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Publication Date

2018

DOI

10.1016/j.envres.2017.10.031

Peer reviewed

HHS Public Access

Author manuscript

Environ Res. Author manuscript; available in PMC 2019 February 15.

Published in final edited form as:

Environ Res. 2018 January ; 160: 541–546. doi:10.1016/j.envres.2017.10.031.

The association between p,p′-DDE levels and left ventricular mass is mainly mediated by obesity

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Abstract

Background and objectives: The pesticide metabolite p,p′-DDE has been associated with left ventricular (LV) mass and known risk factors for LV hypertrophy in humans and in experimental models. We hypothesized that the associations of p,p′-DDE with LV hypertrophy risk factors, namely elevated glucose, adiposity and hypertension, mediate the association of p,p′-DDE with LV mass.

Methods: p,p′-DDE was measured in plasma from 70-year-old subjects (n = 988) of the Prospective Study of the Vasculature in Uppsala Seniors (PIVUS). When these subjects were 70-, 75- and 80- years old, LV characteristics were measured by echocardiography, while fasting glucose, body mass index (BMI) and blood pressure were assessed with standard clinical techniques.

Results: We found that p,p′-DDE levels were associated with increased fasting glucose, BMI, hypertension and LV mass in separate models adjusted for sex. Structural equation modeling revealed that the association between p,p′-DDE and LV mass was almost entirely mediated by BMI (70%), and also by hypertension (19%).

Conclusion: The obesogenic effect of p,p′-DDE is a major determinant responsible for the association of p,p′-DDE with LV mass.

Keywords

P,p′-DDE; Left ventricular hypertrophy; Obesity; Glucose; Hypertension

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.envres.2017.10.031.

1. Introduction

Cardiovascular disease (CVD) remains the leading cause of mortality worldwide (Mortality and Causes of Death, 2016). Increased risk of CVD mortality is consistently associated with increased left ventricular (LV) mass and hypertrophy (Levy et al., 1990). LV hypertrophy is also a risk factor for heart failure, stroke and coronary heart disease (Gradman and Alfayoumi, 2006). As such, LV hypertrophy is an important indicator of preclinical CVD. A minority of cases of LV hypertrophy, known as hypertrophic cardiomyopathies, are attributable to genetic risk (Gersh et al., 2011). However, the majority of LV hypertrophy cases without a genetic cause are attributed to hypertension (Gradman and Alfayoumi, 2006). Other metabolic risk factors for LV hypertrophy include elevations in blood glucose (Chen et al., 2015) and adiposity (Chumlea et al., 2009).

The possibility that LV hypertrophy could result from environmental causes is exemplified by salt intake, where a high salt diet is a risk factor for developing both hypertension and cardiac hypertrophy (de la Sierra et al., 1996; Lal et al., 2003). The persistent organic pollutant (POP) 1,1-dichloro-2,2-bis(4-dichlordiphenyl) ethylene (p,p′-DDE), the metabolite of the organochlorine pesticide 1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane (p,p′-DDT) appears to be another type of environment influence that may serves as a risk factor for cardiac hypertrophy by targeting metabolic abnormalities. Numerous recent systematic reviews and meta-analyses found p,p′-DDE was positively associated with obesity, diabetes mellitus, and hypertension (Evangelou et al., 2016; Park et al., 2016; Song et al., 2016; Tang-Peronard et al., 2011; Wang et al., 2016). Two meta-analyses estimated meta odds ratios (95% confidence intervals) for the association of highest to lowest p,p′-DDE concentration categories and type 2 diabetes of 1.95 (1.44, 2.66) and 2.30 (1.81, 2.93) among studies in North America, Europe, and Asia-Pacific (Evangelou et al., 2016; Song et al., 2016). This was further supported by dose response analysis (Song et al., 2016). Additionally, a meta-analysis of prospective studies found a positive association between p,p′-DDE exposure and later adiposity (meta-beta = 0.13 BMI z-score (95% CI 0.01; 0.25) per log increase of p,p′-DDE (Cano-Sancho et al., 2017)). Cano-Sancho et al. (2017) classified p,p′-DDE and p,p′-DDT as presumed to be obesogenic in humans based on the human meta-analysis, increased adiposity of two rodent species exposed to p,p′-DDT (and thus p,p′-DDE), and meta-analysis of obesity-related outcomes *in vitro*.

Two studies suggest that p,p′-DDT and p,p′-DDE are also associated with increased left ventricular mass. In the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study, after adjusting for hypertension, diabetes and obesity, the association between p,p′-DDE and left ventricular mass was no longer significant (Sjoberg Lind et al., 2013), raising the possibility of mediation by these LV hypertrophy risk factors. Indeed, a second study that was performed in mice recently suggested that increased LV mass was a consequence of exposure to technical DDT (La Merrill et al., 2016). These DDT-exposed mice also had elevated blood pressure, adiposity and insulin resistance (La Merrill et al., 2014, 2016), raising the possibility that their increased LV mass was mediated by these metabolic risk factors for LV hypertrophy. Given the mice exposed to technical DDT had circulating levels of p,p′-DDT and p,p′-DDE that were within the range reported in people

from North America, Europe, and Africa, their resulting cardiometabolic toxicities could be relevant to human p,p′-DDT and/or p,p′-DDE exposure conditions.

To explore the intricate interplay between p,p′-DDE exposure and LV hypertrophy risk factors on one hand, and p,p′-DDE exposure and LV mass on the other hand, we utilized longitudinal follow-up data from the PIVUS cohort to evaluate whether p,p′-DDE exposure is associated with increased LV mass over time, and explicitly tested whether such an association was mediated by hypertension and metabolic risk factors for LV hypertrophy using structural equation modeling (SEM).

2. Material and methods

2.1. Study Subjects

All subjects confirmed to be living in the community of Uppsala, Sweden according to the register of community living and 70 years old were eligible for this study. The subjects received an invitation by letter within two months of their 70th birthday in randomized order. Of the 2025 invited subjects, 1016 subjects participated (50.1%). Fifty % of the population were female. The baseline investigation was started in April 2001 and completed June 2004 (Lind et al., 2005). The participants were asked to answer a questionnaire about their medical history, smoking and regular medication. All participants were investigated in the morning after an overnight fast. No medication or smoking were allowed after midnight. After five and ten years, all individuals were invited to re-examinations. 826 and 604 subjects participated in the two re-examinations, respectively. The protocol was essentially the same at all investigations, except that serum p,p′-DDE levels were only measured at age 70 years. The study was approved by the Ethics Committee of Uppsala University in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) and the participants gave written informed consent.

2.2. Metabolic LV hypertrophy risk factors

Blood pressure was measured to the nearest mmHg by a calibrated mercury sphygmomanometer while subjects were in the supine position after at least 30 min of rest, and the average of three recordings was used. In order to avoid misclassification bias associated with blood pressure levels among subjects taking antihypertensive treatment, hypertension was defined as blood pressure > 140/90 mmHg or use of antihypertensive treatment. Given BMI is more strongly associated with LV hypertrophy than other available measures of adiposity (Hu et al., 2015), adiposity was evaluated by body mass index (BMI), defined as height/squared weight as ascertained from clinical measurements. Fasting blood glucose was assessed by the standard hexokinase technique (Lee et al., 2011).

2.3. Echocardiography

A comprehensive two-dimensional and Doppler echocardiography was performed with an Acuson XP124 cardiac ultrasound unit (Acuson, California, USA) and a 2.5 MHz transducer as detailed previously (Lind, 2008). Briefly, LV dimensions were measured with M-mode on-line from the parasternal projections, using a leading edge to leading edge convention. Measurements included interventricular septal thickness, posterior wall thickness, and left

ventricular diameter in end-diastole (LVEDD). LV wall thickness was defined as the sum of interventricular septal thickness and posterior wall thickness divided by LVEDD. LV mass was determined from the Penn convention and indexed for height$^{2.7}$ (LVMI, (Mureddu et al., 2001)).

2.4. Measurement of p,p′-DDE

p,p′-DDE was measured in stored plasma samples. Analyses of p,p′-DDE was performed using a high-resolution chromatography coupled to high-resolution mass spectrometry (HRGC/HRMS) system (Micromass Autospec Ultima, Waters, Mildford, MA, USA) with some modifications to the method by Sandau et al. (Sandau et al., 2003). The calculated method detection limit was 2.13 ng/g lipid. All subjects had values above that level. All details on the p,p′-DDE analyses have been reported elsewhere (Salihovic et al., 2012a, 2012b). The p,p′-DDE levels were normalized for circulating total lipid levels, which were defined by an established summation formula based on serum cholesterol and serum triglyceride concentrations (Rylander et al., 2006). Thereafter, normalized p,p′-DDE levels were obtained by dividing the wet-weight concentrations of p,p′-DDE by the estimated lipid level.

2.5. Statistical analyses

Variables with a skewed distribution, such as fasting glucose and p,p′-DDE, were natural log-transformed to achieve a normal distribution. In the analyses of the relationships between p,p′-DDE levels and hypertension, BMI and fasting glucose, as well as for the echocardiographical variables, we used all cardiometabolic measurements collected at ages 70, 75, and 80 to evaluate their longitudinal relationship with p,p′-DDE exposure.

Initially, mixed models with random intercepts were used to evaluate possible relationships between p,p′-DDE levels and the well known LV hypertrophy risk factors hypertension, BMI and fasting glucose (Lieb et al., 2014) in separate models using sex as confounder. Linear mixed models (xtmixed) were used for continuous data, while logistic mixed models (xtlogit) were used when the outcome was binary, such as hypertension. Also possible interactions between sex and p,p′-DDE levels regarding the LV hypertrophy risk factors were evaluated.

Potential confounders, such as smoking, education level and alcohol intake were not included in the models since they were not related to p,p′-DDE levels ($p > 0.07$ for all). Therefore, the models were just adjusted for sex (age same in all subjects).

Second, mixed models with random intercepts for subject were used to evaluate relationships between p,p′-DDE levels and the echo-cardiographical variables LVMI, LVEDD and LV thickness. The first set of models of echocardiographical variables were adjusted only for sex, while the second set of models were also adjusted for hypertension, BMI and fasting glucose. Also possible interactions between sex and p,p′-DDE levels regarding the echocardiographic variables were evaluated. To evaluate if the relationship between p,p′-DDE levels and LVMI was linear or not, predictive margins was used in a model with p,p′-DDE levels on the original scale, also including a squared term for p,p′-DDE levels. A significant squared term is taken as evidence of a non-linear relationship.

Third, structural equation modeling (SEM) was used to evaluate the degree of mediation of hypertension, glucose and BMI on the p,p′-DDE vs LVMI relationship (Rabe-Hesketh et al., 2004; Sobel, 1987). The maximum likelihood with missing values method was used. Less than 5% of the observations of the mediators were missing. To account for the longitudinal design, robust standard errors using the generalized Huber/White/sandwich estimator were produced. The direct effect was given by the coefficient between DDE and LVMI. The other three paths leading from DDE to LVMI (DDE- > HT- > LVMI, DDE- > BMI-> LVMI, and DDE- > BMI- > HT- > LVMI) defined the indirect effects. The indirect effect for each of these three parts was given by multiplying the coefficients within each path. The total indirect effect was then given by adding up the effect of the three indirect paths. The total effect was given by adding the direct effect with the indirect effects. For all models, $p < 0.05$ was considered significant and STATA14 (Stata Inc, College Station, TX, US) was used for calculations.

3. Results

The subjects of this study had a 7.9% prevalence of medicated diabetes (Table 1), a mean BMI of 27 (Table 2), and a 72% prevalence of hypertension (Table 2) including 31.5% prevalence of people taking medication for their hypertension (Table 1). It was hypothesized that the increased prevalence of LV hypertrophy risk factors associated with p,p′-DDE elsewhere would extend to elevated hypertension, BMI, and fasting blood glucose across 70–80 year old Swedes who had p,p′-DDE levels ranging from 1.9 to 4260 ng/g lipid (median value 308 ng/g lipid) when 70 years old. Indeed, p,p′-DDE levels were related to hypertension, BMI and fasting glucose in three separate models adjusted for sex ($p < 0.001$ for all, for details, see Table 3). No significant interactions between p,p′-DDE levels and sex were found regarding hypertension, BMI or fasting glucose.

Indeed, p,p′-DDE levels were associated with LVMI in a sex-adjusted model of aging Swedes when all data on LVMI from ages 70, 75 and 80 years were taking into account ($p < 0.001$, Table 4). As could be seen in Fig. 1 this relationship was fairly linear when plotted on the original scale for p,p′-DDE. This linear relationship was confirmed by the absence of significance of the squared form of p,p′-DDE with LVMI. Further analyses of the relationships between p,p′-DDE and LV thickness and LVEDD indicated that this relationship between p,p′-DDE and LVMI was due to an association of p,p′-DDE with LV thickness, and not with LVEDD (Table 4). Exclusion of subjects with a myocardial infarction (n=105) did not alter these relationships. As was seen with the LV hypertrophy risk factor analysis (Table 3), no significant interactions between p,p′-DDE levels and sex were found regarding the echo-cardiographic variables ($p = 0.24$ for p,p′-DDE X sex interaction regarding LVMI).

Given p,p′-DDE was associated with LVMI and related risk factors (Table 2–4) and the significant correlations between BMI, glucose, systolic blood pressure and LMVI (Table 5), it was suspected that the association between p,p′-DDE and LVMI would be mediated by metabolic risk factors for LV hypertrophy. Consistent with this hypothesis, when p,p′-DDE levels were related to LVMI in a model also including the hypertension, BMI and fasting

glucose observed among 70-, 75- and 80- year old Swedes, the relationship between p,p′-DDE levels and LVMI was markedly attenuated and no longer significant (p=0.90).

To empirically test the hypothesis that p,p′-DDE exposure was associated with LV mass through mediating effects of the association of p,p′-DDE with BMI, fasting glucose, and hypertension, SEM modeling was preformed. Sex was considered as a confounder in the model and was not included in the direct or indirect effects. Glucose was excluded from final SEM models due to lack of significance. In the SEM model (Fig. 2), only 3.7% of the effect of p,p′-DDE levels on LVMI was a direct effect (p = 0.83). BMI mediated 70.2% and hypertension 19.4% of the total effect of p,p′-DDE on LVMI. The pathway going from p,p′-DDE to BMI to hypertension and finally to LVMI mediated a further 6.7% of the effect of p,p′-DDE levels on LVMI (all three pathways p < 0.001, Fig. 2). If glucose was also included in the SEM model, only < 1% was mediated by that pathway.

4. Discussion

Our SEM model indicated that p,p′-DDE is not an independent risk factor for elevated LV mass. Instead, in support of our hypothesis, the majority of the association of p,p′-DDE with LV mass appeared to be mediated by BMI and to a lesser degree, hypertension.

Previous meta-analyses indicate the p,p′-DDE has a consistent positive association with obesity and hypertension across studies in Europe, North America, and the Asia-Pacific (Cano-Sancho et al., 2017; Park et al., 2016). Indeed in the Swedish subjects of PIVUS, p,p′-DDE has also been associated with increased cross-sectional measures of obesity, adiposity, and prevalent hypertension (Lee et al., 2012; Lind et al., 2014; Ronn et al., 2011) which we confirmed here in longitudinal analysis. The SEM results build on what was implied by regression models here and in a previous study of LV mass in PIVUS that indicated that p,p′-DDE was associated with LV mass until further adjustment by these metabolic risk factors (Sjoberg Lind et al., 2013).

The contribution of metabolic risk factors in mediating the p,p′-DDE and LV mass relationship in elderly Swedes is also supported by previous mouse research where p,p′-DDT exposure increased LV mass among mice with both increased adiposity and systolic blood pressure (La Merrill et al., 2014, 2016). The internal dose of p,p′-DDT and p,p′-DDE measured in the dams of these mice after their exposure period is within the range of exposures reported in studies from the United States, Mexico, Norway, Sweden (PIVUS), and South Africa (Bouwman et al., 1992; Cox et al., 2007; La Merrill et al., 2013; Rylander et al., 2009). This suggests that these toxicology experiments could relate to health associations with DDT and DDE in human populations across the world.

“Effect” is an established terminology used in SEM for relationships, such as X - > Y. This term was therefore used also in the present paper for the SEM relationships, but it must be remembered that an “effect” in this sense does not imply causality. It is a description of the relationships defined in the model (Fig. 2). An underlying assumption of our SEM model was p,p′-DDE - > BMI - > LVMI. An alternative explanation of our SEM results could be BMI - > LVMI along with BMI - > p,p′-DDE. This alternative directed acyclic graph (DAG)

came from a hypothesis evoked due to cross-sectional human data that conflicted with known POP dilution by excess tissue mass and concentration dependent elimination of POPs, which predicted that a larger fat compartment causes lower concentrations and slower elimination rates of POPs, respectively (Ritter et al., 2009; Wolff et al., 2007, 2005). Because cross-sectional assessment of p,p′-DDT and p,p′-DDE instead indicated that these chemicals were positively correlated to BMI, the 'cross-over' hypothesis was proposed- that relatively rapid elimination of a higher concentration of DDT in lean people eventually leads to absolute DDT levels which are lower than DDT levels simultaneously observed in people of higher BMI (Wolff et al., 2007).

The DAG based on the cross-over hypothesis has been a historically popular conceptual framework yet empirical data does not support pharmacokinetics as a sole explanation for positive relationships between p,p′-DDE and adiposity. For example, a meta-analysis restricted to prospective studies found a positive association between p,p′-DDE and later measures of adiposity in recent studies which was supported by both *in vivo* and *in vitro* evidence (Cano-Sancho et al., 2017). Further, 45 years ago the founder of the International Agency for Research on Cancer demonstrated that DDT subsequently increased body mass in mice (Tomatis et al., 1972). More recently, DDT exposure was shown to increase fat mass in both mice and rats (La Merrill et al., 2014; Skinner et al., 2013). These data highlight the importance of considering experimental evidence when developing causal models as we have done here. An animal study of DDE exposure that prevents increased LV mass by intervening with the earlier development of increased adiposity and blood pressure would strengthen the causal evidence for mediation by obesity and hypertension to further support the assumptions of our SEM model.

Amongst the strengths of the present study is the fact that we repeated the measurements of LVMI and metabolic variables three times and therefore obtained a more precise measurement of LV mass that longitudinally extended beyond exposure assessment. As with many environmental epidemiology studies, this study does not completely measure environmental exposures. Developmental exposures and some concurrent exposures that may have been present concurrent with p,p′-DDE have not all been assessed in PIVUS. It is possible that these exposures and/or other POPs measured in PIVUS might well be of importance as confounders in the relationship between p,p′-DDE and LVMI. However, a major analytical problem is that the correlation between the POPs in PIVUS samples are quite high (most often $r > 0.50$) and therefore these other measured POPs cannot be used together in normal parametric models due to the problem of co-linearity. Other more recently developed methods, such as the Boosted regression trees we recently used to study mixture effects of environmental contaminants (Lind et al., 2017), are not yet developed to be combined with SEM analysis. Another limitation is that the sample consists of elderly Caucasians, restricting the generalizability to other age and ethnic groups. The participation rate in the study was quite low (50%), and in an elderly population it could be assumed that healthy subjects are overrepresented in the sample attending the study. How this would affect the results of this particular analysis is unclear since we do have a large range in LVMI, as well as other variables used in the models also in this rather healthy subsample of the underlying population. Further epidemiological research of p,p′-DDE, adiposity, and

cardiac imaging should attempt to replicate our results in population- based prospective studies to justify their generalizability across diverse populations.

5. Conclusions

In accordance with a previous analysis in this cohort (Sjoberg Lind et al., 2013), we see no independent association of p,p′-DDE exposure with LVMI. Our new finding suggests that the 'presumed' obesogenic effect of p,p′-DDE (Cano-Sancho et al., 2017) is responsible for the majority of the association between p,p′-DDE and LV mass, as opposed to a direct cardiotoxic effect. Further, this study reassuringly supports the notion that measuring well known risk factors for LV hypertrophy, such as BMI and hypertension, may be sufficient to capture any risk of LV hypertrophy that may be associated with p,p′-DDE exposure.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We acknowledge all the individuals who participated in this study. We greatly acknowledge Helen Björnfoth, Jessika Hagberg, and Lisa Mattioli for their technical assistance with the chemical analysis.

Funding

This study was supported by the Swedish Research Council (VR, Grant number 2012–2407), the Swedish Research Council for Environment, Agricultural Sciences and Spatial Planning (FORMAS, Grant number 2007–2047), the USDA National Institute of Food and Agriculture (Hatch project 1002182), and the National Institutes of Health (ES019919, ES023513). The funding agencies had no role in study design, in the collection, analysis and interpretation of data, in writing the article or in the decision to submit the article for publication.

Abbreviations:

BMI	Body mass index
CVD	cardiovascular disease
LV	left ventricular
LVEDD	left ventricular diameter in end-diastole
LVMI	left ventricular mass index
POPs	persistent organic pollutants
PIVUS	Prospective Investigation of the Vasculature in Uppsala Seniors

References

Bouwman H, et al., 1992 Transfer of DDT used in malaria control to infants via breast milk. Bull. World Health Organ 70, 241–250. [PubMed: 1632883]

Cano-Sancho G, et al., 2017 Association between exposure to p,p′-DDT and its meta-bolite p,p′-DDE with obesity: integrated systematic review and meta-analysis. Environ. Health Perspect 10.1289/EHP527. (Accepted 5/9/17; Published 9/18/17).

Chen L, et al., 2015 Red cell distribution width and inappropriateness of left ventricular mass in patients with untreated essential hypertension. PLoS One 10, e0120300. [PubMed: 25793884]

Chumlea WC, et al., 2009 Left ventricular mass, abdominal circumference and age: the Fels longitudinal study. J. Nutr. Health Aging 13, 821–825. [PubMed: 19812873]

Cox S, et al., 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. [PubMed: 18087594]

Evangelou E, et al., 2016 Exposure to pesticides and diabetes: a systematic review and meta-analysis. Environ. Int 91, 60–68. [PubMed: 26909814]

Gersh BJ, et al., 2011 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: executive summary: a report of the American College of Cardiology Foundation/ American Heart Association Task Force on Practice Guidelines. Circulation 124, 2761–2796. [PubMed: 22068435]

Gradman AH, Alfayoumi F, 2006 From left ventricular hypertrophy to congestive heart failure: management of hypertensive heart disease. Prog. Cardiovasc Dis 48, 326–341. [PubMed: 16627048]

Hu T, et al., 2015 Which measures of adiposity predict subsequent left ventricular geometry? Evidence from the Bogalusa Heart Study. Nutr. Metab. Cardiovasc Dis 25, 319–326. [PubMed: 25534865]

La Merrill M, et al., 2013 Prenatal exposure to the pesticide DDT and hypertension diagnosed in women before age 50: a longitudinal birth cohort study. Environ. Health Perspect 121, 594–599. [PubMed: 23591545]

La Merrill M, et al., 2014 Perinatal exposure of mice to the pesticide DDT impairs energy expenditure and metabolism in adult female offspring. PLoS One. 9, e103337. [PubMed: 25076055]

La Merrill MA, et al., 2016 Perinatal DDT Exposure induces hypertension and cardiac hypertrophy in adult mice. Environ. Health Perspect 124, 1722–1727. [PubMed: 27325568]

Lal A, et al., 2003 Prevention of high salt diet-induced cardiac hypertrophy and fibrosis by spironolactone. Am. J. Hypertens 16, 319–323. [PubMed: 12670750]

Lee DH, et al., 2011 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. [PubMed: 21700918]

Lee DH, et al., 2012 Associations of persistent organic pollutants with abdominal obesity in the elderly: the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study. Environ. Int 40, 170–178. [PubMed: 21835469]

Levy D, et al., 1990 Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. N. Engl. J. Med 322, 1561–1566. [PubMed: 2139921]

Lieb W, et al., 2014 The natural history of left ventricular geometry in the community: clinical correlates and prognostic significance of change in LV geometric pattern. JACC Cardiovasc. Imaging 7, 870–878. [PubMed: 25129518]

Lind L, et al., 2005 A comparison of three different methods to evaluate endothelium-dependent vasodilation in the elderly: the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study. Arterioscler. Thromb. Vasc. Biol 25, 2368–2375. [PubMed: 16141402]

Lind L, 2008 Left ventricular mass is related to endothelium-dependent vasodilation in the forearm, but not in the brachial artery, in elderly subjects: the Prospective Investigation of the Vasculature in Uppsala Seniors study. J. Hum. Hypertens 22, 767–773. [PubMed: 18548090]

Lind L, et al., 2017 Mixture effects of 30 environmental contaminants on incident metabolic syndrome-A prospective study. Environ. Int 107, 8–15. [PubMed: 28648904]

Lind PM, et al., 2014 Circulating levels of p,p′-DDE are related to prevalent hypertension in the elderly. Environ. Res 129, 27–31. [PubMed: 24528999]

Mortality GBD, Causes of Death C, 2016 Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global burden of disease study 2015. Lancet 388, 1459–1544. [PubMed: 27733281]

Mureddu GF, et al., 2001 Appropriate or inappropriate left ventricular mass in the presence or absence of prognostically adverse left ventricular hypertrophy. J. Hypertens 19, 1113–1119. [PubMed: 11403361]

Park SH, et al., 2016 Body burden of persistent organic pollutants on hypertension: a meta-analysis. Environ. Sci. Pollut. Res. Int

Rabe-Hesketh S, et al., 2004 Generalized multilevel structural equation modeling. Psychometrika 69, 167–190.

Ritter R, et al., 2009 A multi-individual pharmacokinetic model framework for interpreting time trends of persistent chemicals in human populations: application to a postban situation. Environ. Health Perspect 117, 1280–1286. [PubMed: 19672409]

Ronn M, et al., 2011 Circulating levels of persistent organic pollutants associate in divergent ways to fat mass measured by DXA in humans. Chemosphere 85, 335–343. [PubMed: 21767864]

Rylander C, et al., 2009 Associations between marine food consumption and plasma concentrations of POPs in a Norwegian coastal population. J. Environ. Monit 11, 370–376. [PubMed: 19212595]

Rylander L, et al., 2006 A simplified precise method for adjusting serum levels of persistent organohalogen pollutants to total serum lipids. Chemosphere 62, 333–336. [PubMed: 16005493]

Salihovic S, et al., 2012a Circulating levels of persistent organic pollutants (POPs) among elderly men and women from Sweden: results from the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS). Environ. Int 44, 59–67. [PubMed: 22361238]

Salihovic S, et al., 2012b A rapid method for screening of the Stockholm Convention POPs in small amounts of human plasma using SPE and HRGC/HRMS. Chemosphere 86, 747–753. [PubMed: 22153485]

Sandau CD, et al., 2003 Comprehensive solid-phase extraction method for persistent organic pollutants. Validation and application to the analysis of persistent chlorinated pesticides. Anal. Chem 75, 71–77. [PubMed: 12530820]

de la Sierra A, et al., 1996 Increased left ventricular mass in salt-sensitive hypertensive patients. J. Hum. Hypertens 10, 795–799. [PubMed: 9140784]

Sjoberg Lind Y, et al., 2013 Persistent organic pollutants and abnormal geometry of the left ventricle in the elderly. J. Hypertens 31, 1547–1553. [PubMed: 23743808]

Skinner MK, et al., 2013 Ancestral dichlorodiphenyltrichloroethane (DDT) exposure promotes epigenetic transgenerational inheritance of obesity. BMC Med. 11, 228–244. [PubMed: 24228800]

Sobel M, 1987 Direct and indirect effects in linear structural equation models. Sociol. Methods Res 16, 155–176.

Song Y, et al., 2016 Endocrine-disrupting chemicals, risk of type 2 diabetes, and diabetes-related metabolic traits: a systematic review and meta-analysis. J. Diabetes 8, 516–532. [PubMed: 26119400]

Tang-Peronard JL, et al., 2011 Endocrine-disrupting chemicals and obesity development in humans: a review. Obes. Rev 12, 622–636. [PubMed: 21457182]

Tomatis L, et al., 1972 The effect of long-term exposure to DDT on CF-1 MICE. Int. J. Cancer 10, 489–506. [PubMed: 4358037]

Wang Y, et al., 2016 Do environmental pollutants increase obesity risk in humans? Obes. Rev 17, 1179–1197. [PubMed: 27706898]

Wolff MS, et al., 2005 Improving organochlorine biomarker models for cancer research. Cancer Epidemiol. Biomark. Prev 14, 2224–2236.

Wolff MS, et al., 2007 Pharmacokinetic variability and modern epidemiology – the example of dichlorodiphenyltrichloroethane, body mass index, and birth cohort. Cancer Epidemiol. Biomark. Prev 16, 1925–1930.

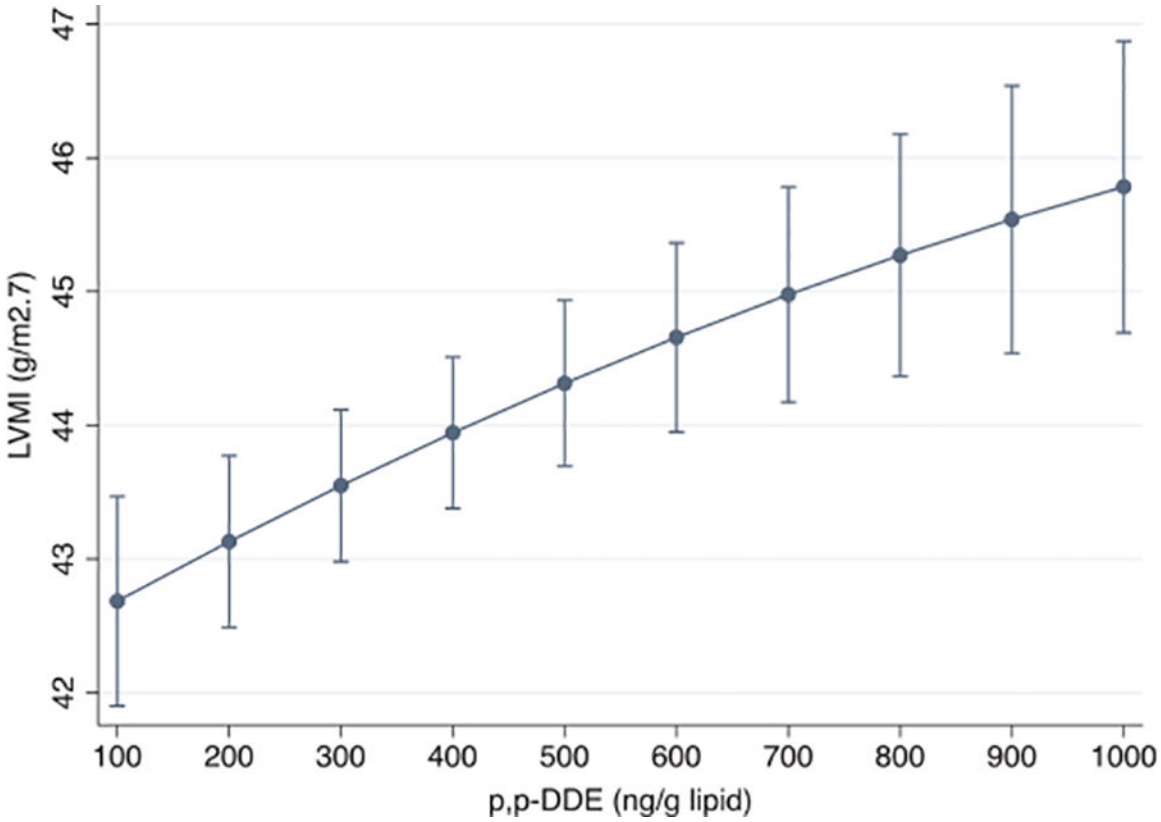

Fig. 1.

Relationship between p, p′-DDE levels and LV mass (LVMI indexed for height$^{2.7}$). Predicted margins are given together with 95% confidence intervals. See Supplemental Methods for the full STATA code.

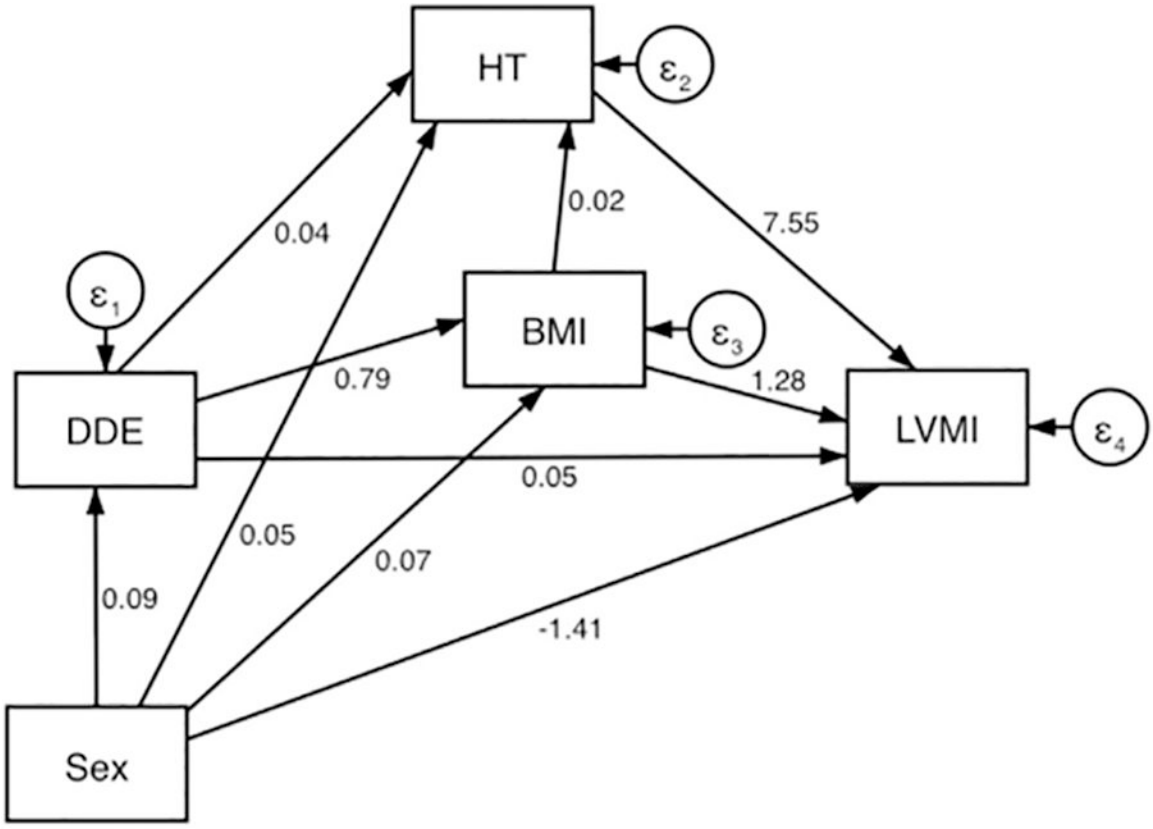

Fig. 2.

Structural equation model (SEM) for the relationship between p, p′-DDE (DDE) levels and left ventricular mass (LVMI) with hypertension (HT) and BMI as mediators and sex as confounder. The number by the arrows is the coefficient for the relationship given by the arrow.

Table 1

Descriptive characteristics of the study subjects at 70 years.

Characteristic	Number of observations	Summary statistic	Variance estimate
Discrete variables	**N**	**Prevalence (%)**	***(Not applicable)***
Sex (% female)	1016	50.1	
Smoker (% current)	1015	10.5	
Education level (years in school)			
≤ 9	570	56.7	
10–12	182	18.1	
> 12	253	25.2	
Medicated hypertension (% cases)	1007	31.5	
Using insulin therapy (% cases)	1014	1.8	
Using oral anti-diabetes medications (% cases)	1015	6.1	
Continuous variables (units)	**N**	**Means**	**Standard deviation**
Alcohol consumption (g/week)	861	6.7	7.7/
Systolic blood pressure (mmHg)	1012	149.6	22.7
Diastolic blood pressure (mmHg)	1012	78.7	10.2

Table 2

Means and SD (or prevalence) for the studied variables at ages 70, 75 and 80 years.

	Characteristic (units)	Number of observations	Mean	Standard deviation
Age 70				
	DDE (ng/g lipid)[a]	988	308	170–570
	Fasting blood glucose (mmol/l)[a]	1013	5.0	4.6–5.4
	BMI (kg/m^2)	1016	27	4
	Hypertensive (% cases)	1016	72	
	LVMI (g/m$^{2.7}$)	922	43	13
	LVEDD (mm)	924	47	5
	LV wall thickness (mm)	922	21	3
Age 75				
	Fasting blood glucose (mmol/l)[a]	826	4.9	4.5–5.4
	BMI (kg/m^2)	826	27	4
	Hypertensive (% cases)	897	83	
	LVMI (g/m$^{2.7}$)	777	43	13
	LVEDD (mm)	781	50	6
	LV wall thickness (mm)	777	19	3
Age 80				
	Fasting blood glucose (mmol/l)[a]	599	4.9	4.6–5.6
	BMI (kg/m^2)	604	27	4
	Hypertensive (% cases)	607	80	
	LVMI (g/m$^{2.7}$)	542	46	12
	LVEDD (mm)	561	52	6
	LV wall thickness (mm)	560	19	2

[a]Median and interquartile range reported due to log-transformation.

Table 3

The association of p,p′-DDE levels in 70 year old Swedes and longitudinal occurrence of three risk factors for LV hypertrophy, hypertension, BMI and glucose, at ages 70, 75 and 80 years. Models were adjusted for sex only.

Dependent variable	Type of estimate	Estimate for p,p′-DDE (ng/g)	95% confidence interval boundaries	p-value
Hypertension (presence)	Odds ratio	1.7	(1.3, 2.3)	< 0.001
BMI (kg/m^2)	Regression coefficient	0.8	(0.5, 1.1)	< 0.001
Fasting glucose (mmol/l)	Regression coefficient	0.03	(0.02, 0.04)	< 0.001

Table 4

The association of p,p′-DDE levels in 70 year old Swedes and longitudinal occurrence of LV characteristics/geometry at ages 70, 75 and 80 years.

Dependent variable	Regression coefficient for p,p′-DDE (ng/g)	95% confidence interval (lower, upper) boundaries	p-value
LV mass ($g/m^{2.7}$)[a]	1.47	(0.70, 2.24)	< 0.001
LV mass ($g/m^{2.7}$)[b]	0.04	(−0.58, 0.66)	0.90
LVEDD (mm)[a]	0.30	(0.00, 0.061)	0.05
LVEDD (mm)[b]	−0.05	(−0.33, 0.24)	0.73
LV thickness (mm)[a]	0.32	(0.16, 0.49)	< 0.001
LV thickness (mm)[b]	0.03	(−0.11, 0.18)	0.64

[a]Models were adjusted for sex only.

[b]Models were adjusted for sex, hypertension, BMI, and fasting glucose.

Table 5

Pearsons´correlation coefficient is given for the pairwise relations between BMI, glucose (mmol/l), systolic blood pressure (SBP, mmHg), body mass index (BMI, kg/m^2), and left ventricular mass index (LVMI, g/m$^{2.7}$). The p-value is given below the correlation coefficient (r).

	Glucose	**SBP**	**BMI**	**LVMI**
Glucose	-			
SBP	0.04	-		
	0.0516			
BMI	0.21	0.15	-	
	0.0001	0.0001		
LVMI	0.20	0.30	0.47	-
	0.0001	0.0001	0.0001	