrease in fT4 and the increase in TSH with increase in OCP levels in this study is that OCP may affect the peripheral deiodination of T4, and thereby reduce T3 levels (Gerlienke Schuur et al., 1998). T4 is released from the thyroid gland then converted to T3, which then promotes metabolic activity, decreases TSH release from the anterior pituitary gland, and increases the release of fT4 (Brent, 2012). However, OCP may influence peripheral deiodination of T4 by inactivating deiodinase enzymes, and thereby lead to reduced T3 levels (Gerlienke Schuur et al., 1998). As T3 level decreases, the release of TSH may increase whereas the release of fT4 may decrease (Brent, 2012). In fact, the concentration of OCPs in the human body has a negative association with T3 levels (Dallaire et al., 2009). Another potential mechanism is that these compounds affect the thyroxine-binding globulin, and thereby reduce the binding capacity of thyroid hormones (Schussler, 2000). Thyroxine-binding globulin is a major transport protein of thyroid hormones, so changes in thyroxine-binding globulin may cause a decrease in T3 concentration (Schussler, 2000). Despite the

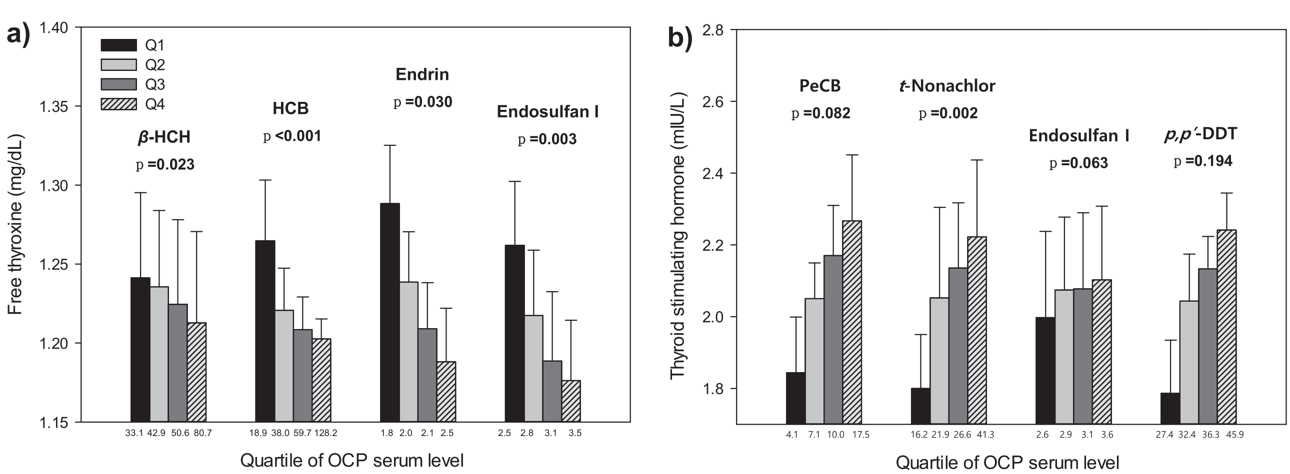

Fig. 6. Adjusted means of thyroid hormone with increasing quartile of OCP serum concentration (ng/g lipid); (a) free thyroxine (fT4) (mg/dL) and (b) thyroid-stimulating hormone (TSH) (mlU/L) according to OCP serum concentrations. Adjusted variables were sex, age, BMI, and lipids. Among the OCPs, only major compounds or those that have meaningful associations with thyroid hormone were shown in the figure. Error bar shows standard deviation, and *p*-value of each compound is indicated above the bar. OCP level of each quartile group is shown below the bar.

uncertaintly of the mechanisms by which OCPs affect thyroid function, these results suggest that exposure to high OCP levels may lead to hypothyroidism, which is associated with decreased fT4 and increased TSH.

3.4.6. Diabetes

In this study, 55 patients were diagnosed with diabetes. They had significantly higher concentrations of β-HCH ($p = 0.002$), *cis*-heptachlor epoxide ($p < 0.001$), oxychlordane ($p = 0.003$), dieldrin ($p = 0.003$), *p,p*′-DDT ($p = 0.03$), and *p,p*′-DDE ($p = 0.01$) than those without diabetes (Fig. S6). This result is similar to previous studies that reported that some OCPs are associated with diabetes prevalence in the general population (Philibert et al., 2009; Cox et al., 2007; Codru et al., 2007; Son et al., 2010). Previous studies have demonstrated a positive association between the incidence of type-2 diabetes and *p,p*′-DDE serum levels (Rignell-Hydbom et al., 2009; Turyk et al., 2009), and a positive association between diabetes and low-dose POP exposure (Rignell-Hydbom et al., 2009; Son et al., 2010; Turyk et al., 2009). Rats dosed with environmental levels of POPs can experience non-alcoholic fatty liver, chronic low-grade inflammation, insulin resistance, and visceral obesity, whereas rats given high doses did not show these symptoms (Ruzzin et al., 2010). A mixture of polychlorinated biphenyls and DDTs has the strongest inhibitory influence on insulin reaction in 3T3L1 cells (Ruzzin et al., 2010). *In vivo* experiment with cells showed associations between decreased insulin secretion and increased levels of *p,p*′-DDE, β-HCH, and *trans*-nonachlor (Lee et al., 2017).

One possible mechanism by which OCP can induce onset of type-2 diabetes is that OCPs cause mitochondrial dysfunction, which increases fatty acid content in the blood and thereby results in insulin resistance (Parish and Petersen, 2005). OCP can produce oxidative stress by generating reactive oxygen species (ROS) that reduce the state of antioxidants (Abdollahi et al., 2004). Mitochondria are susceptible to ROS, which cause defects that can lead to increased fatty acid concentrations, which interfere with insulin signaling and cause insulin resistance; if this effect persists, diabetes can occur (Parish and Petersen, 2005). In adipocytes of model mice that had type-2 diabetes, and of diabetic patients, the production of peroxisome proliferator-activated receptors, which regulate mitochondrion reproduction, was reduced (Bogacka et al., 2005; Choo et al., 2006; Hammarstedt et al., 2003). Another potential mechanism is that chronic exposure to OCPs may affect insulin secretion by triggering the dysfunction of pancreatic β-cells which help to regulate glucose homeostasis by storing and releasing insulin in the human body (Muoio and Newgard, 2008). When the blood glucose level rises, the concentration gradient is lowered by the insulin-responsive glucose transporter (GLUT4), and the β-cells catalyze glycolysis by using glucokinase (German, 1993). In humans, POPs may cause direct toxicity to β-cells (Jørgensen et al., 2008; Park et al., 2016), and may decrease expression of GLUT4 (Fujiyosh et al., 2006).

These results suggest that exposure to OCPs may be associated with the induction of type-2 diabetes. However, opinions on the mechanisms of the effects of OCP exposure on type-2 diabetes and insulin resistance are divided, and the current study does not show a definite trend due to the small number of diabetic patients. Therefore, to identify the associations between OCP exposure and diabetes prevalence, additional large-scale studies are needed.

4. Conclusions

The body burden of OCPs is influenced by their half-lives, timing of exposure, and national regulations. The OCP levels decreased in the human body over a period of 12 y, indicating a success of national and global regulations for the production and use of OCPs, emission source management, and emission-reduction policies for OCPs. The total OCP levels were higher in females than in males, possibly as a result of differences in dietary habits, metabolism, and likelihood of environmental exposure. OCP levels increased with subject age; this trend may be attributed to deteriorating metabolic capacity, long exposure periods, and differences in lifestyle. Also, OCP levels increased as BMI increased, possibly as a result of dietary intake, the lipophilicity of OCPs, and the influence of OCPs on methanobacteria in the gut.

The PCA suggested possible differences in disease manifestation depending on the composition of OCPs. The inverted U-shape association between OCP levels and TC and LDL cholesterol levels suggested low-dose effects of OCPs and that OCPs might act as endocrine-disrupting chemicals. β-HCH levels differed between individuals with and without hypertension; a possible explanation is that OCPs may cause hypertension by mechanisms associated with androgen receptors. Serum levels of uric acid and creatinine increased with increase in concentrations of *cis*-heptachlor epoxide, *p,p*′-DDE, and *p,p*′-DDT. *p,p*′-DDE was also significantly associated with hyperuricemia. These results suggest that OCPs might have an influence on renal transport systems and disrupt the homeostasis of uric acid and creatinine. fT4 level decreased as β-HCH, HCB, endrin, endosulfan I, and endosulfan II levels increased, whereas TSH level increased as *trans*-nonachlor level increased. These results suggest that human exposure to high OCP levels may lead to hypothyroidism. Individuals with diabetes had higher exposure levels of OCPs than those without diabetes; this result suggests that OCPs may interfere with the insulin signaling cascade, or affect insulin secretion.

Our findings have identified the possibility that OCPs may induce or may be risk factors of metabolic dysfunction, and that each OCP compound may be associated with different health effects. To the best of our knowledge, the inverted U-shaped associations of heptachlor epoxide and endosulfan with cholesterol and the epidemiological associations of *trans*-nonachlor and endosulfan with thyroid hormones have not been previously reported in the general population, although the potential toxicological effects have been demonstrated in studies using animal models treated with OCPs (Cheek et al., 1999; Gerlienke Schuur et al., 1998; Ruzzin et al., 2010; van Raaij et al., 1993). Further, this is the first study that identified statistically significant associations between the disturbance in homeostasis of uric acid and creatinine and the exposure to *cis*-heptachlor expoxide, *p,p*′-DDE, and *p,p*′-DDT in the general population.

We recognize the limitations of the cohort design. Our study suffered from uncertainties due to the differences in timing of sample collection in the cross-sectional study, the potential confounding from covariates on the OCP levels over years, the changes in the participants over the 12 years, the representativeness of study participants, the possibility of false discoveries, and the lack of information of participants, such as smoking, that could influence clinical factors. In addition, the joint effects and mechanisms of action of OCPs still remain controversial. To minimize uncertainties, sampling, analyses, and statistical analysis were conducted according to the Korean Standard Operational Procedure for POPs.

Despite these limitations, this has been the first long-term study to show the temporal trends of 28 OCPs in serum and the associations with various health indicators in Korea. The validity and quality, particularly in terms of health influences, should be significantly improved in future cohort studies. The present study contributes to expand the current knowledge about potential metabolic disrupting impacts of OCPs by identifying associations with various health effects, suggests a good framework for futher work, and is a definitive reference for future cohort studies.

CRediT authorship contribution statement

Sung-Hee Seo: Writing – original draft. **Sung-Deuk Choi:** Writing – review & editing. **Stuart Batterman:** Writing – review & editing. **Yoon-Seok Chang:** Supervision, Project administration.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIP) (NO. NRF-2017R1A2B3012681).

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jhazmat.2021.127381.

References

Abdollahi, M., Ranjbar, A., Shadnia, S., Nikfar, S., Rezaie, A., 2004. Pesticides and oxidative stress: a review. Med. Sci. Monit. 10, 141–148. ⟨https://pubmed.ncbi.nlm.nih.gov/15173684/⟩.

Agency for Toxic Substances and Disease Registry (ATSDR), 2013. Toxicological Profile for Endosulfan. ⟨https://www.atsdr.cdc.gov/toxprofiles/tp41.pdf⟩.

Agency for Toxic Substances and Disease Registry (ATSDR), 2002. ToxGuide for DDT/DD/DDE. ⟨https://www.atsdr.cdc.gov/toxguides/toxguide-35.pdf⟩.

Agency for Toxic Substances and Disease Registry (ATSDR), 2007. Heptachlor and Heptachlor Epoxide. ⟨https://www.atsdr.cdc.gov/toxfaqs/tfacts12.pdf⟩.

Akishita, M., Fukai, S., Hashimoto, M., Kameyama, Y., Nomura, K., Nakamura, T., Ogawa, S., Iijima, K., Eto, M., Ouchi, Y., 2010. Association of low testosterone with metabolic syndrome and its components in middle-aged Japanese men. Hypertens. Res. 33, 587–591. https://doi.org/10.1038/hr.2010.43.

Alvarez, L., Hernández, S., Martinez-De-Mena, R., Kolliker-Frers, R., Obregón, M.J., Kleiman De Pisarev, D.L., 2005. The role of type I and type II 5′ deiodinases on hexachlorobenzene- induced alteration of the hormonal thyroid status. Toxicology 207, 349–362. https://doi.org/10.1016/j.tox.2004.10.006.

Amodio, E., Turci, R., Massenti, M.F., Di Gaudio, F., Minoia, C., Vitale, F., Firenze, A., Calamusa, G., 2012. Serum concentrations of persistent organic pollutants (POPs) in the inhabitants of a Sicilian city. Chemosphere 89, 970–974. https://doi.org/10.1016/j.chemosphere.2012.06.054.

Angulo Lucena, R., Farouk Allam, M., Serrano Jimenez, S., Luisa Jodral Villarejo, M., 2007. A review of environmental exposure to persistent organochlorine residuals during the last fifty years. Curr. Drug Saf. 2, 163–172. https://doi.org/10.2174/157488607780598313.

Araki, A., Miyashita, C., Mitsui, T., Goudarzi, H., Mizutani, F., Chisaki, Y., Itoh, S., Sasaki, S., Cho, K., Moriya, K., Shinohara, N., Nonomura, K., Kishi, R., 2018. Prenatal organochlorine pesticide exposure and the disruption of steroids and reproductive hormones in cord blood: The Hokkaido study. Environ. Int. 110, 1–13. https://doi.org/10.1016/j.envint.2017.10.006.

Arrebola, J.P., Fernández, M.F., Martin-Olmedo, P., Bonde, J.P., Martín-Rodriguez, J.L., Expósito, J., Rubio-Domínguez, A., Olea, N., 2015. Historical exposure to persistent organic pollutants and risk of incident hypertension. Environ. Res. 138, 217–223. https://doi.org/10.1016/j.envres.2015.02.018.

Arrebola, J.P., Ocaña-Riola, R., Arrebola-Moreno, A.L., Fernández-Rodríguez, M., Martin-Olmedo, P., Fernández, M.F., Olea, N., 2014. Associations of accumulated exposure to persistent organic pollutants with serum lipids and obesity in an adult cohort from Southern Spain. Environ. Pollut. 195, 9–15. https://doi.org/10.1016/j.envpol.2014.08.003.

Arrebola, J.P., Ramos, J.J., Bartolomé, M., Esteban, M., Huetos, O., Cañas, A.I., López-Herranz, A., Calvo, E., Pérez-Gómez, B., Castaño, A., 2019. Associations of multiple exposures to persistent toxic substances with the risk of hyperuricemia and subclinical uric acid levels in BIOAMBIENT.ES study. Environ. Int. 123, 512–521. https://doi.org/10.1016/j.envint.2018.12.030.

Arsenescu, V., Arsenescu, R.I., King, V., Swanson, H., Cassis, L.A., 2008. Polychlorinated biphenyl-77 induces adipocyte differentiation and proinflammatory adipokines and promotes obesity and atherosclerosis. Environ. Health Perspect. 116, 761–768. https://doi.org/10.1289/ehp.10554.

Axmon, A., Rignell-Hydbom, A., 2006. Estimations of past male and female serum concentrations of biomarkers of persistent organochlorine pollutants and their impact on fecundability estimates. Environ. Res. 101, 387–394. https://doi.org/10.1016/j.envres.2005.10.005.

Barakat, A.O., Mostafa, A., Wade, T.L., Sweet, S.T., El Sayed, N.B., 2012. Spatial distribution and temporal trends of persistent organochlorine pollutants in sediments from Lake Maryut, Alexandria, Egypt. Mar. Pollut. Bull. 64, 395–404. https://doi.org/10.1016/j.marpolbul.2011.12.019.

Barber, J.L., Sweetman, A.J., Van Wijk, D., Jones, K.C., 2005. Hexachlorobenzene in the global environment: emissions, levels, distribution, trends and processes. Sci. Total Environ. 349, 1–44. https://doi.org/10.1016/j.scitotenv.2005.03.014.

Barghi, M., Choi, S.D., Kwon, H.O., Lee, Y.S., Chang, Y.S., 2016. Influence of non-detect data-handling on toxic equivalency quantities of PCDD/Fs and dioxin-like PCBs: a case study of major fish species purchased in Korea. Environ. Pollut. 214, 532–538. https://doi.org/10.1016/j.envpol.2016.04.065.

Ben Hassine, S., Hammami, B., Ben Ameur, W., El Megdiche, Y., Barhoumi, B., El Abidi, R., Driss, M.R., 2014. Concentrations of organochlorine pesticides and polychlorinated biphenyls in human serum and their relation with age, gender, and BMI for the general population of Bizerte, Tunisia. Environ. Sci. Pollut. Res. 21, 6303–6313. https://doi.org/10.1007/s11356-013-1480-9.

Bernert, J.T., Turner, W.E., Patterson, D.G., Needham, L.L., 2007. Calculation of serum “total lipid” concentrations for the adjustment of persistent organohalogen toxicant measurements in human samples. Chemosphere 68, 824–831. https://doi.org/10.1016/j.chemosphere.2007.02.043.

Blanco-Muñoz, J., Lacasaña Navarro, M., Aguilar-Garduño, C., Rodríguez-Barranco, M., Bassol, S., Cebrián, M.E., López-Flores, I., Ruiz-Pérez, I., 2012. Effect of exposure to p,p′-DDE on male hormone profile in Mexican flower growers. Occup. Environ. Med. 69, 5–11. https://doi.org/10.1136/oem.2010.059667.

Blaylock, B.L., 2005. Chlordane. Encycl. Toxicol, Second ed., pp. 540–542. https://doi.org/10.1016/B0-12-369400-0/00211-8

Bloom, M.S., Weiner, J.M., Vena, J.E., Beehler, G.P., 2003. Exploring associations between serum levels of select organochlorines and thyroxine in a sample of New York state sportsmen: The New York State Angler Cohort Study. Environ. Res. 93, 52–66. https://doi.org/10.1016/S0013-9351(02)00085-3.

Bogacka, I., Xie, H., Bray, G.A., Smith, S.R., 2005. Pioglitazone induces mitochondrial biogenesis in human subcutaneous adipose tissue in vivo. Diabetes 54, 1392–1399. https://doi.org/10.2337/diabetes.54.5.1392.

Brent, G.A., 2012. Mechanisms of thyroid hormone action. J. Clin. Invest. 122, 3035–3043. https://doi.org/10.1172/JCI60047.

Cheek, A.O., Kow, K., Chen, J., McLachlan, J.A., 1999. Potential mechanisms of thyroid disruption in humans: Interaction of organochlorine compounds with thyroid receptor, transthyretin, and thyroid-binding globulin. Environ. Health Perspect. 107, 273–278. https://doi.org/10.1289/ehp.99107273.

Chevrier, J., Eskenazi, B., Holland, N., Bradman, A., Barr, D.B., 2008. Effects of exposure to polychlorinated biphenyls and organochlorine pesticides on thyroid function during pregnancy. Am. J. Epidemiol. 168, 298–310. https://doi.org/10.1093/aje/kwn136.

Choi, H.G., Moon, H.B., Choi, M., Yu, J., 2011. Monitoring of organic contaminants in sediments from the Korean coast: spatial distribution and temporal trends (2001-2007). Mar. Pollut. Bull. 62, 1352–1361. https://doi.org/10.1016/j.marpolbul.2011.03.029.

Choo, H.J., Kim, J.H., Kwon, O.B., Lee, C.S., Mun, J.Y., Han, S.S., Yoon, Y.S., Yoon, G., Choi, K.M., Ko, Y.G., 2006. Mitochondria are impaired in the adipocytes of type 2 diabetic mice. Diabetologia 49, 784–791. https://doi.org/10.1007/s00125-006-0170-2.

Codru, N., Schymura, M.J., Negoita, S., Rej, R., Carpenter, D.O., 2007. Diabetes in relation to serum levels of polychlorinated biphenyls and chlorinated pesticides in adult native Americans. Environ. Health Perspect. 115, 1442–1447. https://doi.org/10.1289/ehp.10315.

Cox, S., Niskar, A.S., Venkat Narayan, K.M., Marcus, M., 2007. Prevalence of self-reported diabetes and exposure to organochlorine pesticides among Mexican Americans: Hispanic health and nutrition examination survey, 1982-1984. Environ. Health Perspect. 115, 1747–1752. https://doi.org/10.1289/ehp.10258.

Dallaire, R., Dewailly, É., Pereg, D., Dery, S., Ayotte, P., 2009. Thyroid function and plasma concentrations of polyhalogenated compounds in inuit adults. Environ. Health Perspect. 117, 1380–1386. https://doi.org/10.1289/ehp.0900633.

De Pisarev, D.L.K., de Molina, M., del, C.R., de Viale, L.C.S.M., 1990. Thyroid function and thyroxine metabolism in hexachlorobenzene-induced porphyria. Biochem. Pharmacol. 39, 817–825. https://doi.org/10.1016/0006-2952(90)90195-Q.

Dearth, M.A., Hites, R.A., 1991. Depuration rates of chlordane compounds from rat fat. Environ. Sci. Technol. 25, 1125–1128. https://doi.org/10.1021/es00018a016.

Dirtu, A.C., Cernat, R., Dragan, D., Mocanu, R., Van Grieken, R., Neels, H., Covaci, A., 2006. Organohalogenated pollutants in human serum from Iassy, Romania and their relation with age and gender. Environ. Int. 32, 797–803. https://doi.org/10.1016/j.envint.2006.04.002.

Dirtu, A.C., Covaci, A., 2010. Estimation of daily intake of organohalogenated contaminants from food consumption and indoor dust ingestion in Romania. Environ. Sci. Technol. 44, 6297–6304. https://doi.org/10.1021/es101233z.

El Megid, A.A., Abd Al Fatah, M.E., El Asely, A., El Senosi, Y., Moustafa, M.M.A., Dawood, M.A.O., 2020. Impact of pyrethroids and organochlorine pesticides residue on IGF-1 and CYP1A genes expression and muscle protein patterns of cultured Mugil capito. Ecotoxicol. Environ. Saf. 188, 109876 https://doi.org/10.1016/j.ecoenv.2019.109876.

Ellsworth, R.E., Kostyniak, P.J., Chi, L.H., Shriver, C.D., Costantino, N.S., Ellsworth, D.L., 2018. Organochlorine pesticide residues in human breast tissue and their relationships with clinical and pathological characteristics of breast cancer. Environ. Toxicol. 33, 876–884. https://doi.org/10.1002/tox.22573.

Eraly, S.A., Vallon, V., Rieg, T., Gangoiti, J.A., Wikoff, W.R., Siuzdak, G., Barshop, B.A., Nigam, S.K., 2008. Multiple organic anion transporters contribute to net renal excretion of uric acid. Physiol. Genom. 33, 180–192. https://doi.org/10.1152/physiolgenomics.00207.2007.

Francisco, A.C., Leon, J., Saénz, J.M., Fernandez, M.F., Piedad, M.O., Olea, N., Arrebola, J.P., 2016. Contribution of persistent organic pollutant exposure to the adipose tissue oxidative microenvironment in an adult cohort: a multipollutant approach. Environ. Sci. Technol. 50, 13529–13538. https://doi.org/10.1021/acs.est.6b03783.

Freire, C., Koifman, R.J., Sarcinelli, P.N., Rosa, A.C.S., Clapauch, R., Koifman, S., 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, 370–378. https://doi.org/10.1016/j.ijheh.2013.07.012.

Fujiyosh, P.T., Michalek, J.E., Matsumura, F., 2006. Molecular epidemiologic evidence for diabetogenic effects of dioxin exposure in U.S. Air Force veterans of the Vietnam war. Environ. Health Perspect. 114, 1677–1683. https://doi.org/10.1289/ehp.9262.

Gerlienke Schuur, A., Brouwer, A., Bergman, Å., Coughtrie, M.W.H., Visser, T.J., 1998. Inhibition of thyroid hormone sulfation by hydroxylated metabolites of polychlorinated biphenyls. Chem. Biol. Interact. 109, 293–297. https://doi.org/10.1016/S0009-2797(97)00140-3.

German, M.S., 1993. Glucose sensing in pancreatic islet beta cells: The key role of glucokinase and the glycolytic intermediates. Proc. Natl. Acad. Sci. U. S. A. 90, 1781–1785. https://doi.org/10.1073/pnas.90.5.1781.

Gómez-Ramírez, P., Pérez-García, J.M., León-Ortega, M., Martínez, J.E., Calvo, J.F., Sánchez-Zapata, J.A., Botella, F., María-Mojica, P., Martínez-López, E., García-Fernández, A.J., 2019. Spatiotemporal variations of organochlorine pesticides in an apex predator: Influence of government regulations and farming practices. Environ. Res. 176, 108543 https://doi.org/10.1016/j.envres.2019.108543.

Hammarstedt, A., Jansson, P.A., Wesslau, C., Yang, X., Smith, U., 2003. Reduced expression of PGC-1 and insulin-signaling molecules in adipose tissue is associated with insulin resistance. Biochem. Biophys. Res. Commun. 301, 578–582. https://doi.org/10.1016/S0006-291X(03)00014-7.

Hayden, M.R., Tyagi, S.C., 2004. Uric acid: a new look at an old risk marker for cardiovascular disease, metabolic syndrome, and type 2 diabetes mellitus: The urate redox shuttle. Nutr. Metab. 1, 3–13. https://doi.org/10.1186/1743-7075-1-10.

Heinig, M., Johnson, R.J., 2006. Role of uric acid in hypertension, renal disease, and metabolic syndrome. Cleve. Clin. J. Med. 73, 1059–1064. https://doi.org/10.3949/ccjm.73.12.1059.

Hinck, J.E., Norstrom, R.J., Orazio, C.E., Schmitt, C.J., Tillitt, D.E., 2009. Persistence of organochlorine chemical residues in fish from the Tombigbee River (Alabama, USA): Continuing risk to wildlife from a former DDT manufacturing facility. Environ. Pollut. 157, 582–591. https://doi.org/10.1016/j.envpol.2008.08.021.

Holt, E., Audy, O., Booij, P., Melymuk, L., Prokes, R., Klánová, J., 2017. Organochlorine pesticides in the indoor air of a theatre and museum in the Czech Republic: Inhalation exposure and cancer risk. Sci. Total Environ. 609, 598–606. https://doi.org/10.1016/j.scitotenv.2017.07.203.

Itoh, H., Iwasaki, M., Hanaoka, T., Kasuga, Y., Yokoyama, S., Onuma, H., Nishimura, H., Kusama, R., Tsugane, S., 2009. Serum organochlorines and breast cancer risk in Japanese women: a case-control study. Cancer Causes Control 20, 567–580. https://doi.org/10.1007/s10552-008-9265-z.

Jaraczewska, K., Lulek, J., Covaci, A., Voorspoels, S., Kaluba-Skotarczak, A., Drews, K., Schepens, P., 2006. Distribution of polychlorinated biphenyls, organochlorine pesticides and polybrominated diphenyl ethers in human umbilical cord serum, maternal serum and milk from Wielkopolska region, Poland. Sci. Total Environ. 372, 20–31. https://doi.org/10.1016/j.scitotenv.2006.03.030.

Jiang, G., Li, X., 2020. A new paradigm toxicology chemistry and for environmental: From concepts to insights. ⟨https://link.springer.com/content/pdf/10.1007/978–981-13–9447-8.pdf⟩.

Jørgensen, M.E., Borch-Johnsen, K., Bjerregaard, P., 2008. A cross-sectional study of the association between persistent organic pollutants and glucose intolerance among Greenland Inuit. Diabetologia 51, 1416–1422. https://doi.org/10.1007/s00125-008-1066-0.

Jung, D., Becher, H., Edler, L., Flesch-Janys, D., Gurn, P., Konietzko, J., M, A., P, O., 1997. Elimination of β-hexachlorocyclohexane in occupationally exposed persons. J. Toxicol. Environ. Health 51, 23–34. ⟨https://pubmed.ncbi.nlm.nih.gov/9169059/⟩.

Kang, J.H., Park, H., Chang, Y.S., Choi, J.W., 2008. Distribution of organochlorine pesticides (OCPs) and polychlorinated biphenyls (PCBs) in human serum from urban areas in Korea. Chemosphere 73, 1625–1631. https://doi.org/10.1016/j.chemosphere.2008.07.087.

Kang, J.H. and Chang, Y.S., 2011. Organochlorine pesticides in human serum, Pesticides: Strategies for Pesticides Analysis. ⟨https://www.researchgate.net/profile/Margarita-Stoytcheva/publication/275883453_Pesticides_-Strategies_for_Pesticides_Analysis/links/55487e9f0cf2b0cf7acec580/Pesticides-Strategies-for-Pesticides-Analysis.pdf#page=228⟩.

Kataria, A., Trachtman, H., Malaga-Dieguez, L., Trasande, L., 2015. Association between perfluoroalkyl acids and kidney function in a cross-sectional study of adolescents. Environ. Heal. A Glob. Access Sci. Source 14, 1–13. https://doi.org/10.1186/s12940-015-0077-9.

Khuman, S.N., Vinod, P.G., Bharat, G., Kumar, Y.S.M., Chakraborty, P., 2020. Spatial distribution and compositional profiles of organochlorine pesticides in the surface soil from the agricultural, coastal and backwater transects along the south-west coast of India. Chemosphere 254, 126699. https://doi.org/10.1016/j.chemosphere.2020.126699.

Kim, B.H., Lee, S.J., Mun, S.J., Chang, Y.S., 2005. A case study of dioxin monitoring in and around an industrial waste incinerator in Korea. Chemosphere 58, 1589–1599. https://doi.org/10.1016/j.chemosphere.2004.10.041.

Kim, L., Jeon, J.W., Son, J.Y., Kim, C.S., Ye, J., Kim, H.J., Lee, C.H., Hwang, S.M., Choi, S. D., 2020. Nationwide levels and distribution of endosulfan in air, soil, water, and sediment in South Korea. Environ. Pollut. 265, 115035 https://doi.org/10.1016/j.envpol.2020.115035.

Kim, S.K., 2020. Trophic transfer of organochlorine pesticides through food-chain in coastal marine ecosystem. Environ. Eng. Res. 25, 43–51. https://doi.org/10.4491/eer.2019.003.

Kim, S.K., Yoon, J., 2014. Chronological trends of emission, environmental level and human exposure of POPs over the last 10years (1999-2010) in Korea: Implication to science and policy. Sci. Total Environ. 470–471, 1346–1361. https://doi.org/10.1016/j.scitotenv.2013.07.031.

Kim, Sunmi, Park, J., Kim, H.J., Lee, J.J., Choi, G., Choi, S., Kim, Sungjoo, Kim, S.Y., Moon, H.B., Kim, Sungkyoon, Choi, K., 2013. Association between several persistent organic pollutants and thyroid hormone levels in serum among the pregnant women of Korea. Environ. Int. 59, 442–448. https://doi.org/10.1016/j.envint.2013.07.009.

Kutz, F.W., Wood, P.H., Bottimore, D.P., 1991. Organochlorine pesticides and polychlorinated biphenyls in human adipose tissue. Rev. Environ. Contam. Toxicol. 120. ⟨https://link.springer.com/chapter/10.1007/978-1-4612-3080-9_1⟩.

Lee, D.H., Lind, P.M., Jacobs, D.R., Salihovic, S., Van Bavel, B., Lind, L., 2011a. Polychlorinated biphenyls and organochlorine pesticides in plasma predict development of type 2 diabetes in the elderly: The Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study. Diabetes Care 34, 1778–1784. https://doi.org/10.2337/dc10-2116.

Lee, D.H., Steffes, M.W., Sjödin, A., Jones, R.S., Needham, L.L., Jacobs, D.R., 2011b. Low dose organochlorine pesticides and polychlorinated biphenyls predict obesity, dyslipidemia, and insulin resistance among people free of diabetes. PLoS One 6. https://doi.org/10.1371/journal.pone.0015977.

Lee, H.S., Lee, J.C., Lee, I.K., Moon, H.B., Chang, Y.S., Jacobs, D.R., Lee, D.H., 2011. Associations among organochlorine pesticides, methanobacteriales, and obesity in Korean women. PLoS One 6, 4–9. https://doi.org/10.1371/journal.pone.0027773.

Lee, S.A., Dai, Q., Zheng, W., Gao, Y.T., Blair, A., Tessari, J.D., Tian Ji, B., Shu, X.O., 2007. Association of serum concentration of organochlorine pesticides with dietary intake and other lifestyle factors among urban Chinese women. Environ. Int. 33, 157–163. https://doi.org/10.1016/j.envint.2006.08.010.

Lee, S.E., Han, K., Kang, Y.M., Kim, S.O., Cho, Y.K., Ko, K.S., Park, J.Y., Lee, K.U., Koh, E. H., 2018. Trends in the prevalence of metabolic syndrome and its components in South Korea: findings from the Korean National Health Insurance Service Database (2009–2013). PLoS One 13. https://doi.org/10.1371/journal.pone.0194490.

Lee, Y.M., Bae, S.G., Lee, S.H., Jacobs, D.R., Lee, D.H., 2013. Persistent organic pollutants and hyperuricemia in the U.S. general population. Atherosclerosis 230, 1–5. https://doi.org/10.1016/j.atherosclerosis.2013.06.012.

Lee, Y.M., Ha, C.M., Kim, S.A., Thoudam, T., Yoon, Y.R., Kim, D.J., Kim, H.C., Moon, H. B., Park, S., Lee, I.K., Lee, D.H., 2017. Low-dose persistent organic pollutants impair insulin secretory function of pancreatic b-cells: human and in vitro evidence. Diabetes 66, 2669–2680. https://doi.org/10.2337/db17-0188.

Lee, Y.M., Kim, K.S., Kim, S.A., Hong, N.S., Lee, S.J., Lee, D.H., 2014. Prospective associations between persistent organic pollutants and metabolic syndrome: a nested case-control study. Sci. Total Environ. 496, 219–225. https://doi.org/10.1016/j.scitotenv.2014.07.039.

Li, J., Zhang, G., Guo, L., Xu, W., Li, X., Lee, C.S.L., Ding, A., Wang, T., 2007. Organochlorine pesticides in the atmosphere of Guangzhou and Hong Kong: regional sources and long-range atmospheric transport. Atmos. Environ. 41, 3889–3903. https://doi.org/10.1016/j.atmosenv.2006.12.052.

Lim, J.U., Lee, J.H., Kim, J.S., Hwang, Y., Il, Kim, T., Yong, S., Yoo, K.H., 2017. Comparison of World Health Organization and Asia-Pacific Body Mass Index Classifications in Copd Patient. Respirology 22, 4. https://doi.org/10.1111/resp.13206.

Lind, P.M., Penell, J., Salihovic, S., van Bavel, B., Lind, L., 2014. Circulating levels of p,p′-DDE are related to prevalent hypertension in the elderly. Environ. Res. 129, 27–31. https://doi.org/10.1016/j.envres.2013.12.003.

Louis, E.D., Factor-Litvak, P., Parides, M., Andrews, L., Santella, R.M., Wolff, M.S., 2006. Organochlorine pesticide exposure in essential tremor: a case-control study using biological and occupational exposure assessments. Neurotoxicology 27, 579–586. https://doi.org/10.1016/j.neuro.2006.03.005.

Maervoet, J., Vermeir, G., Covaci, A., Van Larebeke, N., Koppen, G., Schoeters, G., Nelen, V., Baeyens, W., Schepens, P., Viaene, M.K., 2007. Association of thyroid hormone concentrations with levels of organochlorine compounds in cord blood of neonates. Environ. Health Perspect. 115, 1780–1786. https://doi.org/10.1289/ehp.10486.

Maisano, M., Cappello, T., Oliva, S., Natalotto, A., Giannetto, A., Parrino, V., Battaglia, P., Romeo, T., Salvo, A., Spanò, N., Mauceri, A., 2016. PCB and OCP accumulation and evidence of hepatic alteration in the Atlantic bluefin tuna, T. thynnus, from the Mediterranean Sea. Mar. Environ. Res. 121, 40–48. https://doi.org/10.1016/j.marenvres.2016.03.003.

Masi, C.M., Hawkley, L.C., Berry, J.D., Cacioppo, J.T., 2006. Estrogen metabolites and systolic blood pressure in a population-based sample of postmenopausal women. J. Clin. Endocrinol. Metab. 91, 1015–1020. https://doi.org/10.1210/jc.2005-2339.

Meng, J., Hong, S., Wang, T., Li, Q., Yoon, S.J., Lu, Y., Giesy, J.P., Khim, J.S., 2017. Traditional and new POPs in environments along the Bohai and Yellow Seas: an overview of China and South Korea. Chemosphere 169, 503–515. https://doi.org/10.1016/j.chemosphere.2016.11.108.

Ministry of Environment (MOE), 2019. Restrictions on the manufacture, export and use of persistent organic pollutants. ⟨https://ncis.nier.go.kr/main.do⟩.

Mocking, R.J.T., Assies, J., Lok, A., Ruhé, H.G., Koeter, M.W.J., Visser, I., Bockting, C.L. H., Schene, A.H., 2012. Statistical methodological issues in handling of fatty acid data: percentage or concentration, imputation and indices. Lipids 47, 541–547. https://doi.org/10.1007/s11745-012-3665-2.

Moon, H.B., Park, B.K., Kim, H.S., 2009. Human health risk of chlorobenzenes associated with seafood consumption in Korea. Toxicol. Environ. Health Sci. 1, 49–55. https://doi.org/10.1007/BF03216463.

Müller, M.H.B., Polder, A., Brynildsrud, O.B., Karimi, M., Lie, E., Manyilizu, W.B., Mdegela, R.H., Mokiti, F., Murtadha, M., Nonga, H.E., Skaare, J.U., Lyche, J.L., 2017. Organochlorine pesticides (OCPs) and polychlorinated biphenyls (PCBs) in human breast milk and associated health risks to nursing infants in Northern

Tanzania. Environ. Res. 154, 425–434. https://doi.org/10.1016/j.envres.2017.01.031.
Muoio, D.M., Newgard, C.B., 2008. Mechanisms of disease: Molecular and metabolic mechanisms of insulin resistance and β-cell failure in type 2 diabetes. Nat. Rev. Mol. Cell Biol. 9, 193–205. https://doi.org/10.1038/nrm2327.
National Center for Biotechnology Information (NCBI), 2005a. Endrin. ⟨https://pubchem.ncbi.nlm.nih.gov⟩ ⟩ compound ⟩ Endrin.
National Center for Biotechnology Information (NCBI), 2005b. Mirex. ⟨https://pubchem.ncbi.nlm.nih.gov⟩ ⟩ compound ⟩ Mirex.
Natlonal institute of environmental research (NIER), 2017. Clean Air Policy Support System (CAPSS). ⟨http://airemiss.nier.go.kr/⟩.
Nowell, L.H., Crawford, C.G., Gilliom, R.J., Nakagaki, N., Stone, W.W., Thelin, G.P., Wolock, D.M., 2009. Regression models for explaining and predicting concentrations of organochlorine pesticides in fish from streams in the United States. Environ. Toxicol. Chem. 28, 1346–1358. https://doi.org/10.1897/08-508.1.
Ogden, C.L., Fryar, C.D., Carroll, M.D., Flegal, K.M., 2004. Mean body weight, height, and body mass index, United States 1960-2002. Adv. Data 1–17. ⟨https://pubmed.ncbi.nlm.nih.gov/15544194/⟩.
Panaretakis, T., Shabalina, I.G., Grandér, D., Shoshan, M.C., Depierre, J.W., 2001. Reactive oxygen species and mitochondria mediate the induction of apoptosis in human hepatoma HepG2 cells by the rodent peroxisome proliferator and hepatocarcinogen, perfluorooctanoic acid. Toxicol. Appl. Pharmacol. 173, 56–64. https://doi.org/10.1006/taap.2001.9159.
Parish, R., Petersen, K.F., 2005. Mitochondrial dysfunction and type 2 diabetes. Curr. Diab. Rep. 5, 177–183. https://doi.org/10.1007/s11892-005-0006-3.
Park, S.H., Ha, E., Hong, Y.S., Park, H., 2016. Serum levels of persistent organic pollutants and insulin secretion among children age 7–9 years: A prospective cohort study. Environ. Health Perspect. 124, 1924–1930. https://doi.org/10.1289/EHP147.
Park, S.K., Son, H.K., Lee, S.K., Kang, J.H., Chang, Y.S., Jacobs, D.R., Lee, D.H., 2010. Relationship between serum concentrations of organochlorine pesticides and metabolic syndrome among non-diabetic adults. J. Prev. Med. Public Heal. 43, 1–18. https://doi.org/10.3961/jpmph.2010.43.1.1.
Perrone, R.D., Madias, N.E., Levey, A.S., 1992. Serum creatinine as an index of renal function: New insights into old concepts. Clin. Chem. 38, 1933–1953. https://doi.org/10.1093/clinchem/38.10.1933.
Petrik, J., Drobna, B., Pavuk, M., Jursa, S., Wimmerova, S., Chovancova, J., 2006. Serum PCBs and organochlorine pesticides in Slovakia: Age, gender, and residence as determinants of organochlorine concentrations. Chemosphere 65, 410–418. https://doi.org/10.1016/j.chemosphere.2006.02.002.
Philibert, A., Schwartz, H., Mergler, D., 2009. An exploratory study of diabetes in a first nation community with respect to serum concentrations of p,p′-DDE and PCBs and fish consumption. Int. J. Environ. Res. Public Health 6, 3179–3189. https://doi.org/10.3390/ijerph6123179.
Polder, A., Thomsen, C., Lindström, G., Løken, K.B., Skaare, J.U., 2008. Levels and temporal trends of chlorinated pesticides, polychlorinated biphenyls and brominated flame retardants in individual human breast milk samples from Northern and Southern Norway. Chemosphere 73, 14–23. https://doi.org/10.1016/j.chemosphere.2008.06.002.
Porta, M., López, T., Gasull, M., Rodríguez-Sanz, M., Garí, M., Pumarega, J., Borrell, C., Grimalt, J.O., 2012. Distribution of blood concentrations of persistent organic pollutants in a representative sample of the population of Barcelona in 2006, and comparison with levels in 2002. Sci. Total Environ. 423, 151–161. https://doi.org/10.1016/j.scitotenv.2012.02.001.
Qiu, Y.W., Zhang, G., Guo, L.L., Cheng, H.R., Wang, W.X., Li, X.D., Wai, O.W.H., 2009. Current status and historical trends of organochlorine pesticides in the ecosystem of Deep Bay, South China. Estuar. Coast. Shelf Sci. 85, 265–272. https://doi.org/10.1016/j.ecss.2009.08.010.
Rignell-Hydbom, A., Lidfeldt, J., Kiviranta, H., Rantakokko, P., Samsioe, G., Agardh, C. D., Rylander, L., 2009. Exposure to p,p′-DDE: A risk factor for type 2 diabetes. PLoS One 4, 5–10. https://doi.org/10.1371/journal.pone.0007503.
Roberts, E.M., English, P.B., Grether, J.K., Windham, G.C., Somberg, L., Wolff, C., 2007. Maternal residence near agricultural pesticide applications and autism spectrum disorders among children in the California Central Valley. Environ. Health Perspect. 115, 1482–1489. https://doi.org/10.1289/ehp.10168.
Ruzzin, J., Petersen, R., Meugnier, E., Madsen, L., Lock, E.J., Lillefosse, H., Ma, T., Pesenti, S., Sonne, S.B., Marstrand, T.T., Malde, M.K., Du, Z.Y., Chavey, C., Fajas, L., Lundebye, A.K., Brand, C.L., Vidal, H., Kristiansen, K., Frøyland, L., 2010. Persistent organic pollutant exposure leads to insulin resistance syndrome. Environ. Health Perspect. 118, 465–471. https://doi.org/10.1289/ehp.0901321.
Saoudi, A., Fréry, N., Zeghnoun, A., Bidondo, M.L., Deschamps, V., Göen, T., Garnier, R., Guldner, L., 2014. Serum levels of organochlorine pesticides in the French adult population: The French National Nutrition and Health Study (ENNS), 2006-2007. Sci. Total Environ. 472, 1089–1099. https://doi.org/10.1016/j.scitotenv.2013.11.044.
Schade, G., Heinzow, B., 1998. Organochlorine pesticides and polychlorinated biphenyls in human milk of mothers living in northern Germany: current extent of contamination, time trend from 1986 to 1997 and factors that influence the levels of contamination. Sci. Total Environ. 215, 31–39. https://doi.org/10.1016/S0048-9697(98)00008-4.
Schisterman, E.F., Whitcomb, B.W., Buck Louis, G.M., Louis, T.A., 2005. Lipid adjustment in the analysis of environmental contaminants and human health risks. Environ. Health Perspect. 113, 853–857. https://doi.org/10.1289/ehp.7640.
Schussler, G.C., 2000. The thyroxine-binding proteins. Thyroid 10, 141–149. https://doi.org/10.1089/thy.2000.10.141.
Seo, S.H., Kwon, S.Y., Choi, S.D., Chang, Y.S., 2020. Twenty-year trends and exposure assessment of polychlorinated dibenzodioxins and dibenzofurans in human serum from the Seoul citizens. Chemosphere, 128558. https://doi.org/10.1016/j.chemosphere.2020.128558.
Seo, S.H., Son, M.H., Choi, S.D., Lee, D.H., Chang, Y.S., 2018. Influence of exposure to perfluoroalkyl substances (PFASs) on the Korean general population: 10-year trend and health effects. Environ. Int. 113, 149–161. https://doi.org/10.1016/j.envint.2018.01.025.
Seoul Resource Recovery Facility (SRRF), 2017. The Health Assessment Study of Seoul Citizens, 2006–2017. ⟨https://rrf.seoul.go.kr/content/ecena512.do⟩.
Serdar, B., LeBlanc, W.G., Norris, J.M., Miriam Dickinson, L., 2014. Potential effects of polychlorinated biphenyls (PCBs) and selected organochlorine pesticides (OCPs) on immune cells and blood biochemistry measures: a cross-sectional assessment of the NHANES 2003-2004 data. Environ. Heal. A Glob. Access Sci. Source 13, 1–12. https://doi.org/10.1186/1476-069X-13-114.
Shankar, A., Klein, R., Klein, B.E.K., Nieto, F.J., 2006. The association between serum uric acid level and long-term incidence of hypertension: Population-based cohort study. J. Hum. Hypertens. 20, 937–945. https://doi.org/10.1038/sj.jhh.1002095.
Sharma, B.M., Bharat, G.K., Tayal, S., Nizzetto, L., Čupr, P., Larssen, T., 2014. Environment and human exposure to persistent organic pollutants (POPs) in India: A systematic review of recent and historical data. Environ. Int. 66, 48–64. https://doi.org/10.1016/j.envint.2014.01.022.
Siddarth, M., Datta, S.K., Mustafa, M.D., Ahmed, R.S., Banerjee, B.D., Kalra, O.P., Tripathi, A.K., 2014. Increased level of organochlorine pesticides in chronic kidney disease patients of unknown etiology: Role of GSTM1/GSTT1 polymorphism. Chemosphere 96, 174–179. https://doi.org/10.1016/j.chemosphere.2013.10.029.
Siddharth, M., Datta, S.K., Bansal, S., Mustafa, M., Banerjee, B.D., Kalra, O.P., Tripathi, A.K., 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, 241–247. https://doi.org/10.1002/jbt.21416.
Soliman, A.S., Bondy, M.L., Smith, M.A., Cooper, S.P., McPherson, R.S., Ismail, K., Seifeldin, I.A., Khaled, H., Ismail, S., 1997. Serum organochlorine pesticide levels in patients with colorectal cancer in egypt. Arch. Environ. Health 52, 409–415. https://doi.org/10.1080/00039899709602219.
Son, H.K., Kim, S.A., Kang, J.H., Chang, Y.S., Park, S.K., Lee, S.K., Jacobs, D.R., Lee, D.H., 2010. Strong associations between low-dose organochlorine pesticides and type 2 diabetes in Korea. Environ. Int. 36, 410–414. https://doi.org/10.1016/j.envint.2010.02.012.
Svartberg, J., von Mühlen, D., Schirmer, H., Barrett-Connor, E., Sundfjord, J., Jorde, R., 2004. Association of endogenous testosterone with blood pressure and left ventricular mass in men. The Tromsø study. Eur. J. Endocrinol. 150, 65–71. https://doi.org/10.1530/eje.0.1500065.
Takser, L., Mergler, D., Baldwin, M., de Grosbois, S., Smargiassi, A., Lafond, J., 2005. Thyroid hormones in pregnancy in relation to environmental exposure to organochlorine compounds and mercury. Environ. Health Perspect. 113, 1039–1045. https://doi.org/10.1289/ehp.7685.
The Stockholm Convention (SC), 2019. All POPs listed in the Stockholm Convention. ⟨http://www.pops.int/TheConvention/⟩.
Thomas, A., Toms, L.M.L., Harden, F.A., Hobson, P., White, N.M., Mengersen, K.L., Mueller, J.F., 2017. Concentrations of organochlorine pesticides in pooled human serum by age and gender. Environ. Res. 154, 10–18. https://doi.org/10.1016/j.envres.2016.12.009.
Thomas, M., Lazartigues, A., Banas, D., Brun-Bellut, J., Feidt, C., 2012. Organochlorine pesticides and polychlorinated biphenyls in sediments and fish from freshwater cultured fish ponds in different agricultural contexts in north-eastern France. Ecotoxicol. Environ. Saf. 77, 35–44. https://doi.org/10.1016/j.ecoenv.2011.10.018.
Turyk, M., Anderson, H., Knobeloch, L., Imm, P., Persky, V., 2009. Organochlorine exposure and incidence of diabetes in a cohort of great lakes sport fish consumers. Environ. Health Perspect. 117, 1076–1082. https://doi.org/10.1289/ehp.0800281.
United States Environmental Protection Agency (US EPA)United States Environmental Protection Agency (US EPA), 1991. Chemical Concentration Data Near The Detection Limit. ⟨https://nepis.epa.gov/Exe/tiff2png.exe/9100S9OP.PNG?-r+75+-g+7+D%3A%5CZYFILES%5CINDEX%20Dat%5C91THRU94%5CTIFF%5C00002404%5C9100S9OP.TIF⟩.
van Raaij, J.A.G.M., Kaptein, E., Visser, T.J., van den Berg, K.J., 1993. Increased glucuronidation of thyroid hormone in hexachlorobenzene-treated rats. Biochem. Pharmacol. 45, 627–631. https://doi.org/10.1016/0006-2952(93)90136-K.
Waliszewski, S.M., Caba, M., Herrero-Mercado, M., Saldariaga-Noreña, H., Meza, E., Zepeda, R., Martínez-Valenzuela, C., Arroyo, S.G., Pietrini, R.V., 2012. Organochlorine pesticide residue levels in blood serum of inhabitants from Veracruz, Mexico. Environ. Monit. Assess. 184, 5613–5621. https://doi.org/10.1007/s10661-011-2366-2.
Woodruff, T.J., Zota, A.R., Schwartz, J.M., 2011. Environmental chemicals in pregnant women in the united states: NHANES 2003- 2004. Environ. Health Perspect. 119, 878–885. https://doi.org/10.1289/ehp.1002727.
World Health Organization (WHO)World Health Organization (WHO), 2018. Pesticide. ⟨https://www.who.int/topics/pesticides/en/⟩.
Xu, L., Freeman, G., Cowling, B.J., Schooling, C.M., 2013. Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomized trials. BMC Med 11. https://doi.org/10.1186/1741-7015-11-108.
Xu, M.X., Yan, J.H., Lu, S.Y., Li, X.D., Chen, T., Ni, M.J., Dai, H.F., Wang, F., Cen, K.F., 2009. Concentrations, profiles, and sources of atmospheric PCDD/Fs near a municipal solid waste incinerator in Eastern China. Environ. Sci. Technol. 43, 1023–1029. https://doi.org/10.1021/es802183b.

Zhang, G., Pan, Z., Bai, A., Li, J., Li, X., 2014. Distribution and bioaccumulation of organochlorine pesticides (OCPs) in food web of Nansi Lake, China. Environ. Monit. Assess. 186, 2039–2051. https://doi.org/10.1007/s10661-013-3516-5.

Zhou, P., Zhao, Y., Li, J., Wu, G., Zhang, L., Liu, Q., Fan, S., Yang, X., Li, X., Wu, Y., 2012. Dietary exposure to persistent organochlorine pesticides in 2007 Chinese total diet study. Environ. Int. 42, 152–159. https://doi.org/10.1016/j.envint.2011.05.018.

Zhou, S., Yang, H., Zhang, A., Li, Y.F., Liu, W., 2014. Distribution of organochlorine pesticides in sediments from Yangtze River Estuary and the adjacent East China Sea: Implication of transport, sources and trends. Chemosphere 114, 26–34. https://doi.org/10.1016/j.chemosphere.2014.03.100.