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HEALS

Health and Environment-wide Associations
based on Large population Surveys

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D16.1 “Report on overview of cohorts/studies relating adverse health outcomes related to adiposity as an intermediate phenotypes of overweight, obesity, diabetes and metabolic disorders to environmental exposures of endocrine disruptors”

WP 16: Obesity and childhood diabetes - link with endocrine disruptors

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	D16.1 - Report on overview of cohorts/studies relating adverse health outcomes related to adiposity as an intermediate phenotypes of overweight, obesity, diabetes and metabolic disorders to environmental exposures of endocrine disruptors		
	WP16: Obesity and childhood diabetes - link with endocrine disruptors	Security: PU	
	Author(s): V Mendes; I Delgado; B Peleteiro; J Araújo; H Barros; E Ramos; D Sarigiannis; N Baiz; I Annesi-Maesano	Version: 1	2/221

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List of Abbreviations

BDE – Brominated Diphenyl Ether
 BDL – Below detected Levels
 BIA – Bioelectric Impedance Analysis
 BMI – Body Mass Index
 BPA – Bisphenol A
 BW – Birthweight
 CC – Case-control
 CDS – Child Development Study
 CHAMACOS –
 CI – Confidence Interval
 CS – Cross-sectional
 DALYs – Disability Adjusted Life Years
 DCP – Dichlorophenol

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DDE – Dichlorodiphenyldichloroethylene
 DDT – Dichlorodiphenyltrichloroethane
 DM – Diabetes Mellitus
 DXA – Dual-energy X-ray Absorptiometry
 ECD – Electron Capture Detector
 EDC – Endocrine Disrupting Chemical
 ESI – Electrospray Ionization
 FM – Fat Mass
 FRIENDS – Fox River Environment and Diet Study
 GC – Gas Chromatography
 GLC – Gas-liquid Chromatography
 H – Height
 HCB – Hexachlorobenzene
 HCH – Hexachlorocyclohexane
 HpCDD – Heptachlorodibenzo-p-dioxin
 HpCDF – Heptachlorodibenzofuran
 HPLC – High Performance Liquid Chromatography
 HRGC – High Resolution Gas Chromatography
 HRMS – High Resolution Mass Spectrometry
 HxCDD – Hexachlorodibenzo-p-dioxin
 HxCDF – Hexachlorodibenzofuran
 ID – Isotope Dilution
 mBP – mono-butyl Phthalate
 MBzP – Mono-benzyl Phthalate
 MCHP – Monocyclohexyl Phthalate
 MCOP – Mono(carboxyoctyl) Phthalate
 MCMHP – Mono(2-carboxymethylhexyl) Phthalate
 MCNP – Mono(carboxynonyl) Phthalate
 MCPP – Mono-(3-carboxypropyl) Phthalate
 MECPP – Mono(2-ethyl-5-carboxypentyl) Phthalate

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MEP – Mono-ethyl Phthalate

MEHP – Mono-(2-ethylhexyl) Phthalate

MEHHP – Mono-(2-ethyl-5-hydroxyhexyl) Phthalate

MEOHP – Mono-(2-ethyl-5-oxohexyl) Phthalate

MHBP – Mono-(3-hydroxy-n-butyl) Phthalate

MiBP – Mono-iso-butyl Phthalate

MMP – Mono-methyl Phthalate

MnBP – Mono-n-butyl Phthalate

MRI – Magnetic Resonance Imaging

MS – Mass Spectrometry

NCC – Nested Case-control

NHANES – National Health and Nutrition Examination Survey

NW – Normal Weight

OCDD – Octachlorodibenzodioxin

OCDF – Octachlorodibenzofuran

OR – Odds Ratio

OW – Overweight

PA – Physical Activity

PBB – Polybrominated Biphenyl

PBDE – Polybrominated Diphenyl Ethers

PC – Prospective Cohort

PCB – Polychlorinated Biphenyl

PCDD – Polychlorinated Dibenzodioxins

PCDF – Polychlorinated Dibenzofurans

PeCDD – Pentachlorodibenzo-p-dioxin


PeCDF – Pentachlorodibenzofuran

PFCA – Perfluorinated Carboxylic Acid

PFHxS – Perfluorohexanesulfonic Acid

PFOA – Perfluorooctanoic Acid

PFOS – Perfluorooctane Sulfonate

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PFNA – Perfluorononanoic Acid

PIR – Poverty Income Ratio

PIVUS – Prospective Investigation of the Vasculature in Uppsala Seniors

RP – Reversed Phase

SAT – Subcutaneous Adipose Tissue

SDS – Standard Deviation Score

SES – Socioeconomic Status

SPE – Solid-phase Extraction

TC – Total Cholesterol

TCDD – Tetrachlorodibenzo-p-dioxin

TCDF – Tetrachlorodibenzo-p-furan

TG – Triglycerides

TLC – Thin Layer Chromatography

TMS – Tandem Mass Spectrometry

UPLC – Ultra Performance Liquid Chromatography

VAT – Visceral Adipose Tissue

W – Weight

WC – Waist Circumference


WfL – Weight for Length

WHO – World Health Organization

WtHR – Waist to Hip Ratio


Background

Exposure to environmental chemicals has become one of the major concerns in the past decades. The global burden of disease accountable to environmental exposures and management of chemicals amounts to at least 4.9 million deaths (86 million DALYs) per year, representing 8.3% of mortality and 5.7% of the total burden of disease in DALYs worldwide [1].

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Some environmental chemicals present harm to humans and wildlife and may persist in the environment, accumulate in the food chain and travel large distances from where they are released. Some of these chemicals have the ability to interfere with endocrine systems, by disrupting their normal function, and were designated endocrine disrupting chemicals (EDCs). According to the International Programme for Chemical Safety (IPCS - involving the World Health Organization (WHO), the United Nations Environment Programme and the International Labour Organization), an EDC can be defined as “*an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations*”. A potential endocrine disrupting chemical is “*an exogenous substance or mixture that possesses properties that might be expected to lead to endocrine disruption in an intact organism, or its progeny, or (sub)populations*” [2]. A large number of chemicals have already been identified as EDCs or potential EDCs [3].


Whether they are naturally occurring chemicals or manufactured substances these compounds have several applications and their use is widespread all over the world. Manufactured chemicals include agricultural, industrial and consumer products such as pesticides, processed metals, petroleum products and products of combustion as toxic gases, particles from industrial emissions and burning of fuel [2]. Some of these products are manufactured for specific uses, while others are unwanted by-products, wastes, or products of combustion. Consumer goods, such as cosmetics and other personal care products, chemical stabilizing agents, plasticizers, solvents and metals are also known sources of EDCs [2]. Cleaning agents, furniture, building materials, paints, clothes and toys, have a wide range of chemicals including flame retardants (as polybrominated diphenyl ethers). EDCs may also be found in pharmaceuticals, such as synthetically-produced hormones, including oral contraceptives and hormone replacement treatment, lipid regulators, beta-blockers, anti-depressants and antibiotics. Some of these pharmaceuticals are then excreted in

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urine and feces as metabolites and can be found in wastewaters at much higher levels than their precursors [4].


These compounds have such a diversified use that virtually all humans are exposed to these chemicals through the ingestion of food, dust and water, inhalation of gases and particles in the air and skin contact. EDCs may also be transferred during pregnancy to the developing fetus and to the offspring through mother's milk. With all these routes of exposure, humans and animals are frequently exposed to complex mixtures of these substances, even if at low concentrations. The susceptibility of each organism to these chemicals will then depend on the intrinsic properties of the substance, on the amount, duration, frequency and route of exposure.

EDCs may be classified into persistent and non-persistent chemicals. Non-persistent chemicals have short half-lives, i.e., they are rapidly broken in the environment and are usually less harmful to human and wildlife health. However, they remain a concern since humans may be frequently and continuously exposed to these substances. On the contrary, persistent chemicals have a greater potential to accumulate in the environment, increasing not only the probability of contact but also the concentration at exposure. When chemicals bioaccumulate, animals higher on the food chain, including humans, will accumulate higher concentrations in their system, since their food and water sources will also contain higher levels of the persistent chemical. The most commonly persistent chemicals are organochlorine pesticides, as dichlorodiphenyltrichloroethane (DDT), industrial chemicals such as polychlorinated biphenyls (PCB), as well as unintentional by-products as polychlorinated dibenzo-p-dioxins (PCDD) and dibenzofurans (PCDF). Although some of these substances were banned or severely restricted in several countries (namely PCBs and DDT) and their levels in humans are decreasing, their harmful consequences are still felt due mainly to metabolites that remain in the environment for very long periods of time.

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In general, EDCs interfere with the functioning of the endocrine system by mimicking the action of naturally-produced hormones and then setting off similar chemical reactions in the body, by blocking hormone receptors in cells, and then preventing the action of normal hormones, or by affecting the synthesis, transport, metabolism and excretion of hormones [2]. Given that the endocrine system has a great multiplicity of targets and actions, it is expected that exogenous compounds with similar properties or actions to those of human hormones have an extremely wide range of implications in health. However, the mechanisms of action for most associations between EDCs and health-related outcomes are still not well established. The links between EDCs and disease have raised great concern since these chemicals seem to be implicated in the development of several conditions, which prevalence have greatly increased all over the world, and present a significant burden in populations [5, 6]. In vitro and in vivo studies have shown that EDCs can act at multiple sites and through multiple mechanisms of action. More recently, studies have shown that in humans, exposures to EDCs have been associated with increasing male and female reproductive disorders [7, 8], thyroid-related disorders [2], neurodevelopmental problems [2], cancer and malformations [9, 10], disruption of the immune system [2] and metabolic diseases, namely increased levels of triglycerides and cholesterol [11], impaired fasting glucose, diabetes and obesity [12, 13].


In recent decades, scientific evidence has shown that some EDCs may act as obesogens, i.e. chemical compounds that may act by regulating and promoting inappropriately lipid accumulation and adipogenesis, leading to obesity [14]. Although it is still unclear by which mechanisms EDCs may have an effect on obesity, some biologic hypothesis have been proposed. EDCs may interfere with steroid hormones function [15], which are hormones involved in weight homeostasis that influence fat quantity and distribution [16]. Some phthalate compounds are potential antiandrogens in humans [17, 18] and there is also evidence showing that a number of environmental chemicals (PCBs, phthalates, dichlorodiphenyldichloroethylene (DDE) and other substances) may have an effect on the activity of relevant enzymes such aromatase

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[19-22]. Compounds, such as PCBs, polybrominated biphenyls (PBBs), bisphenol A (BPA), phthalates and some of their metabolites, seem to bind to thyroid receptors and reduce circulating thyroid hormone levels [23] which may involve the reduction of energy expenditure. Acting on peroxisome proliferator-activated receptor- α and - γ may also be a mean to promote obesity, since these receptors have a relevant role in adipogenesis and lipid metabolism [14]. Some organotins [24] and phthalates [25] seem to act as PPAR- γ agonists, promoting adipocyte differentiation and maturation, and thus promoting weight gain. EDCs may also have an impact on weight by increasing energy intake, since they can disrupt the action of hormones implicated in appetite regulation and energy balance [14].


In 2002, Baillie-Hamilton suggested that environmental chemicals could play a role in the etiology of obesity in humans by noticing that the obesity epidemic coincided with a higher increase of industrial chemicals in the environment [26]. After this review, a growing body of evidence has started to emerge in order to address the effects of environmental chemicals in weight, although these studies were mainly in animals. Excess weight gain due to EDCs was first shown in animals treated with diethylstilbestrol and BPA [27, 28]. In another study, female progeny of rats presented accelerated growth compared to controls, after being exposed to PCB 153 [29]. Weight gain was also observed in rodents after the exposure to phthalates [25]. However, these conclusions need to be carefully considered when extrapolating from in vitro data to in vivo effects, in predicting effects from limited in vivo data, and in extrapolating from experimental data to human subjects.

Some systematic reviews have already been published regarding the associations between EDCs and adiposity. Kelishadi, R *et al.* (2013) included studies mainly using animal or mechanistic models and focused on EDCs mechanisms of action [30]. De Cock, M and van de Bor, M (2014) summarized the available information from observational studies on the relationship between perinatal exposures of six classes of chemicals and overweight later in life [31], while Tang-Péronard, JL *et*

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al. (2011), have sought to synthesize data on the association between EDCs and body size, but with a limited scope, since it included only twenty four studies for a wide range of chemical compounds [32]. Another systematic review has analysed the published literature on the effect of phthalates as obesogens, but presented results for outcomes other than overweight/obesity, such as diabetes or cardiovascular diseases [33]. The association between BPA and adiposity has also been previously reviewed in Lakind, JS *et al.* (2014) [34] and in Oppeneer, S *et al.* (2015) [35] but results were not statistically summarized. With the growing number of studies being published in the past few years, it is essential to synthesize the information provided from epidemiological evidence in order to draw more definite conclusions on the impact of EDCs in human health. To our knowledge, no meta-analysis regarding this matter was performed so far. In the 2002 IPCS assessment [36] the authors have stated that the available evidence was not enough to conclude that human health is adversely affected by the exposure to EDCs. Several scientific papers, reports and reviews have been published since then, showing emerging research for several adverse health effects of EDCs among human subjects. Nevertheless, evidence for the effect of EDCs in adiposity among humans is still limited, but the increasing burden of endocrine disruptors and the fact that all humans are potentially exposed to multiple EDCs, highlight the public health importance of these exposures.

The effect of the exposure to EDCs on adiposity is an utterly important area for research, with the potential to broaden or even change significantly the understanding of obesity etiology and to improve the impact of prevention efforts and interventions. It is well known that obesity is a major public health concern. In 2014, WHO has estimated that the worldwide prevalence of overweight was 39% in adults aged 18 or over, and 13% for obesity [37]. The numbers have also dramatically increased among children in past decades, presenting significant challenges for present and future global health. Obesity is also a major risk factor for several other chronic diseases, namely cardiovascular disease, diabetes, muscle skeletal diseases and cancer. The global burden associated with overweight and obesity was estimated in 2010 to cause 3.4

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million deaths, 4% of years of life lost, and 4% of DALYs [38]. Although the aetiology of obesity has been largely studied in the last decades, there is still much uncertainty about the causes of this epidemic. A sedentary lifestyle and excessive caloric intake have been indicated as the main factors responsible for overweight and obesity, especially in a background of genetic predisposition. More recently, the focus has changed from individual characteristics to a wider approach. Obesity is now regarded as a disease caused by a complex interaction between genetic, behavioural and environmental factors, requiring a comprehensive and coordinated effort in order to tackle this major public health concern.

The purpose of this report is to synthesize results from published literature on the association between the exposure to EDCs and adiposity in humans as intermediate phenotype of overweight, adiposity, diabetes and metabolic disorders. This work will allow the identification of literature gaps and will provide insight into new areas of research.

Methods

Literature search

We searched PubMed from inception up to October 2014, to retrieve original papers reporting data on the association between EDCs and adiposity, in adults and children, using the following search expression: (*"Endocrine disruptor" OR Endocrine disruptor[mh] OR Pesticide OR "Bisphenol A" OR "Brominated flame retardants" OR DDT OR DDE OR Hexachlorobenzene OR Organochlorine OR Organotin OR PFOS OR PFOA OR "Polybrominated diphenyl ethers" OR Polybrominated diphenyl ethers[mh] OR PCB OR phthalic acids[mh] OR phthalate*) AND (*Obesity OR*


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Overweight OR BMI OR "Body fat" OR Adipose tissue[mh] OR Body size[mh] OR "body size" OR "body weight" OR Anthropometry OR "anthropometric measures") AND (humans[mh]). The systematic review flowchart is presented in figure 1.

References were reviewed independently by two researchers (ID and VM) according to the following exclusion criteria: 1) studies not involving human subjects, 2) studies not presenting original data (review articles, editorials, reports, comments or guidelines), 3) case reports or case series, 4) studies with results not related to EDCs or addressing other outcomes than adiposity, 5) studies assessing maternal exposure to EDCs or birthweight as the outcome, 6) duplicates or studies involving the same sample and 7) studies not providing association measures. When more than one study referred to the same sample, we considered the one presenting data for the largest sample or, if the sample size was the same, we have chosen the one providing results with more detail. On the other hand, if two publications studying the same sample reported complementary results that otherwise would be lost if only one was included (i.e. presenting estimates for different adiposity measures), both of them were considered eligible for data extraction. Any of the reports could be used to obtain information on the study characteristics if necessary.

Publications were reviewed in two steps. In step one the exclusion of papers was based on title and/or abstract and in step two based on full text. When the abstract of a particular paper was not available, the article was selected for evaluation in step two, except when the title unequivocally presented information for exclusion (non-human subjects, review articles, editorials, reports, comments or guidelines and case reports). Decisions taken independently by the two reviewers were compared in both steps and disagreements were resolved by consensus or after discussion with a third researcher (ER). The agreement between the reviewers was 68.1% in step one and 72.3% in step two.

Our search identified 2442 publications of which 98 presented original data on the association between EDCs and adiposity (figure 1). Included papers and reviews that evaluated the association between EDCs and adiposity identified in step one and two were also screened to identify potential eligible studies.

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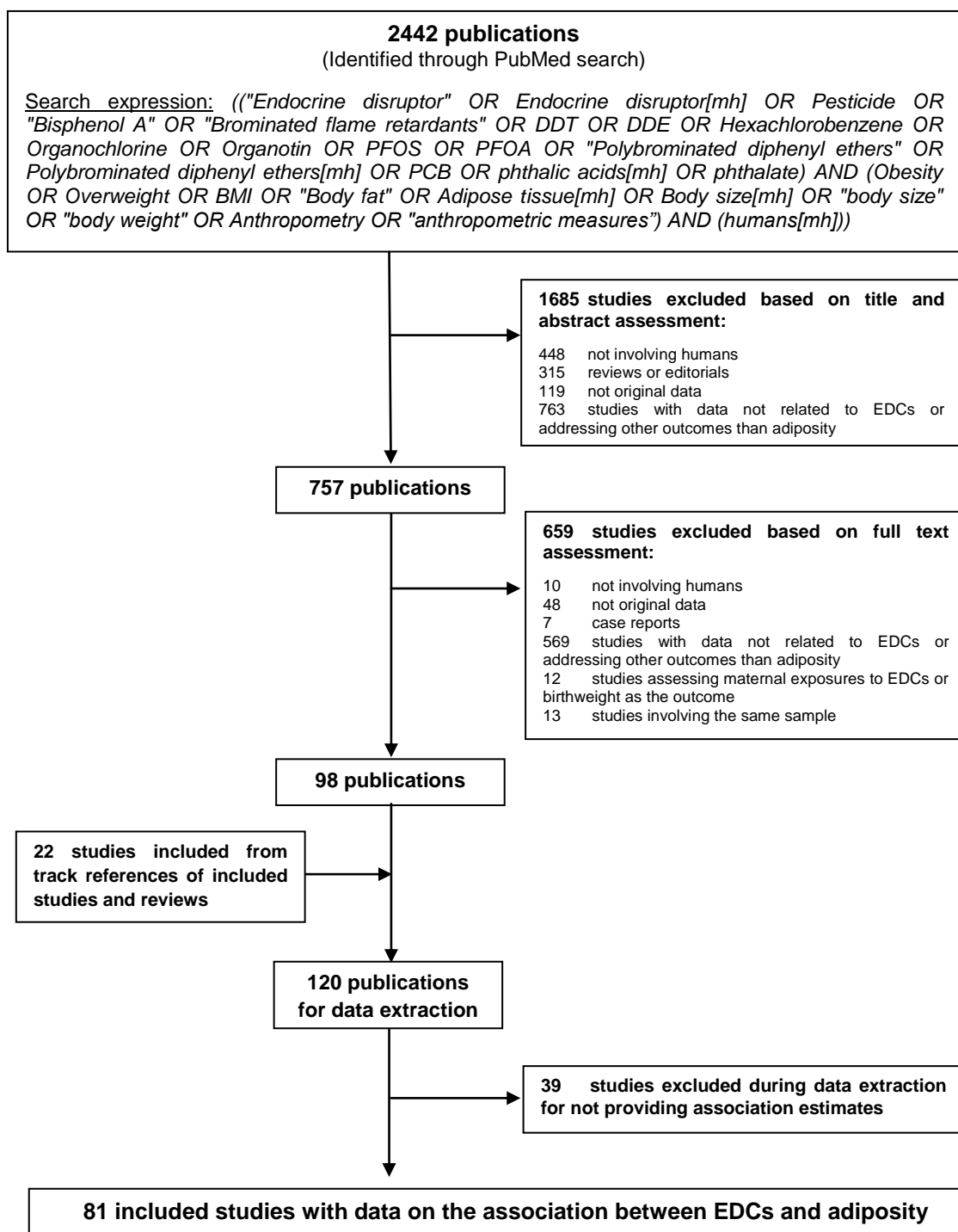



Figure 1. Systematic review flow-chart

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The literature search was then completed by backward citation tracking of the papers considered for data extraction. We have further included 22 original publications from the reference list of reviews and previously included publications, resulting on a total of 120 papers eligible for data extraction.

Data Extraction


Two researchers have independently evaluated full texts of the selected studies. During data extraction, 39 papers were excluded for not providing association measures.

The following information was then extracted: 1) study design (type of study and period of data collection), 2) sample characteristics (country, type of population, sex, age and sample size), 3) exposure characteristics (EDC substance, measurement site and assessment method), 4) outcome characteristics (adiposity measure and assessment method), 5) descriptive measures and 6) association measures. Estimates of the association between exposure to EDCs and adiposity were extracted for the whole sample. When available, age- or sex-stratified estimates were also extracted. If the exposure variable was presented in categories, we have extracted only the estimate provided for the group with higher exposure levels.

After data extraction, 81 publications with data on the association between EDC and adiposity were considered for the systematic review. Given the high number of EDCs evaluated, for the purpose of this report, we have combined the identified chemicals in 15 groups, according to their chemical properties.

Meta-analysis

For the 81 papers included in the systematic review, additional exclusion criteria were considered regarding the meta-analysis in order to improve comparability


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between studies. We excluded papers performed in individuals with a diagnosed disease (e.g. cancer) and studies performed among pregnant women because all this conditions could induce changes in adiposity and consequently modify the estimates for the association between EDCs and adiposity. Samples composed exclusively by individuals with high exposure to EDCs (e.g. workers involved in mixing or applying pesticides) were also excluded from meta-analysis, since these are individuals who have presumably been exposed to much higher doses of EDCs than individuals from other study samples, and therefore, levels of exposure reported in those studies are not comparable with results reported in studies performed in the general population.

We decided to perform separate analysis for adults and children, as the same measure of adiposity may have a different meaning in each of these age groups. When studies performed among children were in limited number and meta-analysis could not be performed, data regarding children is presented only in descriptive tables.

We have found studies presenting association measures that were not possible to combine (e.g. ORs with correlation coefficients). Since most studies provided correlation or beta coefficients to assess the association between EDCs and adiposity, we have decided to further exclude from meta-analysis studies presenting not compatible association measures, such ORs, relative risks or hazard ratios. We have also excluded from meta-analysis studies that provided coefficients for log transformed variables since they were not compatible with those provided for untransformed variables.

The number of included studies in the systematic review and meta-analysis per EDCs is presented in table 1. A meta-analysis was performed for every specific compound whenever three or more estimates evaluating the association of that same substance with adiposity fulfilled the above-mentioned criteria. When estimates for more than one adiposity measure were available for the same sample, the one reported in the largest number of papers for each EDC was selected to be included in meta-analysis.

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Table 1. Number of studies included in the systematic review and in the meta-analysis for each EDC

EDCs	Papers included in systematic review	Papers included in meta-analysis
Chlordanes		
Oxychlordane	6	4
Trans-nonachlor	10	6
Sum of chlordanes	1	-
Dichlorodiphenyltrichloroethane (DDT)		
p,p'-Dichlorodiphenyldichloroethylene (p,p'-DDE)	17	11
Dichlorodiphenyldichloroethylene (DDE - not specified)	8	6
p,p'-DDT	6	4
Sum of DDT	3	-
Polychlorinated Dibenzodioxins (PCDD)*	11	-
Polychlorinated Dibenzofurans (PCDF)*	4	-
Perfluorinated Carboxylic Acid (PFCA)*	2	-
Hexachlorocyclohexane (HCH)		
β-HCH	6	4
Sum of HCH	1	-
Hexachlorobenzene (HCB)	12	9
Organophosphates*	2	-
Dioxin-like Polychlorinated Biphenyls		
PCB 118	10	5
PCB 156	6	3
PCB 105	3	-
PCB 114	1	-
PCB 126	4	-
PCB 157	3	-
PCB 167	1	-
PCB 169	2	-
PCB 189	3	-
Sum of dioxin-like PCBs	5	-
Non-Dioxin-like Polychlorinated Biphenyls		
PCB 99	6	3
PCB 138	12	9
PCB 153	14	8
PCB 170	8	4
PCB 180	11	6
PCB 187	4	3
PCB 28	1	-
PCB 74	5	-
PCB 136	1	-
PCB 183	1	-
PCB 194	4	-
PCB 206	3	-
PCB 209	3	-
Sum of non-dioxin-like PCBs	5	-
Sum of PCBs*	20	-
Organobromines*	6	-
Phthalates		
Mono-butyl Phthalate (mBP)	7	4
Mono-(2-ethylhexyl) Phthalate (MEHP)	12	5
Mono-ethyl Phthalate (MEP)	9	6
Mono-iso-butyl Phthalate (MiBP)	7	3
Mono-methyl Phthalate (MMP)	5	3
Mono-benzyl Phthalate (MBzP)	7	4
Mono-(2-ethyl-5-oxohexyl) Phthalate (MEOHP)	7	3
Mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP)	7	3
Mono-n-butyl Phthalate (MnBP)	2	-
Mono-(3-carboxypropyl) Phthalate (MCPHP)	2	-


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Table 1. Number of studies included in the systematic review and in the meta-analysis for each EDC

EDCs	Papers included in systematic review	Papers included in meta-analysis
Mono (2-ethyl-5-carboxypentyl) Phthalate (MECPP)	5	-
Mono (2-carboxymethylhexyl) Phthalate (MCHHP)	1	-
Mono-cyclohexyl Phthalate (MCHP)	1	-
Mono (3-hydroxybutyl) Phthalate (MHBP)	1	-
Mono (carboxynonyl) Phthalate (MCNP)	1	-
Mono (carboxysooctyl) Phthalate (MCOP)	1	-
Sum of Phthalates	6	-
Bisphenol A	14	7
Other EDCs*	15	-

*Number of included papers is presented for the chemical group as a whole. These groups include several distinct substances with similar chemical properties, not specified in this description.


Statistical Analysis

Standardized regression coefficient effect size and its standard error were calculated in different research approaches of the original studies [39]. When necessary, adjusted or crude regression coefficients and Pearson or Spearman correlation coefficients were converted into standardized regression coefficients, and were used for meta-analyses of data. Meta-analyses based on regression coefficients computed after log transformation of the exposure and/or outcome data were performed separately. Appropriately converted data from the studies were combined using fixed effects meta-analyses to compute summary regression coefficients and corresponding 95% confidence intervals (95% CI) [40]. Heterogeneity between studies was assessed by the I^2 statistic [41]. The statistical analysis was performed with STATA[®], version 11.2 (StataCorp, College Station, TX, USA).

Results

1. Chlordanes

In the systematic review we have identified eleven publications reporting on the association between chlordanes and adiposity outcomes [42-52]. Six papers assessed

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oxychlordane as the exposure [42-47], ten have focused on trans-nonachlor [42-51], while one publication presented estimates for the combination of oxychlordane, transchlordane, cischlordane, trans-nonachlor and cis-nonachlor (sum of chlordanes) [52]. Adiposity was assessed by five different measures (BMI, fat mass, waist circumference, visceral adipose tissue and subcutaneous adipose tissue), with BMI being the most common measure across all compounds.

1.1 Oxychlordane

Of the six papers identified in the systematic review assessing oxychlordane, three (Lee, DH *et al.* (2006) [45], Lee, DH *et al.* (2007) [46] and Cho, MR *et al.* (2011) [47]) were performed using NHANES 1999-2000 and 2001-2002 combined datasets. Lee DH *et al.* (2006) [45] was the one included in the meta-analysis since Lee, DH *et al.* (2007) [46] presented association estimates as ORs and Cho, MR *et al.* (2011) [47] did not assess BMI as the adiposity measure.

We have included four publications in this meta-analysis [42-45], all of them presenting a cross-sectional design. Apart from the NHANES study [45] (n=2016), all others were performed with rather small sample sizes (ranging from 42 to 72 individuals) [42-44]. The overall beta coefficient was 0.08 (95% CI 0.04; 0.12) (figure 1.1). Heterogeneity was considerably high, with a percentage of variance of 91.9%.

One aspect possibly conditioning heterogeneity between studies is different exposure levels between study samples, difficult to evaluate if the information is missing or presented in different formats. Unfortunately, Lee DH *et al.* (2006) [45] and Hue, O *et al.* (2006) [44] did not present the mean values of oxychlordane concentration, while Magnúsdóttir, E *et al.* (2005) [43] and Pelletier, C *et al.* (2002) [42] presented geometric and arithmetic means, respectively, and therefore we are not able to evaluate the impact of exposure levels on the comparability of results. Despite the high percentage of variance found, all studies have shown a positive association

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between oxychlordan and BMI, indicating that higher levels of oxychlordan are associated with higher levels of BMI.

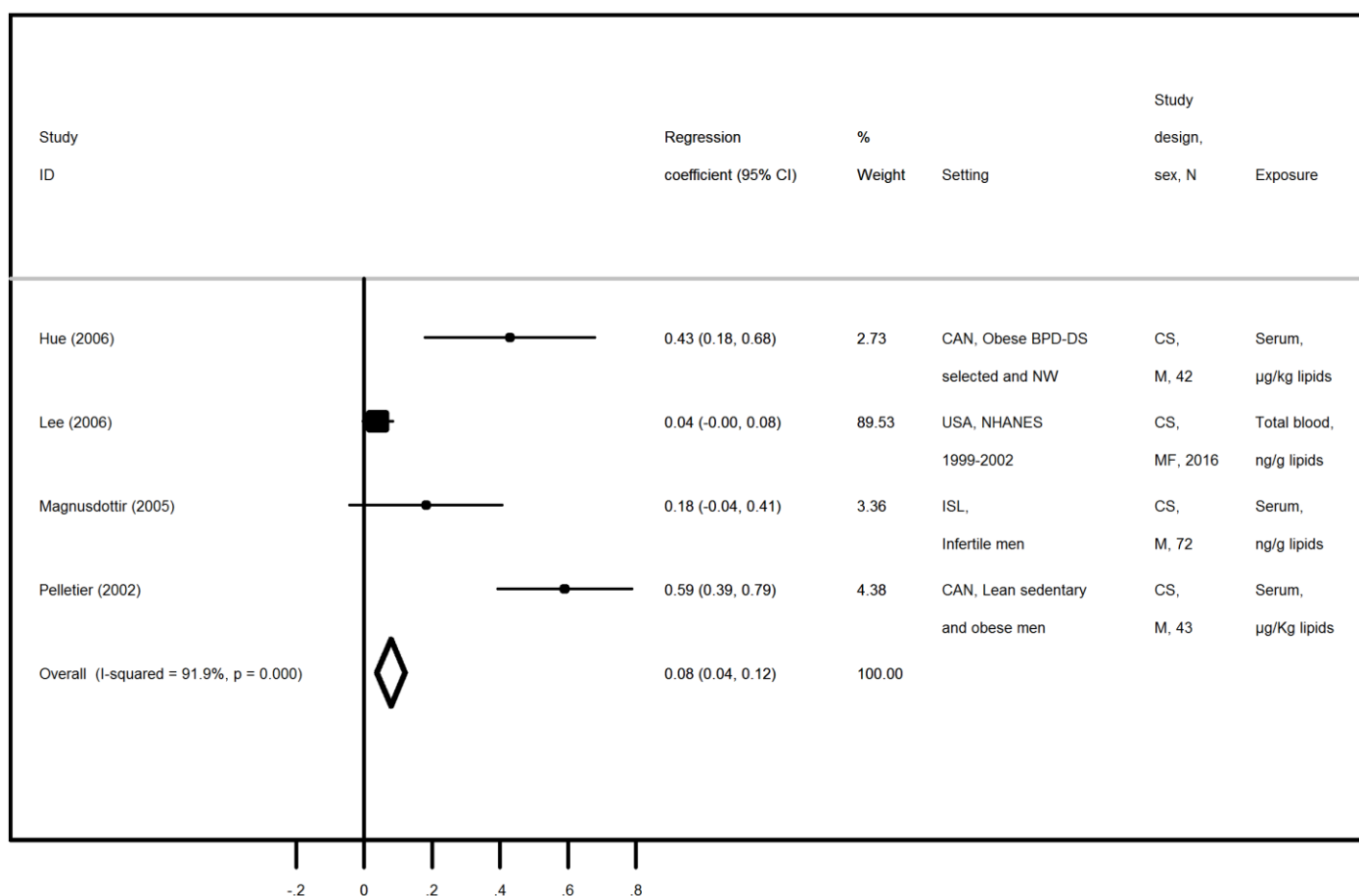



Figure 1.1. Meta-analysis of studies evaluating the association of oxychlordan with BMI in adults. Beta coefficients and corresponding 95% CI (horizontal lines). The size of the black square indicates the study's weight in the analysis (weights are from fixed-effects analysis). The centre of the open diamond indicates the summary estimate and its width represents the 95% CI.

Table 1.1.1 presents the description of publications addressing the association between oxychlordan and other adiposity measures. Pelletier, C *et al.* (2002) [42] and Cho, M *et al.* (2011) [47] provided five estimates for fat mass and have in general observed positive and statistically significant correlations. Lee, DH *et al.* (2006) [45] and Lee, DH *et al.* (2007) [46] evaluated the association between oxychlordan and

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waist circumference and also found positive associations, although with no statistical significance. These estimates were consistent with the associations described for BMI, already represented for the same populations in the meta-analysis shown in figure 1.1.


Table 1.1.1. Description of papers assessing the association between oxychlordan and other adiposity measures

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Fat Mass									
Pelletier, C et al. (2002) [42]	CAN	CS	Lean sedentary and obese men; ♂(n=43)	Adults (36-58)	Serum (GC)	FM (Siri equation)	µg/Kg lipids	ρ=0.41 (p=0.006)	Age
Cho, MR et al. (2011) [47]	USA	CS	NHANES, 1999-2004; ♂(n= 768)	Adults (<50)	Serum (HRGC/IDHRMS)	FM (DXA)	ng/g lipids	r=0.01 (p<0.01)	Age, race, PIR, smoking, PA, height
Cho, MR et al. (2011) [47]	USA	CS	NHANES, 1999-2004; ♂(n= 612)	Adults (≥50)	Serum (HRGC/IDHRMS)	FM (DXA)	ng/g lipids	r=0.19 (p<0.001)	Age, race, PIR, smoking, PA, height
Cho, MR et al. (2011) [47]	USA	CS	NHANES, 1999-2004; ♀(n= 710)	Adults (<50)	Serum (HRGC/IDHRMS)	FM (DXA)	ng/g lipids	r= -0.11 (p<0.01)	Age, race, PIR, smoking, PA, height
Cho, MR et al. (2011) [47]	USA	CS	NHANES, 1999-2004; ♀(n= 679)	Adults (≥50)	Serum (HRGC/IDHRMS)	FM (DXA)	ng/g lipids	r=0.01 (p>0.01)	Age, race, PIR, smoking, PA, height
Waist Circumference									
Lee, DH et al. (2006) [45]	USA	CS	NHANES 1999-2002; ♂(n=903), ♀(n= 1113)	Adults (≥20)	Serum (HRGC/IDHRMS)	WC (measured)	ng/g lipid	ρ=0.04 (p>0.01)	-
Lee, DH et al. (2007) [46]	USA	CS	NHANES Non-diabetic; 1999-2002; ♂♀(n= 721)	Adults (≥20)	Serum (HRGC/IDHRMS)	WC (measured) ♂>102 cm, ♀>88 cm	>75 th vs. BDL	OR=1.2 (0.6; 2.4)	Age, sex, race, PIR, smoking, alcohol, exercise

Shading represents papers for which the same samples were already included in the meta-analysis plot.

CS: Cross-sectional; NHANES: National Health and Nutrition Examination Survey; GC: Gas chromatography; HRGC: High Resolution Gas Chromatography; IDHRMS: Isotope Dilution High Resolution Mass Spectrometry; FM: Fat Mass; WC: Waist Circumference; DXA: Dual-energy X-ray absorptiometry; BDL: Below Detected Levels; ρ: Spearman correlation coefficient; OR: Odds ratio; r: Pearson correlation coefficient; PIR: Poverty Income Ratio; PA: Physical Activity.

Table 1.1.2 summarizes the available results regarding the association between oxychlordan and each adiposity measure, in order to understand if the association found for BMI would hold using different adiposity measures. It is important to highlight that results from studies with ORs or transformed variables (log) were not considered

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for the following summary estimates, since it is not possible to combine them with the remaining results. Furthermore, as we have tried to include as much studies as possible, no sensitivity analysis was taken into account, and a high heterogeneity is expected. These summary estimates should be carefully considered.

The overall beta coefficient for the five estimates provided by the two papers evaluating fat mass [42, 47] was 0.03 (95% CI -0.01; 0.07). As expected, the heterogeneity between estimates was very high ($I^2 = 90.0\%$) and therefore, this result should be carefully considered. Only two papers [45, 46], both in the same population, presented data for waist circumference and also found a positive association. The overall results suggest that higher levels of oxychlordan are associated with higher levels of adiposity, regardless of the adiposity measure used.

Table 1.1.2. Summary estimates for the association between oxychlordan and each adiposity measure

	Number of included estimates	Oxychlordan		
		Summary Estimate*	I^2 (%)	95% CI
Body Mass Index	4 ^a	0.08	91.1	0.04; 0.12
Fat Mass	5 ^b	0.03	90.0	-0.01; 0.07
Waist Circumference	1 ^c	0.04 [†]	-	>0.01 [‡]


I^2 available only when meta-analysis was performed.

*Beta coefficient if not otherwise specified; [†]Spearman correlation coefficient; [‡]p value.

Included studies are: ^aPelletier, C et al. (2002)[42], Magnusdottir, EV et al. (2005)[43], Hue, O et al. (2006)[44] and Lee, DH et al. (2006)[45]; ^bPelletier, C et al. (2002)[42] and Cho, MR et al. (2011)[47] ^cLee, DH et al. (2006)[45].

1.2 Trans-nonachlor

We found ten publications reporting data on the association between trans-nonachlor and adiposity. Three of those presented results using NHANES 1999-2000 and 2001-2002 combined datasets [45-47] and, as in oxychlordan, we have included Lee, DH *et al.* (2006) [45]. The three papers presenting data based on PIVUS study

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[49-51] were also excluded from meta-analysis. Ronn, M *et al.* (2011) [49] and Roos, V *et al.* (2013) [51] were excluded for presenting regression coefficients for log transformed variables and Lee, DH *et al.* (2012) [50] was excluded for presenting results as ORs.

A total of five papers were included in this meta-analysis [42-45, 48]. The overall beta coefficient was 0.04 (95% CI 0.00; 0.08), with a study heterogeneity of 60.3%. Despite the high heterogeneity observed between studies, all publications showed a positive association between trans-nonachlor and adiposity measures.

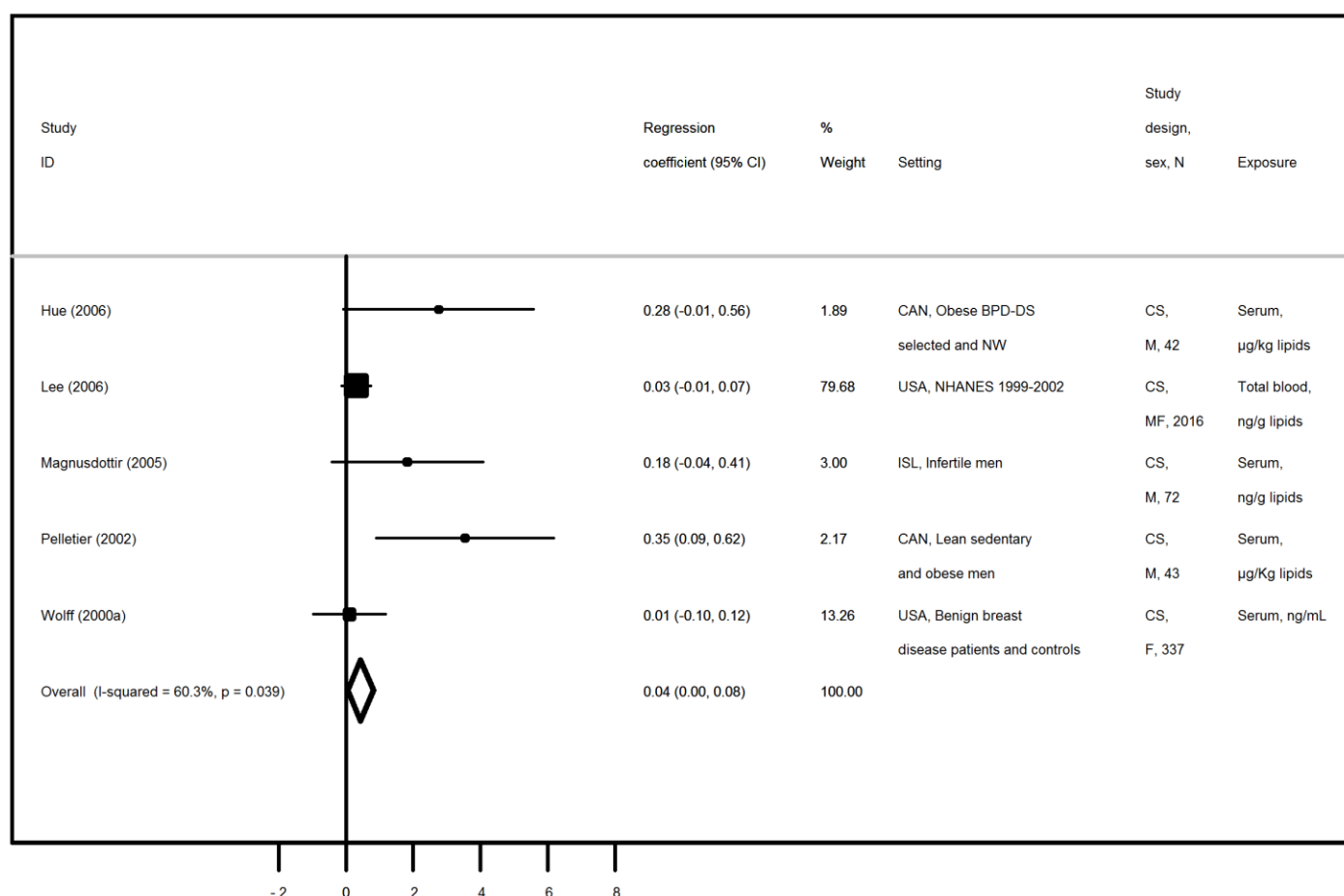


Figure 1.2. Meta-analysis of studies evaluating the association of trans-nonachlor with BMI in adults. Beta coefficients and corresponding 95% CI (horizontal lines). The size of the black square indicates the study's weight in the analysis (weights are from fixed-effects analysis). The centre of the open diamond indicates the summary estimate and its width represents the 95% CI.


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Table 1.2.1 shows the description of papers assessing the association between trans-nonachlor and other adiposity measures. Shading lines represent estimates obtained from samples already included in the meta-analysis plot. Pelletier, C *et al.* (2002) [42], Cho, MR *et al.* (2011) [47] and Ronn, M *et al.* (2011) [49] provided a total of 6 estimates evaluating the association of trans-nonachlor and fat mass. In general, all results were positive but not statistically significant. Similar results were observed for the remaining adiposity measures. The only exception was found in Lee, DH *et al.* (2012) [50] among PIVUS women (OR= 0.9, 95% CI 0.5; 1.8).

Table 1.2.1. Description of papers assessing the association between trans-nonachlor and other adiposity measures

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Fat Mass									
Pelletier, C <i>et al.</i> (2002) [42]	CAN	CS	Lean sedentary and obese men; ♂(n=43)	Adults (36-58)	Serum (GC)	FM (Siri equation)	µg/Kg lipids	ρ=0.23 (p=0.143)	Age
Cho, MR <i>et al.</i> (2011) [47]	USA	CS	NHANES, 1999-2004; ♂(n=768)	Adults (<50)	Serum (HRGC/IDHRMS)	FM (DXA)	ng/g lipids	r=0.01 (p>0.01)	Age, race, PIR, smoking, PA, height
Cho, MR <i>et al.</i> (2011) [47]	USA	CS	NHANES, 1999-2004; ♂(n=612)	Adults (≥50)	Serum (HRGC/IDHRMS)	FM (DXA)	ng/g lipids	r=0.11 (p<0.001)	Age, race, PIR, smoking, PA, and others
Cho, MR <i>et al.</i> (2011) [47]	USA	CS	NHANES, 1999-2004; ♀(n=710)	Adults (<50)	Serum (HRGC/IDHRMS)	FM (DXA)	ng/g lipids	r= -0.13 (p<0.01)	Age, race, PIR, smoking, PA, height
Cho, MR <i>et al.</i> (2011) [47]	USA	CS	NHANES, 1999-2004; ♀(n=679)	Adults (≥50)	Serum (HRGC/IDHRMS)	FM (DXA)	ng/g lipids	r=0.04 (p>0.01)	Age, race, PIR, smoking, PA, and others
Ronn, M <i>et al.</i> (2011) [49]	SWE	PC	PIVUS; ♂(n=431), ♀(n=459)	Adults (70y.o.)	Serum (HRGC/HRMS)	FM (DXA)	Per 1-unit (ln ng/g lipid)	β=1.86 (0.85;2.86)	Sex
Waist Circumference									
Lee, DH <i>et al.</i> (2006) [45]	USA	CS	NHANES 1999-2002; ♂(n=903), ♀(n= 1113)	Adults (≥20)	Serum (HRGC/IDHRMS)	WC (measured)	ng/g lipids	ρ=0.01 (p>0.01)	-
Lee, DH <i>et al.</i> (2007)	USA	CS	NHANES, Non-diabetic;1999-	Adults (≥20)	Serum (HRGC/IDHRMS)	WC (measured)	>75 th vs. BDL	OR=1.4 (0.7; 2.9)	Age, sex, race, PIR,



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Table 1.2.1. Description of papers assessing the association between trans-nonachlor and other adiposity measures

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
[46]			2002; ♂♀n=721			♂>102 ♀>88			smoking, alcohol, exercise
Lee, DH et al. (2012) [50]	SWE	CS	PIVUS, 2001-2004; ♂(n=490)	Adults (70y.o.)	Plasma (HRGC/HRMS)	WC (Measured) ♂>102cm	370-4252 vs. <173 (pg/ml)	OR=2.5 (1.1; 5.6)	Calories, exercise, smoking, TG, TC, alcohol,
Lee, DH et al. (2012) [50]	SWE	CS	PIVUS, 2001-2004; ♀(n=480)	Adults (70y.o.)	Plasma (HRGC/HRMS)	WC (Measured) ♀>88cm	370-4252 vs. <173 (pg/ml)	OR=0.9 (0.5; 1.8)	Calories, exercise, smoking, TG, TC, alcohol,
Lee, DH et al. (2012) [50]	SWE	PC	PIVUS, 2001-2009; ♂(n=305)	Adults (≥75)	Plasma (HRGC/HRMS)	WC (Measured) ♂>102cm	370-4252 vs. <173 (pg/ml)	OR=0.7 (0.2; 2.4)	Calories, exercise, smoking, TG, TC, alcohol,
Lee, DH et al. (2012) [50]	SWE	PC	PIVUS, 2001-2009; ♀(n=206)	Adults (≥75)	Plasma (HRGC/HRMS)	WC (Measured) ♀>88cm	370-4252 vs. <173 (pg/ml)	OR=0.7 (0.2; 1.9)	Calories, exercise, smoking, TG, TC, alcohol,
Visceral Adipose Tissue and Subcutaneous Adipose Tissue									
Roos, V et al. (2013) [51]	SWE	CS	PIVUS; ♂♀(n=287)	Adults (70y.o.)	Plasma (HRGC/HRMS)	VAT (MRI)	Per 1-unit (ln ng/g lipid)	β=17.0 (4.7; 30.0)	Sex, education, exercise, smoking
Roos, V et al. (2013) [51]	SWE	CS	PIVUS; ♂♀(n=287)	Adults (70y.o.)	Plasma (HRGC/HRMS)	SAT (MRI)	Per 1-unit (ln ng/g lipid)	β=19.0 (-2.6; 40.0)	Sex, education, exercise, smoking

Shading represents studies for which the same samples were already included in the meta-analysis plot. CS: Cross-sectional; PC: Prospective cohort; NHANES: National Health and Nutrition Examination Survey; PIVUS: Prospective Investigation of the Vasculature in Uppsala Seniors; GC: Gas chromatography; HRGC: High Resolution Gas Chromatography; IDHRMS: Isotope Dilution High Resolution Mass Spectrometry; FM: Fat Mass; WC: Waist Circumference; DXA: Dual-energy X-ray absorptiometry; VAT: Visceral adipose tissue; SAT: Subcutaneous adipose tissue; MRI: Magnetic Resonance Imaging; Qu: Quintile; BDL: Below detected levels; p: Spearman Coefficient; OR: Odds ratio; r: Pearson coefficient; β: Beta coefficient; PIR: Poverty Income Ratio; PA: Physical Activity; TG: triglycerides; TC: Total Cholesterol. †No further information

Table 1.2.2 summarizes the available data for the association between trans-nonachlor and other adiposity measures. For fat mass the overall beta coefficient for the five estimates evaluating fat mass (excluding Ronn, M *et al.* (2011) [49]) was 0.01 (95% CI -0.03; 0.04), with a percentage of variance of 81.7%. For waist circumference, mixed results were observed, but in general, no significant associations were found. These results suggest a positive, though weak, association between trans-nonachlor and adiposity regardless of the outcome measure, indicating an increase of adiposity with increasing levels of trans-nonachlor. Results regarding visceral and subcutaneous

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adipose tissue were the ones presenting stronger associations but also showing very wide confidence intervals and both from the same study.


Table 1.2.2. Summary estimates for the association between trans-nonachlor and each adiposity measure

	Trans-nonachlor			
	Number of included estimates	Summary Estimate*	I ² (%)	95% CI
Body Mass Index	5 ^a	0.04	60.3	0.00; 0.08
Fat Mass	5 ^b	0.01	81.7	-0.03; 0.04
Waist Circumference	1 ^c	0.01 [†]	-	>0.01 [‡]
Visceral Adipose Tissue	1 ^d	17.0	-	4.7; 30.0
Subcutaneous Adipose Tissue	1 ^d	19.0	-	-2.6; 40.0

I² available only when meta-analysis was performed.

*Beta coefficient if not otherwise specified; [†]Spearman correlation coefficient; [‡]p value.

Included studies are: ^a Wolff, MS et al. (2000a)[48], Pelletier, C et al. (2002)[42], Magnusdottir, EV et al. (2005)[43], Hue, O et al. (2006)[44] and Lee, DH et al. (2006)[45]; ^bPelletier, C et al. (2002)[42] and Cho, MR et al. (2011)[47]; ^c Lee, DH et al. (2006)[45]; ^dRoos, V et al. (2013)[51].

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1.3 Sum of Chlordanes

The only paper using a sum of chlordanes as the exposure variable also had a cross-sectional design, with a sample size of 53 adult South Korean women with ages ranging from 40 to 68 years old. This was the only study of the entire group of chlordanes in which the exposure assessment was measured in the adipose tissue, instead of using blood samples. The spearman correlation coefficient was also positive but without statistical significance ($p=0.23$, $p>0.05$) (table 1.3.1).


Table 1.3. Description of the only paper assessing the association between the sum of chlordanes (oxychlordane, trans-chlordane, cis-chlordane, trans-nonachlor and cis-nonachlor) and adiposity

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Moon, HB et al. (2012)[52]	KOR	CS	Myoma patients; ♀(n=53)	Adults (40-68)	Adipose Tissue (GC/MS)	BMI	ng/g lipid	$p=0.23$ ($p>0.05$)	-

CS: Cross-sectional; GC: Gas chromatography; MS: Mass Spectrometry; BMI: Body Mass Index; p: spearman correlation coefficient.

2. Dichlorodiphenyltrichloroethane (DDT)

In the systematic review we have identified 28 publications [42-70] on the association between DDT and adiposity. Each paper evaluated one or more DDT compounds. Seventeen publications have specifically assessed p,p'-Dichlorodiphenyldichloroethylene (p,p'-DDE) as the exposure [42-45, 47, 50, 53-63], eight have measured DDE (not specified) [48, 49, 51, 65-69], six presented associations regarding p,p'-DDT [42, 46, 48, 61, 63, 64] and finally three studies assessed different combinations of DDT substances as the exposure variable. Considering the whole DDT group, adiposity was assessed by 7 different measures (BMI, fat mass, waist circumference, waist to hip ratio, weight, visceral adipose tissue


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and subcutaneous adipose tissue), being BMI the most common measure across all compounds and studies.

2.1 p,p'-dichlorodiphenyldichloroethylene (p,p'-DDE)

Of the seventeen identified papers with data on the association between p,p'-DDE and adiposity, two were not eligible for meta-analysis for being performed in pregnant women [55, 58], one for including cancer patients [61] and one for including only children [59]. Of the remaining thirteen publications, Cho, MR *et al.* (2011) [47] and Lee DH *et al.* (2006) [45] were performed using NHANES 1999-2000 and 2001-2002 combined datasets; as Cho, MR *et al.* (2011) [47] did not present BMI as the outcome measure, in order to improve homogeneity between studies, Lee DH *et al.* (2006) [45] was included in the meta-analysis. Additionally, Lee, DH *et al.* (2012) [50] was excluded from the meta-analysis for presenting estimates as ORs. Thus, this meta-analysis was based on a total of eleven papers.

Figure 2.1 presents the forest plot with the included studies assessing the association between p,p'-DDE and BMI. The eleven included papers presented data from Spain, Switzerland, Netherlands, Germany and Ireland (EURAMIC study), USA, Canada, Iceland, Belgium, Hong Kong, Slovakia and Thailand and all had a cross-sectional design, involving adult individuals. The overall estimate from meta-analysis was $\beta = 0.19$ (95% CI 0.16; 0.21). The percentage of variance found was very high ($I^2=96.4\%$), limiting the interpretation of the overall estimate. Despite the high heterogeneity found, with the exception of Dirinck, E *et al.* (2014) [62] ($p = -0.07$, 95% CI -0.21; 0.07), all publications provided positive associations.

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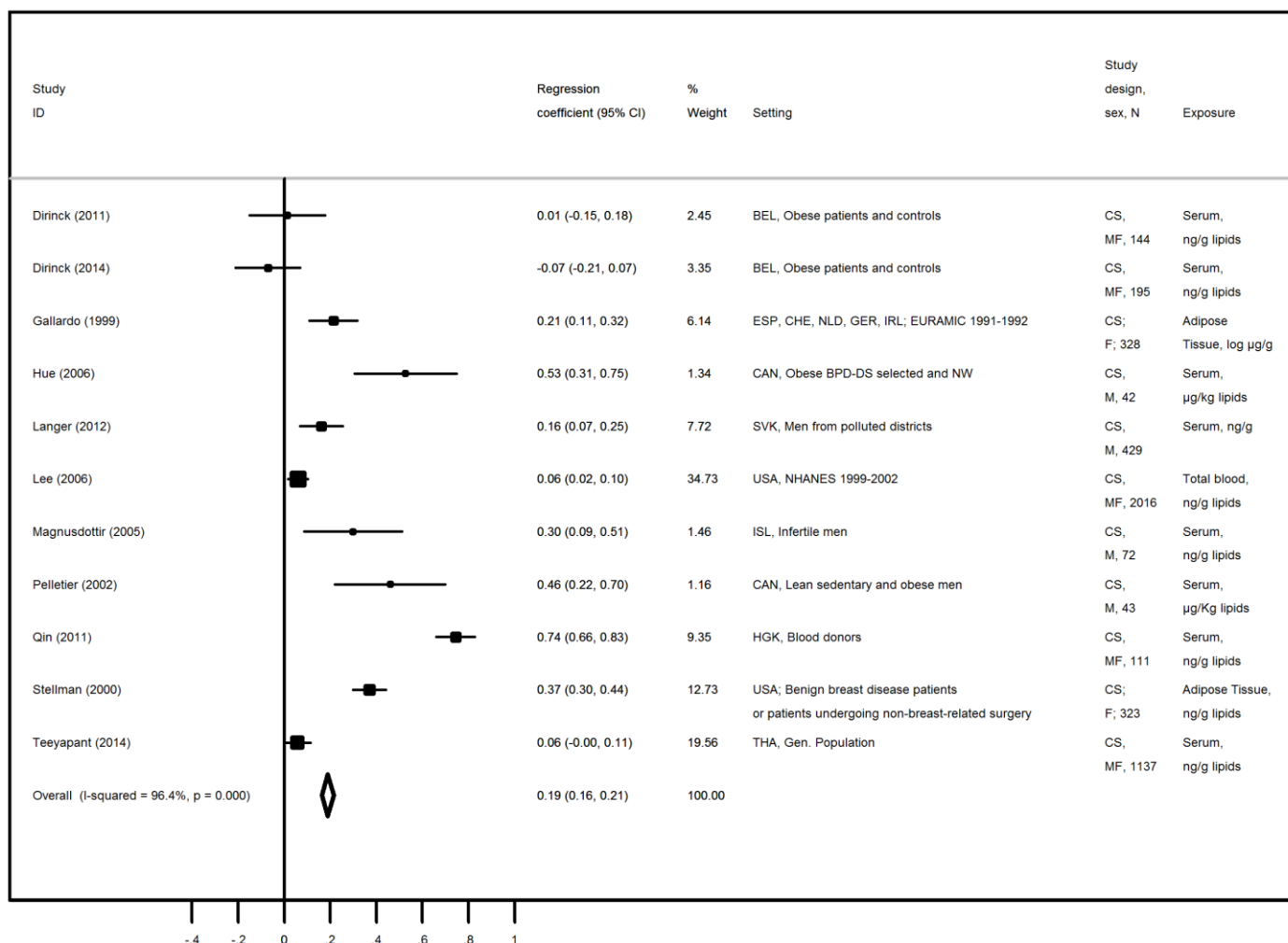


Figure 2.1. Meta-analysis of studies evaluating the association of p,p'-DDE with BMI in adults. Beta coefficients and corresponding 95% CI (horizontal lines). The size of the black square indicates the study's weight in the analysis (weights are from fixed-effects analysis). The centre of the open diamond indicates the summary estimate and its width represents the 95% CI.

Gallardo, I et al. (1999) and Stellman, SD et al. (2000) were the only papers that evaluated p,p'-DDE concentration in the adipose tissue, we have performed a sensitivity analysis excluding both papers in order to understand if their exclusion would improve our results. However, neither the overall estimate changed nor the heterogeneity decreased [β = 0.16 (95% CI 0.13; 0.19), I^2 = 96.8%]. Due to the limited number of included papers, it was not possible to test other sources of heterogeneity.


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Table 2.1.1 shows the description of publications assessing BMI that were not considered in the meta-analysis presented in figure 2.1 [55, 58, 59, 61]. Results from Dorea, J *et al.* (2001) [55] and Wu, H *et al.* (2013) [61] also presented a positive association between p,p'-DDE and BMI. Al-Saleh, I *et al.* (2012) [58] was performed among pregnant women and found a negative association but with no statistical significance, while Burns, JS *et al.* (2012) [59], the only study performed among children, have also found a negative association but statistically significant.

Table 2.1.1. Description of papers assessing the association between p,p'-DDE and BMI not eligible for the meta-analysis

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Dorea, J <i>et al.</i> (2001) [55]	BRA	CS	Pregnant living in the Rio Atoya basin; ♀(n= 52)	Adults (16-42)	Adipose Tissue (GC)	BMI (self-reported)	ng/g	$\rho = 0.0954$ (p= 0.017)	-
Dorea, J <i>et al.</i> (2001)[55]	BRA	CS	Pregnant living in the Rio Atoya basin; ♀(n= 52)	Adults (16-42)	Whole blood (GC)	BMI (self-reported)	ng/g	$\rho = 0.689$ (p= 0.944)	-
Al-Saleh, I <i>et al.</i> (2012)[58]	SAU	CS	Pregnant 1 st T; ♀(n=1518)	Adults (28.47± 6.03)*	Serum (GC)	BMI (measured W&H)	µ/L	$r = -0.035$ (p= 0.37)	-
Al-Saleh, I <i>et al.</i> (2012)[58]	SAU	CS	Pregnant 2 nd T; ♀(n=1518)	Adults (28.47± 6.03)*	Serum (GC)	BMI (measured W&H)	µ/L	$r = -0.023$ (p= 0.541)	-
Al-Saleh, I <i>et al.</i> (2012)[58]	SAU	CS	Pregnant 3 rd T; ♀(n=1518)	Adults (28.47± 6.03)*	Serum (GC)	BMI (measured W&H)	µ/L	$r = -0.017$ (p= 0.633)	-
Wu, H <i>et al.</i> (2013) [61]	USA	PC	Nurses breast cancer study; ♀(n=649)	Adults	Serum (GC)	BMI (self-reported W&H)	ng/g lipids	$\rho = 0.03$ (p>0.05)	Age
Wu, H <i>et al.</i> (2013) [61]	USA	PC	Nurses non-Hodgkin lymphoma study; ♀(n=398)	Adults	Serum (GC)	BMI (self-reported W&H)	ng/g lipids	$\rho = 0.07$ (p>0.05)	Age
Burns, JS <i>et al.</i> (2012)[59]	RUS	PC	Gen. Population; ♂(n=350)	Children (8-9)	Serum (HRMS)	BMI z-score (measured W&H)	550-9370 vs. 48-172 (ng/g lipids)	$\beta = -1.37$ (-1.75; -0.98)	Age, BW, gestational age, income, calories, blood lead levels

CS: Cross-sectional; PC: Prospective Cohort; T: Trimester; GC: Gas chromatography; HRMS: High Resolution Mass Spectrometry; BMI: Body Mass Index; W: Weight; H: Height; Qu: Quintile; ρ : Spearman correlation coefficient; r : Pearson correlation coefficient; β : Beta coefficient; BW: Birthweight. *Mean±sd.


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Table 2.1.2 shows the description of publications addressing the association between p,p'-DDE and other adiposity measures. With the exception of Lee, DH *et al.* (2012) [50] all papers provided estimates for populations already included in the meta-analysis plot. Dirinck, E *et al.* (2014) [62] was the only paper evaluating the association between p,p'-DDE and weight and found a negative correlation among adult patients from a weight management clinic. Regarding fat mass, in general, positive results were found with the exception of one estimate provided by Cho, MR *et al.* (2011) [47] among females aged <50 years old. On the other hand, three of the four papers assessing the relation between p,p'-DDE and waist circumference have observed negative correlations [45, 56, 62]. However, the only publication presenting ORs (Lee, DH *et al.* (2012) [50]) has shown a positive association between waist circumference and p,p'-DDE [OR (95% CI) 2.6 (1.1; 5.7) for men and 1.7 (0.9; 3.1) for women]. Results evaluating waist to hip ratio have also found positive associations [56, 62].

Table 2.1.2. Description of papers assessing the association between p,p'-DDE and other adiposity measures

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Weight									
Dirinck, E <i>et al.</i> (2014)[62]	BEL	CS	Patients weight management clinic; ♂♀n= 195	Adults (18-84)	Serum†	Weight (measured)	ng/g lipids	r= -0.06 (p= 0.39)	-
Fat Mass									
Pelletier, C <i>et al.</i> (2002)[42]	CAN	CS	Lean sedentary and obese men; ♂(n=43)	Adults (36-58)	Serum (GC)	FM (Siri equation)	µg/Kg lipids	p= 0.49 (p<0.001)	Age
Cho, MR <i>et al.</i> (2011)[47]	USA	CS	NHANES 1999-2004; ♂(n= 768)	Adults (<50)	Serum (HRGC/IDHRMS)	FM (DXA)	ng/g lipids	r= 0.13 (p<0.01)	Age, race, PIR, smoking, PA, height
Cho, MR <i>et al.</i> (2011)[47]	USA	CS	NHANES, 1999-2004; ♂(n= 612)	Adults (≥50)	Serum (HRGC/IDHRMS)	FM (DXA)	ng/g lipids	r= 0.14 (p<0.001)	Age, race, PIR, smoking, PA, height
Cho, MR <i>et al.</i> (2011)[47]	USA	CS	NHANES, 1999-2004; ♀(n= 710)	Adults (<50)	Serum (HRGC/IDHRMS)	FM (DXA)	ng/g lipids	r= -0.11 (p<0.01)	Age, race, PIR, smoking, PA, height
Cho, MR <i>et al.</i> (2011)[47]	USA	CS	NHANES, 1999-2004; ♀(n= 679)	Adults (≥50)	Serum (HRGC/IDHRMS)	FM (DXA)	ng/g lipids	r= 0.16 (p<0.001)	Age, race, PIR, smoking, PA, height
Dirinck, E <i>et al.</i> (2011)[56]	BEL	CS	Obese patients and controls; ♂(n=73), ♀(n=71)	Adults (21-60)	Serum (GC/MS)	FM (BIA)	ng/g lipids	p= 0.071 (p>0.05)	-
Dirinck, E <i>et al.</i> (2014)[62]	BEL	CS	Patients weight management clinic; ♂♀ n= 195	Adults (18-84)	Serum†	FM (BIA)	ng/g lipids	r= 0.07 (p= 0.32)	-
Waist Circumference									
Lee, DH <i>et al.</i>	USA	CS	NHANES 1999-	Adults	Serum	WC	ng/g lipids	p= -0.01	Age, sex, race,


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	Author(s): V Mendes; I Delgado; B Peleteiro; J Araújo; H Barros; E Ramos; D Sarigiannis; N Baiz; I Annesi-Maesano		Version: 1 45/221

Table 2.1.2. Description of papers assessing the association between p,p'-DDE and other adiposity measures


Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
al. (2006)[45]			2002; ♂ (n= 903), ♀ (n= 1113)	(≥20)	(HRGC/IDHRMS)	(measured)		(p>0.01)	PIR, BMI, WC
Dirinck, E et al. (2011)[56]	BEL	CS	Obese patients and controls; ♂ (n=73), ♀ (n=71)	Adults (21-60)	Serum (GC/MS)	WC (measured)	ng/g lipids	p= -0.019 (p<0.01)	-
Lee, DH et al. (2012)[50]	SWE	CS	PIVUS, 2001-2004; ♂ (n=490)	Adults (70y.o.)	Plasma (HRGC/HRMS)	WC (measured) >102 cm	4.7-21.6 vs. BDL (pg/mL)	OR= 2.6 (1.1; 5.7)	Calories, exercise, smoking, TG, TC, alcohol
Lee, DH et al. (2012)[50]	SWE	CS	PIVUS, 2001-2004; ♀ (n= 480)	Adults (70y.o.)	Plasma (HRGC/HRMS)	WC (measured) >102 cm	4.7-21.6 vs. BDL (pg/mL)	OR= 1.7 (0.9; 3.1)	Calories, exercise, smoking, TG, TC, alcohol
Lee, DH et al. (2012)[50]	SWE	PC	PIVUS, 2001-2009; ♂ (n=306)	Adults (≥75)	Plasma (HRGC/HRMS)	WC (measured) >102 cm	4.7-21.6 vs. BDL (pg/mL)	OR= 0.6 (0.1; 3.3)	Calories, exercise, smoking, TG, TC, alcohol
Lee, DH et al. (2012)[50]	SWE	PC	PIVUS, 2001-2009; ♀ (n= 206)	Adults (≥75)	Plasma (HRGC/HRMS)	WC (measured) >102 cm	4.7-21.6 vs. BDL (pg/mL)	OR= 1.3 (0.5; 3.6)	Calories, exercise, smoking, TG, TC, alcohol
Dirinck, E et al. (2014)[62]	BEL	CS	Patients weight management clinic; ♂ ♀ n= 195	Adults (18-84)	Serum [†]	WC (measured)	ng/g lipids	r= -0.12 (p= 0.096)	-

Waist to Hip Ratio

Dirinck, E et al. (2011)[56]	BEL	CS	Obese patients and controls; ♂ (n=73), ♀ (n=71)	Adults (21-60)	Serum (GC/MS)	WtHR (measured)	ng/g lipids	p= 0.03 (p>0.05)	-
Dirinck, E et al. (2014)[62]	BEL	CS	Patients weight management clinic; ♂ ♀ n= 195	Adults (18-84)	Serum [†]	WtHR (measured)	ng/g lipids	r= 0.22 (p= 0.02)	-

Shading represents papers for which the same samples were already included in the meta-analysis plot. CS: Cross-sectional; PC: Prospective Cohort; NHANES: National Health and Nutrition Examination Survey; PIVUS: Prospective Investigation of the Vasculature in Uppsala Seniors; GC: Gas chromatography; HRGC: High Resolution Gas Chromatography; HRMS: High Resolution Mass Spectrometry; ID: Isotope Dilution; FM: Fat Mass; DXA: Dual-energy X-ray Absorptiometry; BIA: Bioelectrical Impedance Analysis; WC: Waist Circumference; WtHR: Waist to Hip Ratio; Qu: Quintile; r: Pearson correlation coefficient; p: Spearman correlation coefficient; OR: Odds ratio; PIR: Poverty Income Ratio; PA: Physical Activity; TG: Triglycerides; TC: Total Cholesterol. [†]No further information

Table 2.1.3 summarizes available results regarding the association of p,p'-DDE with each adiposity measure, in order to assess if the pattern found for BMI would be similar using other adiposity measures. Seven estimates reported the association of p,p'-DDE with fat mass [42, 47, 56, 62], with an overall beta coefficient 0.09 (95% CI 0.05; 0.12) and with a percentage of variance of 87.93%. A similar result was found in the summary estimate for the two papers assessing the relation between p,p'-DDE and waist to hip ratio [56, 62]. On the other hand, for waist circumference the overall estimate was negative but not statistically significant (β = -0.02, 95% CI 0.04; 0.25). It is important to highlight that results from studies with ORs or transformed variables (log)

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were not considered for the following summary estimates, since it is not possible to combine them with the remaining results. Estimates provided for children were also excluded. Furthermore, as we have tried to include as much studies as possible, no sensitivity analysis was taken into account. For these reasons, a high heterogeneity was expected and summary estimates should be carefully considered.


Table 2.1.3. Summary estimates for the association between p,p'-DDE and each adiposity measure

	p,p'-DDE			
	Number of included estimates	Summary estimate*	I ²	95% CI**
Body Mass Index	11 ^a	0.19	96.4	0.16; 0.21
Weight	1 ^b	-0.06 [†]	-	0.390 [‡]
Fat Mass	7 ^c	0.09	87.9	0.05; 0.12
Waist Circumference	3 ^d	-0.02	10.0	-0.06; 0.02
Waist to Hip Ratio	2 ^e	0.15	69.0	0.04; 0.25

I² available only when meta-analysis was performed.

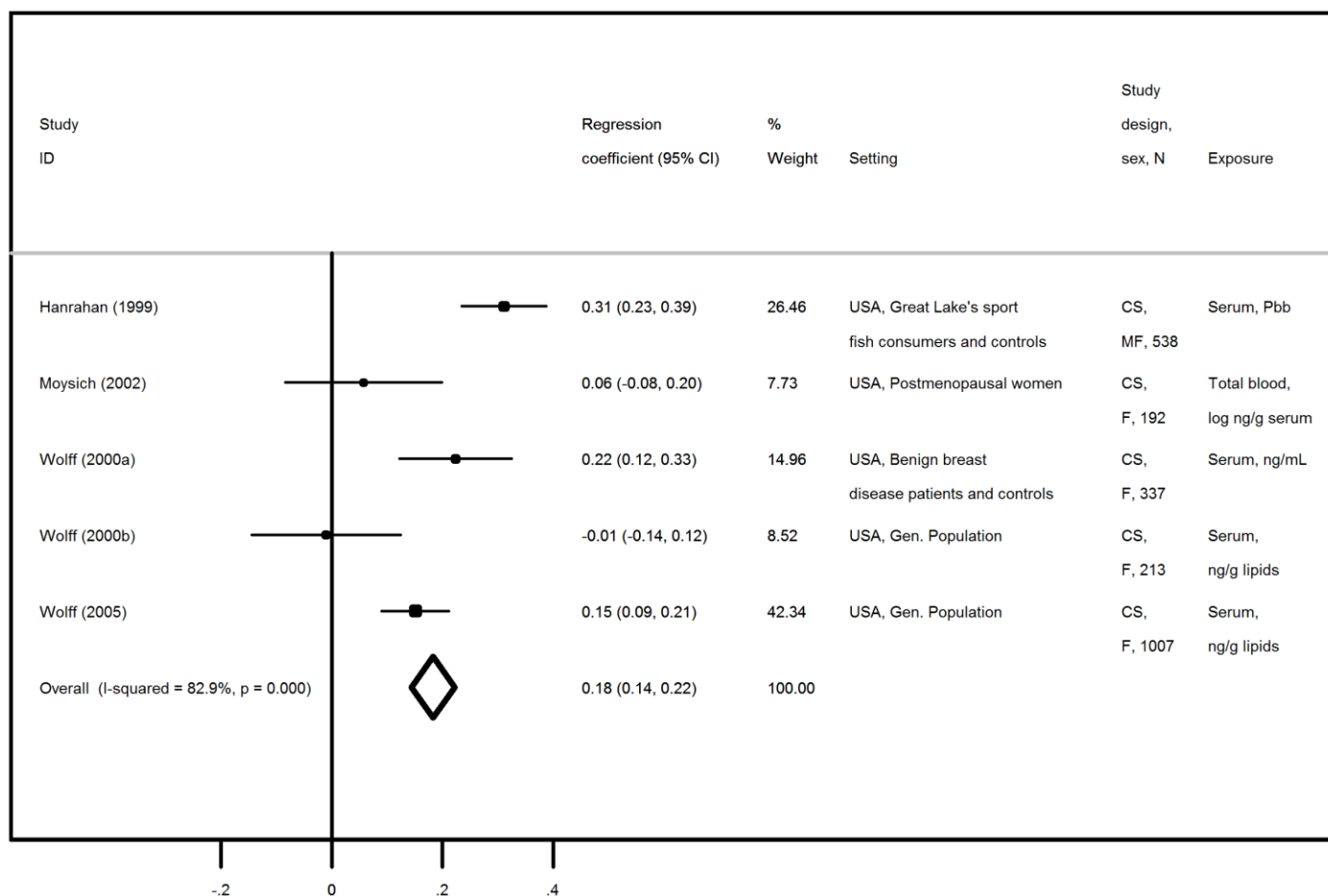
*Beta coefficient if not otherwise specified; [†]Pearson correlation coefficient; [‡]p value.

Included studies are: ^aGallardo, I et al. (1999)[53], Stellman, SD et al. (2000)[54], Pelletier, C et al. (2002a)[42], Magnusdottir, EV et al. (2005)[43], Hue, O et al. (2006)[44], Lee, DH et al. (2006)[45], Dirinck, E et al. (2011)[56], Qin, YY et al. (2011)[57], Langer, P et al. (2012)[60], Dirinck, E et al. (2014)[62] and Teeyapant, P et al. (2014) [63]; ^bDirinck, E et al. (2014)[62]; ^cPelletier, C et al. (2002a)[42], Cho, MR et al. (2011)[47], Dirinck, E et al. (2011)[56] and Dirinck, E et al. (2014)[62]; ^dLee, DH et al. (2006)[45], Dirinck, E et al. (2011)[56] and Dirinck, E et al. (2014)[62]; ^eDirinck, E et al. (2011)[56] and Dirinck, E et al. (2014)[62].

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2.2 Dichlorodiphenyldichloroethylene (DDE – not specified)

We identified eight papers assessing the association of DDE and adiposity-related measures, one was not eligible for meta-analysis since it included pregnant women [69]; Ronn, M *et al.* (2011) [49] and Roos V *et al.* (2013) [51] reported data on PIVUS subjects, but both were excluded for presenting regression coefficients for log transformed variables. Five publications were then summarized in meta-analysis [48, 65-68] resulting in an overall estimate of $\beta = 0.18$ (95% CI 0.14; 0.22) with a percentage of variance of 82.9% (figure 2.2). Despite the high heterogeneity, only Wolff, MS *et al.* (2000b) [66] presented a negative association but very close to zero and non-statistically significant.




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Figure 2.2. Meta-analysis of studies evaluating the association of DDE (not specified) with BMI in adults. Beta coefficients and corresponding 95% CI (horizontal lines). The size of the black square indicates the study's weight in the analysis (weights are from fixed-effects analysis). The centre of the open diamond indicates the summary estimate and its width represents the 95% CI.

Table 2.2.1 shows the description of the only paper assessing BMI that was not included in the meta-analysis presented in figure 2.2 and of those addressing the association between DDE and other adiposity measures. In contrast to most results presented in the forest plot, Brucker-Davis, F *et al.* (2010) [69] found a negative correlation between DDE and BMI at delivery in pregnant women. Only two papers evaluated the association between DDE (not specified) and other adiposity measures [49, 51]. Both Ronn, M *et al.* (2011) [49] and Roos, V *et al.* (2013) [51] are based on PIVUS study and found positive associations between DDE and total fat mass or visceral/subcutaneous adipose tissue.

Table 2.2.1. Description of papers assessing the association between DDE (not specified) and each adiposity measure

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
BMI									
Brucker-Davis, F <i>et al.</i> (2010) [69]	FRA	CS	Primiparous women; ♀(n=86)	Adults (18-40)	Serum (GC/MS)	BMI at delivery [†]	ng/mL	$\rho = -0.30$ (p=0.05)	-
Fat Mass									
Ronn, M <i>et al.</i> (2011) [49]	SWE	PC	PIVUS; ♂♀(n=866)	Adults (70y.o.)	Plasma (HRGC/HRMS)	FM (DXA)	Per 1-unit (ln ng/g lipid)	$\beta = 1.9$ (1.29;2.51)	Sex
Visceral Adipose Tissue and Subcutaneous Adipose Tissue									
Roos, V <i>et al.</i> (2013) [51]	SWE	CS	PIVUS; ♂♀(n=287)	Adults (70y.o.)	Plasma (HRGC/HRMS)	VAT (MRI)	Per 1-unit (ln ng/g lipid)	$\beta = 9.6$ (2.0;17.0)	Sex, education, exercise, smoking
Roos, V <i>et al.</i> (2013) [51]	SWE	CS	PIVUS; ♂♀(n=287)	Adults (70y.o.)	Plasma (HRGC/HRMS)	SAT (MRI)	Per 1-unit (ln ng/g lipid)	$\beta = 23.0$ (10.0;35.0)	Sex, education, exercise, smoking


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Table 2.2.1. Description of papers assessing the association between DDE (not specified) and each adiposity measure

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
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PC: Prospective cohort; CS: Cross-sectional; PIVUS: Prospective Investigation of the Vasculature in Uppsala Seniors; HRGC: High Resolution Gas Chromatography; HRMS: High Resolution Mass Spectrometry; FM: Fat Mass; VAT: Visceral Adipose Tissue; MRI: Magnetic Resonance Imaging; SAT: Subcutaneous Adipose Tissue; β : Beta coefficient. [†]No further information


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Table 2.2.2 summarizes results found on the association between DDE with each adiposity measure (BMI, fat mass, visceral adipose tissue or subcutaneous adipose tissue). In general, all results support a positive association between DDE and adiposity. It is also important to highlight that results from studies with ORs or transformed variables (log) were not considered for the following summary estimates, since it is not possible to combine them with the remaining results. Furthermore, as we have tried to include as much studies as possible, no sensitivity analysis was taken into account. For these reasons, a high heterogeneity was expected and summary estimates should be carefully considered.


Table 2.2.2. Summary estimates for the association between DDE (not specified) and each adiposity measure

	DDE (not specified)			
	Number of included estimates	Summary Estimate*	I ²	95% CI**
Body Mass Index	5 ^a	0.18	82.9	0.14; 0.22
Fat Mass	1 ^b	1.9	-	1.29; 2.51
Visceral Adipose Tissue	1 ^c	9.6	-	2.0; 17.0
Subcutaneous Adipose Tissue	1 ^c	23.0	-	10.0; 35.0

I² available only when meta-analysis was performed.

*Spearman correlation coefficient if not otherwise specified.

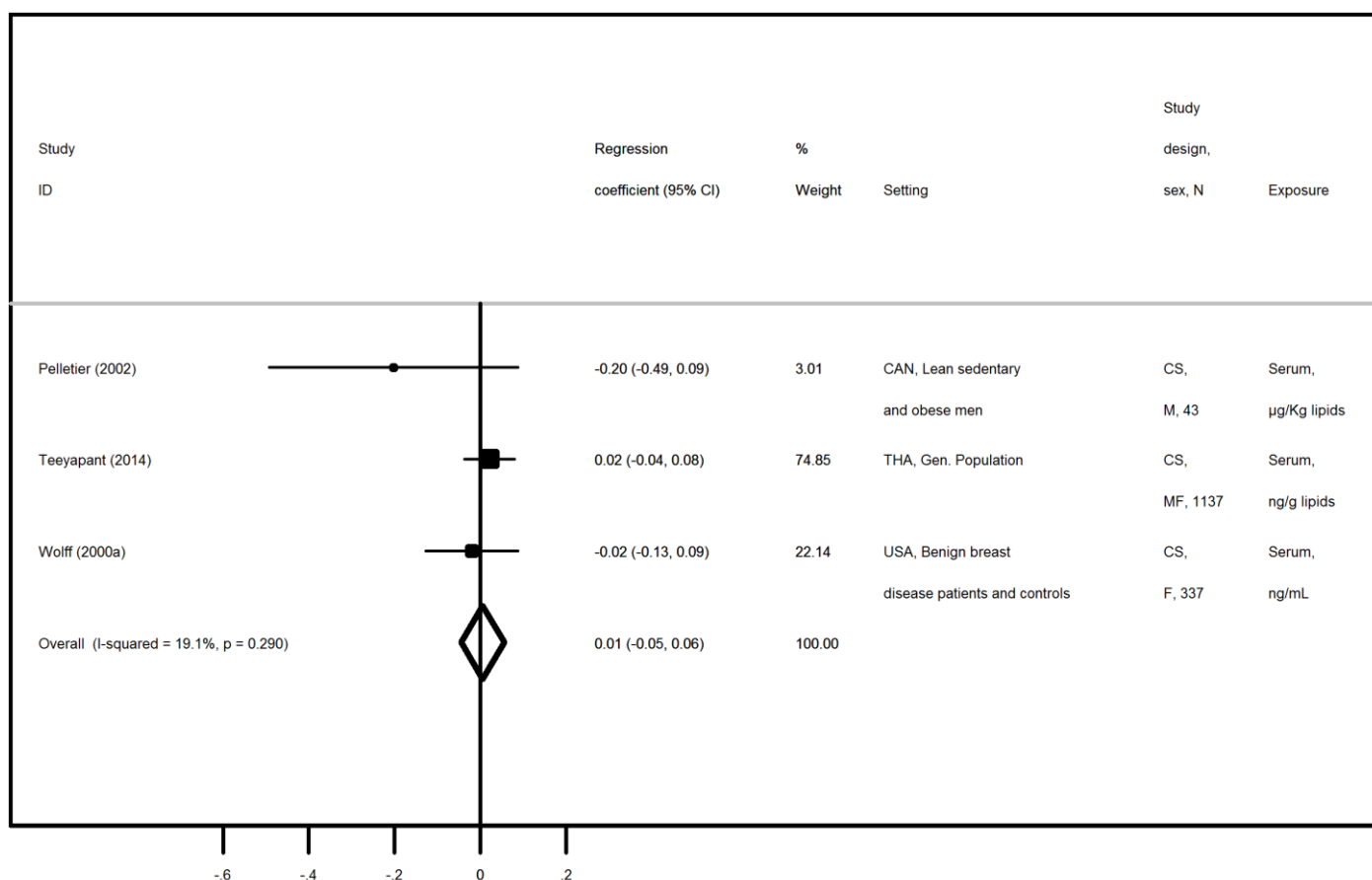
Included studies are: ^aHanrahan, LP et al. (1999)[65], Wolff, MS et al. (2000a)[48], Wolff, MS et al. (2000b)[66], Moysich, KB et al. (2002)[67] and Wolff, MS et al. (2005)[68]; ^bRonn, M et al. (2011)[49]; ^cRoos, V et al. (2013)[51].

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2.3 p,p'-dichlorodiphenyltrichloroethane (p,p'-DDT)

Of the six papers assessing p,p'-DDT as the exposure variable [42, 46, 48, 61, 63, 64], three were excluded from meta-analysis: Wu, H *et al.* (2013) [61] was excluded for including cancer patients; Lee, DH *et al.* (2007) [46] for presenting ORs as association estimates and Elobeid, M *et al.* (2010) [64] for not providing 95% CI for the estimates. Three publications were thus considered in this meta-analysis.

The included papers were performed among samples from USA, Canada and Thailand and all had a cross-sectional design [42, 48, 63]. The overall estimate on the association of p,p'-DDT and BMI was $\beta = 0.01$ (95% CI -0.05; 0.06) with a study heterogeneity of 19.1% (figure 2.3), indicating no association between the two variables.




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Figure 2.3. Meta-analysis of studies evaluating the association of p,p'-DDT with BMI in adults. Beta coefficients and corresponding 95% CI (horizontal lines). The size of the black square indicates the study's weight in the analysis (weights are from fixed-effects analysis). The centre of the open diamond indicates the summary estimate and its width represents the 95% CI.

Table 2.3.1 shows the description of the only paper [61] assessing BMI that was not included in the meta-analysis presented in figure 2.3 and of those addressing the association between p,p'-DDT and other adiposity measures. Wu, H *et al.* (2013) [61] found statistically significant results for BMI only among nurses from the non-Hodgkin lymphoma study ($p=0.2$, $p<0.05$). Regarding publications addressing the association between p,p'-DDT and other adiposity measures, a negative but not significant correlation was found for fat mass [42] (this population is already represented in the meta-analysis plot by results on BMI presented in the same paper). Results on waist circumference also suggest no association. In non-diabetic participants, Lee, DH *et al.* (2007) [46] found no association (OR= 1.0, 95% CI 0.5; 1.9), while Elobeid, M *et al.* (2010) [64] observed a positive association, but did not reach statistical significance ($\beta=0.98$, $p=0.07$).

Table 2.3.1. Description of papers assessing the association between p,p'-DDT and other adiposity measures

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
BMI									
Wu, H <i>et al.</i> (2013)[61]	USA	PC	Nurses from breast cancer study; ♀(n=649)	Adults	Serum (GC)	BMI (self-reported W&H)	ng/g lipids	$p=0.004$ ($p>0.05$)	Age
Wu, H <i>et al.</i> (2013)[61]	USA	PC	Nurses from non-Hodgkin lymphoma study; ♀(n=398)	Adults	Serum (GC)	BMI (self-reported W&H)	ng/g lipids	$p=0.2$ ($p<0.05$)	Age
Fat Mass									
Pelletier, C <i>et al.</i> (2002) [42]	CAN	CS	Lean sedentary and obese men; ♂(n=43)	Adults (36-58)	Serum (GC)	FM (Siri equation)	µg/Kg lipids	$p=-0.2$ ($p=0.201$)	Age
Waist Circumference									


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Table 2.3.1. Description of papers assessing the association between p,p'-DDT and other adiposity measures

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Lee, DH et al. (2007) [46]	USA	CS	NHANES Non-diabetic; 1999-2002; ♂♀(n=721)	Adults (≥20)	Serum (HRGC/IDHRMS)	WC (measured)	>75 th vs. BDL (ng/g lipids)	OR= 1.0 (0.5;1.9)	Age, sex, race, PIR, smoking, alcohol, exercise
Elobeid, M et al. (2010) [64]	USA	CS	NHANES, 1999-2002; ♂(n=1315), ♀(n= 1133)	Adults & Children (≥6)	Serum (HRGC/IDHRMS)	WC (measured)	Per 1-SD increase (ln ng/g lipid)	β= 0.98 (p=0.074)	-

Shading represents studies for which the same samples were already included in the meta-analysis plot.

PC: Prospective Cohort; CS: Cross-sectional; PC: Prospective Cohort; NHANES: National Health and Nutrition Examination Survey; GC: Gas chromatography; HRGC: High Resolution Gas Chromatography; IDHRMS: Isotope Dilution High Resolution Mass Spectrometry; BMI: Body Mass Index; W: Weight; H: Height; WC: Waist Circumference; FM: Fat Mass; p: Spearman correlation coefficient; OR: Odds ratio; β: Beta coefficient; PIR: Poverty Income Ratio.

Table 2.3.2 summarizes the available results on the association between p,p'-DDT with each adiposity measure, showing no significant association between this substance and adiposity.

Table 2.3.2. Summary estimates for the association between p,p'-DDT and each adiposity measure


	p,p'-DDT			
	Number of included estimates	Summary Estimate*	I ²	95% CI**
Body Mass Index	3 ^a	0.01	19.1	-0.05; 0.06
Fat Mass	1 ^b	-0.20 [†]	-	0.201 [‡]
Waist Circumference	1 ^c	0.98	-	0.074 [‡]

I² available only when meta-analysis was performed.

*Beta coefficient if not otherwise specified; [†]Spearman correlation coefficient; [‡]p value.

^aIncluded papers are: ^aPelletier, C et al. (2002a)[42], Wolf, MS et al. (2002a)[48] and Teeyapant, P et al. (2014)[63];

^bPelletier, C et al. (2002a)[42]; ^cElobeid, M et al. (2010)[64].

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	Author(s): V Mendes; I Delgado; B Peleteiro; J Araújo; H Barros; E Ramos; D Sarigiannis; N Baiz; I Annesi-Maesano	Version: 1	54/221

2.4 Sum of dichlorodiphenyltrichloroethane compounds


Three papers have evaluated the association between sums of DDT and BMI (table 2.4). All studies presented a small sample size. Qin, YY *et al.* (2011) [57] and Moon, HM *et al.* (2012) [52] found positive associations between the sum of DDT compounds (sum of p,p'-DDE and p,p'-DDT and sum of p,p' DDT, o,p'-DDE, p,p'-DDE, o,p'-DDD and p,p'-DDD, respectively) and BMI. Mazhitova, Z *et al.* (1998) [70] included 12 Swedish children, hospitalized for multiple medical problems, and found a negative correlation ($\rho = -0.76$, $p < 0.01$).

Table 2.4.1 Description of papers assessing the association between the sum of DDT compounds and adiposity[‡]

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Qin, YY <i>et al.</i> (2011) [57]	HKG	CS	Blood donors; ♂(n=60) ♀(n=51)	Adults	Serum (GC/MS)	BMI (self-reported W&H)	ng/g lipids	$r = 0.613$ ($p < 0.05$)	-
Moon, HB <i>et al.</i> (2012) [52]	KOR	CS	Myoma patients; ♀(n=53)	Adults (40-68)	Adipose Tissue (GC/MS)	BMI [†]	ng/g lipids	$\rho = 0.137$ ($p > 0.05$)	-
Mazhitova, Z <i>et al.</i> (1998)[70]	SWE	CS	Hospitalized children; ♂(n= 6), ♀(n= 6)	Children (7.5-15)	Serum (GC)	BMI [†] -SDS (French standards)	ng/g lipids	$r = -0.76$ ($p < 0.01$)	-

[‡]Sums do not necessarily represent the same combination of substances.

CS: Cross-sectional; GC: Gas chromatography; MS: Mass Spectrometry; BMI: Body Mass Index; W: Weight; H: Height; r: Pearson correlation coefficient. [†]No further information.

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3. Polychlorinated Dibenzodioxins (PCDDs)

Twelve publications assessed the association between Polychlorinated Dibenzodioxins (PCDDs) and adiposity [45-47, 49-51, 71-76]. In this group, substances evaluated in a higher number of papers were octachlorodibenzodioxin (OCDD), with seven publications [45-47, 49-51, 71] and four have specifically measured 1,2,3,6,7,8-Heptachlorodibenzo-p-dioxin (HpCDD) [45-47, 71]. Adiposity was assessed by 5 different measures (BMI, fat mass, waist circumference, visceral adipose tissue and subcutaneous adipose tissue).

Table 3.1.1 shows the description of the twelve publications identified in the systematic review for each PCDD. Regarding OCDD, in general, results support a positive association between exposure levels and adiposity. Negative associations were described only in Cho, MR *et al.* (2011) [47] for males aged <50y.o. and in Lee, DH *et al.* (2012) [50] for males aged ≥75 y.o., both with no statistical significance. The remaining PCDDs have been less studied, but most of the available results found a positive association with adiposity. On the contrary, Moon, H *et al.* (2011) [75] found a negative correlation between the sum of PCDDs and BMI among myoma patients.

These results indicate that higher levels of dioxins may lead to higher levels of adiposity. However, it should be taken into account that most of the retrieved results for this EDC group are based on NHANES and PIVUS study, or samples of highly exposed individuals.


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Table 3.1.1. Description of papers included in the systematic review assessing the association between PCDDs and adiposity

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Octachlorodibenzodioxin (OCDD)									
BMI									
Collins, J et al. (2007) [71]	USA	CS	Former workers DCP; ♂(n= 52)	Adults	Serum (HRGC/ HRMS)	BMI (measured W&H)	Per 1-unit (log ppt)	β= 0.026 (p= 0.0083)	TCDD, years last exposure, smoking, age weight loss
Lee, DH et al. (2006) [45]	USA	CS	NHANES 1999-2002; ♂(n= 903), ♀(n= 1113)	Adults (≥20)	Whole blood (HRGC/ HRMS)	BMI (measured W&H)	pg/g lipids	ρ= 0.13 (p>0.01)	-
Fat Mass									
Cho, MR et al. (2011) [47]	USA	CS	NHANES 1999-2004; ♂(n= 768)	Adults (<50)	Serum (GC/MS)	FM (DXA)	ng/g lipids	r= -0.03 (p>0.05)	Age, race, PIR, smoking, PA, height
Cho, MR et al. (2011) [47]	USA	CS	NHANES 1999-2004; ♂(n= 612)	Adults (≥50)	Serum (GC/MS)	FM (DXA)	ng/g lipids	r= 0.13 (p<0.001)	Age, race, PIR, smoking, PA, height
Cho, MR et al. (2011) [47]	USA	CS	NHANES 1999-2004; ♀(n= 710)	Adults (<50)	Serum (GC/MS)	FM (DXA)	ng/g lipids	r= 0.09 (p<0.05)	Age, race, PIR, smoking, PA, height
Cho, MR et al. (2011) [47]	USA	CS	NHANES 1999-2004; ♀(n= 679)	Adults (≥50)	Serum (GC/MS)	FM (DXA)	ng/g lipids	r= 0.12 (p<0.01)	Age, race, PIR, smoking, PA, height
Ronn, M et al. (2011) [49]	SWE	PC	PIVUS; ♂(n=431), ♀(n=459)	Adults (70y.o.)	Plasma (HRGC/ HRMS)	FM (DXA)	Per 1-unit (ln ng/g lipids)	β= 1.09 (0.11;2.07)	Sex
Waist Circumference									
Lee, DH et al. (2006) [45]	USA	CS	NHANES 1999-2002; ♂(n= 903), ♀(n= 1113)	Adults (≥20)	Whole blood (HRGC/ HRMS)	WC (Measured)	pg/g lipids	ρ= 0.04 (p>0.01)	-
Lee, DH et al. (2007) [46]	USA	CS	NHANES Non-diabetic; 1999-2002; ♂♀(n= 721)	Adults (≥20)	Whole blood (HRGC/ HRMS)	WC (measured) ♂>102; ♀>88 cm	>75th vs. BDL (ng/g)	OR= 1.6 (0.9;2.8)	Age, sex, race, PIR, smoking, alcohol, exercise
Lee, DH et al. (2012) [50]	SWE	CS	PIVUS 2001-2004; ♂(n=490)	Adults (70y.o.)	Plasma (HRGC/ HRMS)	WC (measured) >102 cm	Qu5(4.7-21.6) vs. Qu1(BDL)	OR= 1.1 (0.5; 2.4)	Calories, exercise, smoking, TC,


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	Author(s): V Mendes; I Delgado; B Peleteiro; J Araújo; H Barros; E Ramos; D Sarigiannis; N Baiz; I Annesi-Maesano	Version: 1	57/221

Table 3.1.1. Description of papers included in the systematic review assessing the association between PCDDs and adiposity

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Lee, DH et al. (2012) [50]	SWE	CS	PIVUS 2001-2004; ♀(n= 480)	Adults (70y.o.)	Plasma (HRGC/HRMS)	WC (measured) >88 cm	Qu5(4.7-21.6) vs. Qu1(BDL)	OR= 0.6 (0.3; 1.2)	TG, alcohol
Lee, DH et al. (2012) [50]	SWE	PC	PIVUS 2001-2009; ♂(n=306)	Adults (≥75)	Plasma (HRGC/HRMS)	WC (measured) >102 cm	Qu5(4.7-21.6) vs. Qu1(BDL)	OR= 0.6 (0.1; 2.3)	Calories, exercise, smoking, TC, TG, alcohol
Lee, DH et al. (2012) [50]	SWE	PC	PIVUS 2001-2009; ♀(n= 2005)	Adults (≥75)	Plasma (HRGC/HRMS)	WC (measured) >88 cm	Qu5(4.7-21.6) vs. Qu1(BDL)	OR= 2.4 (0.8; 7.2)	Calories, exercise, smoking, TC, TG, alcohol

Visceral and Subcutaneous Adipose Tissue

Roos, V et al. (2013) [51]	SWE	CS	PIVUS; ♂♀(n=287)	Adults (70y.o.)	Plasma (HRGC/HRMS)	VAT (MRI)	Per 1-unit (ln ng/g lipids)	β= -3.2 (-15; 8.3)	Sex, exercise, education, smoking
Roos, V et al. (2013) [51]	SWE	CS	PIVUS; ♂♀(n=287)	Adults (70y.o.)	Plasma (HRGC/HRMS)	SAT (MRI)	Per 1-unit (ln ng/g lipids)	β=5.1 (-14; 24)	Sex, exercise, education, smoking

1,2,3,6,7,8- Heptachlorodibenzo-p-dioxin

BMI

Collins, J et al. (2007) [71]	USA	CS	Former workers DCP; ♂(n=52)	Adults	Serum (HRGC/HRMS)	BMI (measured W&H)	Per 1-unit (log ppt)	β= 0.009 (p= 0.086)	TCDD, years last exposure, smoking, age, weight loss
Lee, DH et al. (2006) [45]	USA	CS	NHANES 1999-2002; ♂(n=903), ♀(n=1113)	Adults (≥20)	Whole blood (HRGC/HRMS)	BMI (measured W&H)	pg/g lipids	ρ= 0.19 (p<0.01)	-

Fat Mass

Cho, MR et al. (2011) [47]	USA	CS	NHANES 1999-2004; ♂(n=768)	Adults (<50)	Serum (GC/MS)	FM (DXA)	ng/g lipids	r= 0.05 (p>0.05)	Age, race, PIR, smoking, PA, height
Cho, MR et al. (2011) [47]	USA	CS	NHANES 1999-2004; ♂(n=612)	Adults (≥50)	Serum (GC/MS)	FM (DXA)	ng/g lipids	r= 0.19 (p<0.001)	Age, race, PIR, smoking, PA, height
Cho, MR et al. (2011) [47]	USA	CS	NHANES 1999-2004; ♀(n=710)	Adults (<50)	Serum (GC/MS)	FM (DXA)	ng/g lipids	r= 0.2 (p<0.05)	Age, race, PIR, smoking, PA, height
Cho, MR et al. (2011) [47]	USA	CS	NHANES 1999-2004; ♀(n=679)	Adults (≥50)	Serum (GC/MS)	FM (DXA)	ng/g lipids	r= 0.18 (p<0.01)	Age, race, PIR, smoking, PA, height

Waist Circumference

Lee, DH et al. (2006) [45]	USA	CS	NHANES 1999-2002; ♂(n=903), ♀(n=1113)	Adults (≥20)	Whole blood (HRGC/HRMS)	WC (measured)	pg/g lipids	ρ= 0.11 (p<0.01)	-
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Table 3.1.1. Description of papers included in the systematic review assessing the association between PCDDs and adiposity

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Lee, DH et al. (2007) [46]	USA	CS	NHANES Non-diabetic, 1999-2002; ♂♀(n= 721)	Adults (≥20)	Whole blood (HRGC/HRMS)	WC (Measured) ♂>102; ♀>88 cm	>75th vs. BDL (ng/g)	OR= 2.9 (1.4; 4.9)	Age, sex, race, PIR, smoking, alcohol, exercise
1,2,3,4,6,7,8- Heptachlorodibenzo-p-dioxin									
Collins, J et al. (2007) [71]	USA	CS	Former workers DCP; ♂(n=52)	Adults	Serum (HRGC/HRMS)	BMI (measured W&H)	Per 1-unit (log ppt)	β= 0.034 (p>0.001)	TCDD, years last exposure, smoking, age, weight loss
1,2,3,6,7,8- Hexachlorodibenzo-p-dioxin									
Lee, DH et al. (2007) [46]	USA	CS	NHANES Non-diabetic, 1999-2002; ♂♀(n= 721)	Adults (≥20)	Total blood; (HRGC/HRMS)	WC (measured) ♂>102; ♀>88 cm	>75th vs. BDL (ng/g)	OR= 1 (0.6;1.7)	Age, sex, race, PIR, smoking, alcohol, exercise
1,2,3,4,7,8- Hexachlorodibenzo-p-dioxin									
Collins, J et al. (2007) [71]	USA	CS	Former workers DCP; ♂(n=52)	Adults	Serum (HRGC/HRMS)	BMI (measured W&H)	Per 1-unit (log ppt)	β= 0.016 (p= 0.029)	TCDD, years last exposure, smoking, age weight loss
1,2,3,7,8,9- Hexachlorodibenzo-p-dioxin									
Collins, J et al. (2007) [71]	USA	CS	Former workers DCP; ♂(n=52)	Adults	Serum (HRGC/HRMS)	BMI (measured W&H)	Per 1-unit (log ppt)	β= 0.032 (p<0.001)	TCDD, years last exposure, smoking, age weight loss
1,2,3,7,8-Pentachlorodibenzo-p-dioxin									
Collins, J et al. (2007) [71]	USA	CS	Former workers DCP; ♂(n=52)	Adults	Serum (HRGC/HRMS)	BMI (measured W&H)	Per 1-unit (log ppt)	β= 0.013 p= 0.0328	TCDD, years last exposure, smoking, age, weight loss
Tetrachlorodibenzo-p-dioxin (TCDD)									
BMI									
Collins, J et al. (2007) [71]	USA	CS	Former workers DCP; ♂(n=52)	Adults	Serum (HRGC/HRMS)	BMI (measured W&H)	Per 1-unit (log ppt)	β= 0.021 p= 0.0162	TCDD, years last exposure, smoking, weight loss, age
Yi, SW et al. (2013) [73]	KOR	CS	Vietnam veterans; ♂(n=102)	Adults (56.5±3.7)	Serum (HRGC/HRMS)	BMI [†]	log pg/g lipids	r= 0.03 (p= 0.760)	-
Fat Mass									
Michalek, J et al. (1992) [72]	USA	CS	Ranch Hand Veterans; ♂(n= 36)	Adults	Serum (HRGC/HRMS)	FM [†]	ppt	r= 0.118 (p>0.05)	-



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	Author(s): V Mendes; I Delgado; B Peleteiro; J Araújo; H Barros; E Ramos; D Sarigiannis; N Baiz; I Annesi-Maesano	Version: 1	59/221

Table 3.1.1. Description of papers included in the systematic review assessing the association between PCDDs and adiposity

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
TEQ Sum of PCDDs									
Uemura, H et al. (2009) [74]	JPN	CS	Gen. Population; ♂(n=627), ♀(n=747)	Children & Adults (15-73)	Whole blood (GC-MS)	BMI [†] ≥25Kg/m ²	≥11.20 vs. <4.60 (pg TEQ/g lipid)	OR= 1.5 (0.91; 2.4)	Age, sex, smoking, alcohol, regional block, residential area
Moon, H et al. (2011) [75]	KOR	CS	Myoma patients; ♀(n=53)	Adults (40-68)	Adipose tissue (HRGC/HRMS)	BMI [†]	pg TEQ/g lipid weight	ρ= -0.699 (p<0.001)	-
Sum of PCDDs (HxCDD, HpCDD, OCDD)									
BMI									
Ha, MH et al. (2007) [76]	USA	CS	NHANES 1999-2002; ♂(n= 889)	Adults (40-85)	Serum (HRGC/HRMS)	BMI (measured W&H)	ng/g lipid	ρ= 0.21 (p<0.01)	Age
Ha, MH et al. (2007) [76]	USA	CS	NHANES 1999-2002; ♀(n= 889)	Adults (40-85)	Serum (HRGC/HRMS)	BMI (measured W&H)	ng/g lipid	ρ= 0.1 (p<0.05)	Age
Waist Circumference									
Lee, DH et al. (2007) [46]	USA	CS	NHANES Non-diabetic, 1999-2002; ♂♀(n= 721)	Adults (≥20)	Total blood; (HRGC/HRMS)	WC (measured) ♂>102; ♀>88 cm	>75 th vs. BDL (ng/g)	OR=1.8 (1.0;3.0)	Age, sex, race, PIR, smoking, alcohol, exercise

CS: Cross Sectional; PC: Prospective Cohort; DCP: Dow Chemical plant; NHANES: National Health and Nutrition Examination Survey; PIVUS: Prospective Investigation of the Vasculature in Uppsala Seniors; HRGC: High Resolution Gas Chromatography; HRMS: High Resolution Mass Spectrometry; GC: Gas Chromatography; MS: Mass Spectrometry; BMI: Body Mass Index; W:Weight; H: Height; WC: Waist Circumference; FM: Body Fat; DXA: Dual-energy X-ray Absorptiometry; VAT: Visceral Adipose Tissue; MRI: Magnetic Resonance Imaging; SAT: Subcutaneous Adipose Tissue; FM: Body Fat; BDL: Below Detected Levels; SD: Standard Deviation; Qu: Quintile; TEQ: Total toxic equivalent; β: Beta coefficient; ρ: Spearman correlation coefficient; OR: Odds ratio; r: Pearson correlation coefficient ; PIR: Poverty Income Ratio; PA: Physical Activity; TG: Triglycerides; TC: Total Cholesterol.

*Mean±sd; †No further information.

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4. Polychlorinated Dibenzofurans (PCDFs)

Four publications were identified in the systematic review evaluating the association between PCDFs and adiposity [46, 71, 74, 75]. Collins, J et al. (2007) [71] evaluated former workers in a chemical plant and has measured tens specific PCDF substances. For seven of these substances, this is the only available result. Lee, DH *et al.* (2007) [46] provided estimates for three of the substances also assessed in Collins, J et al. (2007) [71], using NHANES 1999-2002 non-diabetic participants. The remaining two papers provided information only for the sum of PCDFs [74, 75]

The description of the identified estimates in the systematic review is presented in table 4.1.1 for each substance.

For all the evaluated compounds the association observed is weak and non-statistically significant. Only Moon, H *et al.* (2011) [75] found a statistically significant association for the relation between the sum of PCDFs and BMI in myoma patients ($p=0.5$, $p<0.001$).


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	Author(s): V Mendes; I Delgado; B Peleteiro; J Araújo; H Barros; E Ramos; D Sarigiannis; N Baiz; I Annesi-Maesano	Version: 1	61/221

Table 4.1.1. Description of papers included in the systematic review assessing the association between PCDFs and adiposity

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
2,3,7,8-Tetrachlorodibenzo-p-furan (TCDF)									
BMI									
Collins, J et al. (2007) [71]	USA	CS	Former workers DCP; ♂(n=52)	Adults	Serum (HRGC/HRMS)	BMI (measured W&H)	Per 1-unit (log ppt)	$\beta = -0.0002$ p=0.9401	TCDD, last exposure, smoker, age, weight loss
2,3,4,7,8-Pentachlorodibenzofuran (2,3,4,7,8-PeCDF)									
BMI									
Collins, J et al. (2007) [71]	USA	CS	Former workers DCP; ♂(n=52)	Adults	Serum (HRGC/HRMS)	BMI (measured W&H)	Per 1-unit (log ppt)	$\beta = -0.0002$ (p= 0.962)	TCDD, last exposure, smoker, age, weight loss
Waist Circumference									
Lee, DH et al. (2007) [46]	USA	CS	NHANES Non-diabetic; 1999-2002; ♂♀(n= 721)	Adults (≥20)	Whole blood; (HRGC/HRMS)	WC (measured) ♂>102; ♀>88 cm	>75 th vs BDL	OR= 0.7 (0.4; 1.3)	Age, sex, PIR, race, alcohol, smoking, exercise
1,2,3,7,8- Pentachlorodibenzofuran (1,2,3,7,8- PeCDF)									
BMI									
Collins, J et al. (2007) [71]	USA	CS	Former workers DCP; ♂(n=52)	Adults	Serum (HRGC/HRMS)	BMI (measured W&H)	Per 1-unit (log ppt)	$\beta = 0.003$ (p= 0.251)	TCDD, last exposure, smoker, age, weight loss
1,2,3,6,7,8-Hexachlorodibenzofuran (1,2,3,6,7,8-HxCDF)									
BMI									
Collins, J et al. (2007) [71]	USA	CS	Former workers DCP; ♂(n=52)	Adults	Serum (HRGC/HRMS)	BMI (measured W&H)	Per 1-unit (log ppt)	$\beta = 0.011$ p=0.0856	TCDD, last exposure, smoker, age, weight loss
2,3,4,6,7,8-Hexachlorodibenzofuran (2,3,4,6,7,8-HxCDF)									
BMI									
Collins, J et al. (2007) [71]	USA	CS	Former workers DCP; ♂(n=52)	Adults	Serum (HRGC/HRMS)	BMI (measured W&H)	Per 1-unit (log ppt)	$\beta = 0.0068$ p=0.2393	TCDD, last exposure, smoker, age, weight loss
1,2,3,7,8,9-Hexachlorodibenzofuran (1,2,3,7,8,9-HxCDF)									
BMI									
Collins, J et al. (2007) [71]	USA	CS	Former workers DCP; ♂(n=52)	Adults	Serum (HRGC/HRMS)	BMI (measured W&H)	Per 1-unit (log ppt)	$\beta = 0.003$ (p= 0.106)	TCDD, last exposure, smoker, age,


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Table 4.1.1. Description of papers included in the systematic review assessing the association between PCDFs and adiposity

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
1,2,3,4,7,8,9-Hexachlorodibenzofuran (1,2,3,4,7,8,9-HxCDF)									
BMI									
Collins, J et al. (2007) [71]	USA	CS	Former workers DCP; ♂(n=52)	Adults	Serum (HRGC/HRMS)	BMI (measured W&H)	Per 1-unit (log ppt)	β= -0.0004 (p= 0.771)	TCDD, last exposure, smoker, age, weight loss
Hexachlorodibenzofuran (HxCDF)									
BMI									
Collins, J et al. (2007) [71]	USA	CS	Former workers DCP; ♂(n=52)	Adults	Serum (HRGC/HRMS)	BMI (measured W&H)	Per 1-unit (log ppt)	β= 0.014 (p= 0.099)	TCDD, last exposure, smoker, age, weight loss
Waist Circumference									
Lee, DH et al. (2007) [46]	USA	CS	NHANES Non-diabetic; 1999-2002; ♂♀(n= 721)	Adults (≥20)	Whole blood; (HRGC/HRMS)	WC (measured) ♂>102; ♀>88 cm	>75 th vs. BDL	OR= 1.6 (0.9; 2.7)	Age, sex, PIR, race, alcohol, smoking, exercise
Heptachlorodibenzofuran (HpCDF)									
BMI									
Collins, J et al. (2007) [71]	USA	CS	Former workers DCP; ♂(n=52)	Adults	Serum (HRGC/HRMS)	BMI (measured W&H)	Per 1-unit (log ppt)	β=0.005 (p=0.435)	TCDD, last exposure, smoker, age, weight loss
Waist Circumference									
Lee, DH et al. (2007) [46]	USA	CS	NHANES Non-diabetic; 1999-2002; ♂♀(n= 721)	Adults (≥20)	Whole blood; (HRGC/HRMS)	WC (measured) ♂>102; ♀>88 cm	>75 th vs. BDL	OR=0.9 (0.5;1.4)	Age, sex, PIR, race, alcohol, smoking, exercise
Octachlorodibenzofuran (OCDF)									
BMI									
Collins, J et al. (2007)	USA	CS	Former workers DCP; ♂(n=52)	Adults	Serum (HRGC/HRMS)	BMI (measured W&H)	Per 1-unit (log ppt)	β=0.0002 p=0.9496	TCDD, last exposure, smoker, age, weight loss
Sum of PCDFs (PeCDF, HxCDF, HpCDF)									
Waist Circumference									
Lee, DH et al.	USA	CS	NHANES Non-	Adults	Whole blood;	WC	>75 th vs.	OR=1	Age, sex, PIR,



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	Author(s): V Mendes; I Delgado; B Peleteiro; J Araújo; H Barros; E Ramos; D Sarigiannis; N Baiz; I Annesi-Maesano	Version: 1	63/221

Table 4.1.1. Description of papers included in the systematic review assessing the association between PCDFs and adiposity

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
al. (2007) [46]			diabetic; 1999-2002; ♂♀(n= 721)	(≥20)	(HRGC /HRMS)	(measured) ♂>102; ♀>88 cm	BDL	(0.6;1.6)	race, alcohol, smoking, exercise
TEQ of Sum of PCDFs (2,3,7,8-TCDF, 1,2,3,7,8-PeCDF, 2,3,4,7,8-PeCDF, 1,2,3,4,7,8-HxCDF, 1,2,3,6,7,8-HxCDF, 1,2,3,7,8,9-HxCDF, 2,3,4,6,7,8-HxCDF, 1,2,3,4,6,7,8-HpCDF, 1,2,3,4,7,8,9-HpCDF and OCDF)									
BMI									
Uemura, H et al. (2009) [74]	JPN	CS	Gen. Population; ♂(n=627), ♀(n=747)	Children & Adults (15-73)	Whole blood (GC-MS)	BMI [†] ≥25Kg/m ²	≥6.80 vs. <2.90 (pg TEQ/g lipid)	OR= 1.3 (0.85; 2.0)	Age, sex, smoking, alcohol, residential area, survey year
Moon, H et al. (2011) [75]	KOR	CS	Myoma patients; ♀(n=53)	Adults (40-68)	Adipose Tissue HRGC/HRMS	BMI [†]	pg TEQ/g lipid weight	ρ= 0.5 (p<0.001)	-

CS: Cross-sectional; DCP: Dow Chemical plant; NHANES: National Health and Nutrition Examination Survey; HRGC: High Resolution Gas Chromatography; HRMS: High Resolution Mass Spectrometry; BMI: Body Mass Index; W: Weight; H: Height; WC: Waist Circumference; BDL: Below Detected Levels; TEQ: Total toxic equivalent; β: Beta coefficient; OR: Odds ratio; ρ: Spearman correlation coefficient; PIR: Poverty Income Ratio.
[†]No further information.

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5. Perfluorinated Carboxylic Acids (PFCAs)

Only two studies were identified in the systematic review assessing the association between PFCAs and adiposity, providing estimates for four specific substances [77, 78]. Nelson, J et al. (2010) [77] have evaluated the four compounds [perfluorononanoic acid (PFNA), perfluorooctanoic acid (PFOA), perfluorooctane sulfonate (PFOS) and perfluorohexanesulfonic acid (PFHxS)] in both adults and children, while Barry, V et al. (2014) [78] has evaluated only PFOA among adult individuals.

The description of the two publications assessing the association between PFCAs and adiposity among adults is shown in table 5.1.1. Nelson, J et al. (2010) [77] did not find statistically significant associations with any of the evaluated substances. Also Barry, V et al. (2014) [78] did not find statistical significance for the relationship between PFOA and BMI even after sex stratification. However, it is important to highlight that Nelson, J et al. (2010) [77] does not present estimates by sex and in Barry, V et al. (2014) [78] PFOA levels were estimated from exposure to contaminated water.


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Table 5.1.1. Description of papers included in the systematic review assessing the association between PFCA and adiposity in adults

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Perfluorononanoic acid (PFNA)									
BMI									
Nelson, J et al. (2010) [77]	USA	CS	NHANES 2003-2004; ♂♀(n=1055)	Adults (20-80)	Serum (HPLC/TMS)	BMI (self-reported W&H)	Q4 vs. Q1 (µg/L)	β= 0.41 (-0.94; 1.76)	Age, sex, race, SES and others
Waist Circumference									
Nelson, J et al. (2010) [77]	USA	CS	NHANES 2003-2004; ♂♀(n=1044)	Adults (20-80)	Serum (HPLC/TMS)	WC (measured)	Q4 vs. Q1 (µg/L)	β= 0.28 (-0.35; 3.91)	Age, sex, race, SES and others
Perfluorooctanoic acid (PFOA)									
BMI									
Nelson, J et al. (2010) [77]	USA	CS	NHANES 2003-2004; ♂♀(n=1055)	Adults (20-80)	Serum (HPLC/TMS)	BMI (self-reported W&H)	Q4 vs. Q1 (µg/L)	β= 0.28 (-1.04; 1.60)	Age, sex, race, SES and others
Barry, V et al. (2014) [78]	USA	RS	C8 Project, 2008-2011; ♂(n=3685)	Adults (20-40)	Estimated exposure contaminated water (0-3y)	BMI (self-reported W&H) ≥25 kg/m ²	Per 1-unit (log ng/mL)	OR= 0.99 (0.98; 1.00)	Age, smoking, education, walking pace
Barry, V et al. (2014) [78]	USA	RS	C8 Project, 2008-2011; ♀(n=5079)	Adults (20-40)	Estimated exposure contaminated water (0-3y)	BMI (self-reported W&H) ≥25kg/m ²	Per 1-unit (log ng/mL)	OR= 1.00 (0.99; 1.00)	Age, smoking, education, walking pace
Barry V et al. (2014) [78]	USA	RS	C8 Project 2008-2011; ♂(n=3685)	Adults (20-40)	Estimated exposure contaminated water (0-3y)	BMI (self-reported W&H) ≥30 kg/m ²	Per 1-unit (log ng/mL)	OR= 0.99 (0.98; 1.00)	Age, smoking, education, walking pace
Barry V et al. (2014) [78]	USA	RS	C8 Project 2008-2011; ♀(n=5079)	Adults (20-40)	Estimated exposure contaminated water (0-3y)	BMI (self-reported W&H) ≥30 kg/m ²	Per 1-unit (log ng/mL)	OR= 0.99 (0.99; 1.00)	Age, smoking, education, walking pace
Waist Circumference									
Nelson, J et al. (2010) [77]	USA	CS	NHANES 2003-2004; ♂♀(n=1044)	Adults (20-80)	Serum (HPLC/TMS)	WC (measured)	Q4 vs. Q1 (µg/L)	β= 0.00 (-2.77; 2.78)	Age, sex, race, SES and others
Perfluorooctane sulfonate (PFOS)									
BMI									
Nelson, J et al. (2010) [77]	USA	CS	NHANES 2003-2004; ♂♀(n=1055)	Adults (20-80)	Serum (HPLC/TMS)	BMI (self-reported W&H)	Q4 vs. Q1 (µg/L)	β= 0.17 (-1.33; 1.68)	Age, sex, race, SES and others
Waist Circumference									
Nelson, J et al. (2010) [77]	USA	CS	NHANES 2003-2004; ♂♀(n=1044)	Adults (20-80)	Serum (HPLC/TMS)	WC (measured)	Q4 vs. Q1 (µg/L)	β= 0.33 (-3.01; 3.67)	Age, sex, race, SES and others
Perfluorohexanesulfonic acid (PFHxS)									


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Table 5.1.1. Description of papers included in the systematic review assessing the association between PFCAs and adiposity in adults

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
BMI									
Nelson, J et al. (2010) [77]	USA	CS	NHANES 2003-2004; ♂♀(n=1055)	Adults (20-80)	Serum (HPLC/TMS)	BMI (self-reported W&H)	Q4 vs. Q1 (µg/L)	β= -1.20 (-2.67; 0.27)	Age, sex, race, SES and others
Waist Circumference									
Nelson, J et al. (2010) [77]	USA	CS	NHANES 2003-2004; ♂♀(n=1044)	Adults (20-80)	Serum (HPLC/TMS)	WC (measured)	Q4 vs. Q1 (µg/L)	β= -2.7 (-5.55; 0.15)	Age, sex, race, SES and others

CS: Cross-sectional; RS: Retrospective Study; NHANES: National Health and Nutrition Examination Survey; C8: Perfluorooctanoic acid; HPLC: High Performance Liquid Chromatography; TMS: Tandem Mass Spectrometry; BMI: Body Mass Index; W: Weight; H: Height; WC: Waist Circumference; Q: Quartile; β: Beta coefficient; OR: Odds ratio; SES: Socioeconomic Status.

The description of the two publications assessing the association between PFCAs and adiposity among children is shown in table 5.1.2. Nelson, J *et al.* (2010) [77] found a sex effect on the association between PFNA and PFOA and adiposity. Results in boys from NHANES 2003-2004 were negative for both substances (β= -0.44, 95% CI -1.94; 1.06 and β= -3.02, 95% CI -7.31; 1.26, respectively) while among girls the association was positive (β= 2.1, 95% CI 0.43; 3.76 and β= 5.60, 95% CI 0.73; 10.48, respectively). Regarding PFOS and PFHxS in both boys and girls a negative association was found between these substances and BMI. Results regarding waist circumference followed the same pattern.

Table 5.1.2. Description of papers included in the systematic review assessing the association between PFCAs and adiposity in children

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Perfluorononanoic acid (PFNA)									
BMI									
Nelson, J et al. (2010) [77]	USA	CS	NHANES 2003-2004; ♂(n=322)	Children (12-19)	Serum (HPLC/TMS)	BMI (self-reported W&H)	Q4 vs. Q1 (µg/L)	β= -0.44 (-1.94; 1.06)	Age, sex, race, SES and others
Nelson, J et al. (2010) [77]	USA	CS	NHANES 2003-2004; ♀(n=263)	Children (12-19)	Serum (HPLC/TMS)	BMI (self-reported W&H)	Q4 vs. Q1 (µg/L)	β= 2.1 (0.43; 3.76)	Age, sex, race, SES and others
Waist Circumference									
Nelson, J et al. (2010) [77]	USA	CS	NHANES 2003-2004; ♂(n=318)	Children (12-19)	Serum (HPLC/TMS)	WC (measured)	Q4 vs. Q1 (µg/L)	β= -3.02 (-7.31; 1.26)	Age, sex, race, SES and others
Nelson, J et al. (2010) [77]	USA	CS	NHANES 2003-2004; ♀(n=263)	Children (12-19)	Serum (HPLC/TMS)	WC (measured)	Q4 vs. Q1 (µg/L)	β= 5.60	Age, sex, race, SES and others


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	Author(s): V Mendes; I Delgado; B Peleteiro; J Araújo; H Barros; E Ramos; D Sarigiannis; N Baiz; I Annesi-Maesano	Version: 1	67/221

Table 5.1.2. Description of papers included in the systematic review assessing the association between PFCAs and adiposity in children

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
al. (2010) [77]			2004; ♀(n=260)	(12-19)	TMS)	(measured)	(µg/L)	(0.73; 10.48)	race, SES and others
Perfluorooctanoic acid (PFOA)									
BMI									
Nelson, J et al. (2010) [77]	USA	CS	NHANES 2003-2004; ♂(n=322)	Children (12-19)	Serum (HPLC/TMS)	BMI (self-reported W&H)	Q4 vs. Q1 (µg/L)	β= -0.82 (-2.28; 0.63)	Age, sex, race, SES and others
Nelson, J et al. (2010) [77]	USA	CS	NHANES 2003-2004; ♀(n=263)	Children (12-19)	Serum (HPLC/TMS)	BMI (self-reported W&H)	Q4 vs. Q1 (µg/L)	β= 1.35 (-1.23; 3.94)	Age, sex, race, SES and others
Waist Circumference									
Nelson, J et al. (2010) [77]	USA	CS	NHANES 2003-2004; ♂(n=318)	Children (12-19)	Serum (HPLC/TMS)	WC (measured)	Q4 vs. Q1 (µg/L)	β= -2.05 (-6.38; 2.28)	Age, sex, race, SES and others
Nelson, J et al. (2010) [77]	USA	CS	NHANES 2003-2004; ♀ (n=263)	Children (12-19)	Serum (HPLC/TMS)	WC (measured)	Q4 vs. Q1 (µg/L)	β=1.35 (-1.23; 3.94)	Age, sex, race, SES and others
Perfluorooctane sulfonate (PFOS)									
BMI									
Nelson, J et al. (2010) [77]	USA	CS	NHANES 2003-2004; ♂(n=322)	Children (12-19)	Serum (HPLC/TMS)	BMI (self-reported W&H)	Q4 vs. Q1 (µg/L)	β= -1.62 (-3.28; 0.03)	Age, sex, race, SES and others
Nelson, J et al. (2010) [77]	USA	CS	NHANES 2003-2004; ♀(n=263)	Children (12-19)	Serum (HPLC/TMS)	BMI (self-reported W&H)	Q4 vs. Q1 (µg/L)	β= -0.76 (-3.71; 2.18)	Age, sex, race, SES and others
Waist Circumference									
Nelson, J et al. (2010) [77]	USA	CS	NHANES 2003-2004; ♂(n=318)	Children (12-19)	Serum (HPLC/TMS)	WC (measured)	Q4 vs. Q1 (µg/L)	β= -2.76 (-6.78; 1.45)	Age, sex, race, SES and others
Nelson, J et al. (2010) [77]	USA	CS	NHANES 2003-2004; ♀(n=260)	Children (12-19)	Serum (HPLC/TMS)	WC (measured)	Q4 vs. Q1 (µg/L)	β= -2.30 (-9.09; 4.49)	Age, sex, race, SES and others
Perfluorohexanesulfonic acid (PFHxS)									
BMI									
Nelson, J et al. (2010) [77]	USA	CS	NHANES 2003-2004; ♂(n=322)	Children (12-19)	Serum (HPLC/TMS)	BMI (self-reported W&H)	Q4 vs. Q1 (µg/L)	β= -0.80 (-3.15; 1.54)	Age, sex, race, SES and others
Nelson, J et al. (2010) [77]	USA	CS	NHANES 2003-2004; ♀(n=263)	Children (12-19)	Serum (HPLC/TMS)	BMI (self-reported W&H)	Q4 vs. Q1 (µg/L)	β= -0.17 (-2.02; 1.69)	Age, sex, race, SES and others
Waist Circumference									
Nelson, J et al. (2010)	USA	CS	NHANES 2003-2004; ♂(n=318)	Children (12-19)	Serum (HPLC/TMS)	WC (measured)	Q4 vs. Q1 (µg/L)	β= -1.62 (-7.91;	Age, sex, race, SES and



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Table 5.1.2. Description of papers included in the systematic review assessing the association between PFCA and adiposity in children

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
[77] Nelson, J et al. (2010)	USA	CS	NHANES 2003-2004; ♀(n=260)	Children (12-19)	Serum (HPLC/TMS)	WC (measured)	Q4 vs. Q1 (µg/L)	4.67) β= -1.39 (-6.32; 3.54)	others Age, sex, race, SES and others

CS: Cross-sectional; NHANES: National Health and Nutrition Examination Survey; HPLC: High Performance Liquid Chromatography; TMS: Tandem Mass Spectrometry; BMI: Body Mass Index; W: Weight; H: Height; WC: Waist Circumference; Q: Quartile; β: Beta coefficient; SES: Socioeconomic Status.

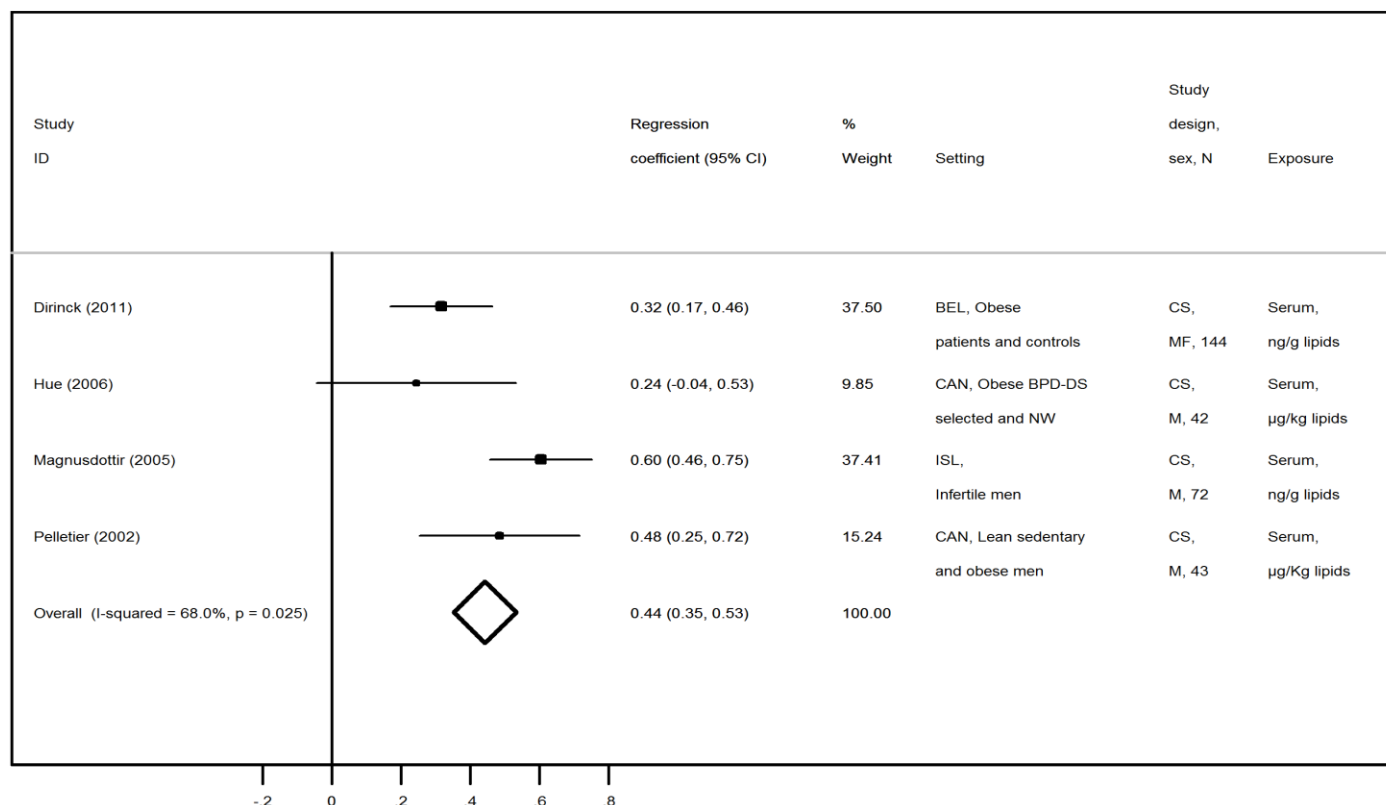
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6. Hexachlorocyclohexane (HCH)

Seven publications assessing the relation between HCH and adiposity were identified in the systematic review [42-44, 46, 52, 56, 59]. Six evaluated specifically β -HCH [42-44, 46, 56, 59], while one focused on the combination of α -, β - and γ -HCH [52]. Adiposity was assessed by 4 different measures (BMI, fat mass, waist circumference and waist to hip ratio).

6.1 Beta-hexachlorocyclohexane (β -HCH)

Of the six publications evaluating the relationship between β -HCH and adiposity, two were excluded from the meta-analysis – one for being performed among children [59] and the other for providing only ORs as the estimate measure [46]. Four papers were then included in the meta-analysis [42-44, 56]. The overall estimate for these four cross-sectional studies was $\beta=0.43$ (95% CI 0.26; 0.60) with a percentage of variance of 68.0%, despite presenting relatively small sample sizes (figure 6.1). All studies showed a positive and statistical significant association between HCH and BMI, with the exception of Hue, O *et al.* (2006) [44] which was also positive but did not reach statistical significance.




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Figure 6.1. Meta-analysis of studies evaluating the association of beta-HCH with BMI in adults. Beta coefficients and corresponding 95% CI (horizontal lines). The size of the black square indicates the study's weight in the analysis (weights are from fixed-effects analysis). The centre of the open diamond indicates the summary estimate and its width represents the 95% CI.

Table 6.1.1 shows the description of the only paper assessing BMI that was not included in the meta-analysis presented in figure 6.1 and of those addressing the association between β -HCH and other adiposity measures. Burns, JS *et al.* (2012) [59] is the only reporting data for children and a negative and statistically significant association between β -HCH and BMI z-score was found ($\beta = -1.32$, 95% CI -1.70; -0.95), contrarily to results observed in studies assessing BMI performed among adults. The two papers that provided results for fat mass are represented in shading because these populations are already represented in the meta-analysis plot by results on the association between β -HCH and BMI. Both found positive and statistical significant correlations coefficients [42, 56]. The only publication assessing waist circumference that presented ORs (Lee, DH *et al.* (2007) [46]), also showed a positive association between β -HCH and waist circumference but with no statistical significance (OR=1.6, 95% CI 0.9; 3.0). Besides BMI and fat mass, Dirinck, E *et al.* (2011) [56] has also evaluated the relation between β -HCH and waist circumference and waist to hip ratio, and found positive and statistical significant associations (similarly to that observed for BMI, which was included in the analysis shown in figure 6.1).

Table 6.1.1. Description of papers assessing the association between β -HCH and each adiposity measure

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
BMI									
Burns, JS <i>et al.</i> (2012) [59]	RUS	PC	Gen. Population; ♂(n=350)	Children (8-9)	Serum (HRMS)	BMI z-score (measured W&H)	303-2860 vs. 39-104 (ng/g lipids)	$\beta = -1.32$ (-1.70; -0.95)	Age, BW, gestational age, income, calories, blood lead levels
Fat Mass									
Pelletier, C <i>et al.</i> (2002) [42]	CAN	CS	Lean sedentary and obese men; ♂(n=43)	Adults (36-58)	Serum (GC)	FM (Siri equation)	$\mu\text{g/Kg}$ lipids	$\rho = 0.44$ ($p = 0.003$)	Age
Dirinck, E <i>et al.</i> (2011) [56]	BEL	CS	Obese patients and controls; ♂(n=73), ♀(n=71)	Adults (21-60)	Serum (GC/MS)	FM (BIA)	ng/g lipids	$\rho = 0.361$ ($p < 0.001$)	-

Waist Circumference


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Table 6.1.1. Description of papers assessing the association between β -HCH and each adiposity measure

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Lee, DH et al. (2007) [46]	USA	CS	NHANES Non-diabetic, 1999-2002; ♂♀(n=721)	Adults (≥ 20)	Whole blood (HRGC/HRMS)	WC (measured) ♂>102; ♀>88 cm	>75 th vs. BDL	OR= 1.6 (0.9; 3.0)	Age, sex, race, PIR, and other
Dirinck, E et al. (2011) [56]	BEL	CS	Obese patients and controls; ♂(n=73), ♀(n=71)	Adults (21-60)	Serum (GC/MS)	WC (measured)	ng/g lipids	$\rho = 0.248$ ($p < 0.01$)	-

Waist to Hip Ratio

Dirinck, E et al. (2011) [56]	BEL	CS	Obese patients and controls; ♂(n=73), ♀(n=71)	Adults (21-60)	Serum (GC/MS)	WtHR (measured)	ng/g lipids	$\rho = 0.235$ ($p < 0.001$)	-
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Shading represents studies for which the same samples are already included in the meta-analysis plot. CS: Cross-sectional; NHANES: National Health and Nutrition Examination Survey; GC: Gas Chromatography; HRGC: High Resolution Gas Chromatography; HRMS: High Resolution Mass Spectrometry; MS: Mass Spectrometry; FM: Fat Mass; WC: Waist Circumference; BIA: Bioelectrical Impedance Analysis; WtHR: Waist to Hip Ratio; BDL: Below Detected Levels; ρ : Spearman correlation coefficient; OR: Odds ratio; PIR: Poverty Income Ratio.

Table 6.1.2 summarizes the available data regarding the association of β -HCH with each adiposity measure. It is important to highlight that results from studies with ORs or transformed variables (log) were not considered for the following summary estimates, since it is not possible to combine them with the remaining results. Estimates provided for children were also excluded. Furthermore, as we have tried to include as much studies as possible, no sensitivity analysis was taken into account, and a high heterogeneity is expected. These summary estimates should be carefully considered.

For all adiposity measures, a positive and statistical significant association was found, suggesting that higher levels of β -HCH are associated with higher levels of adiposity. The overall estimate for the two papers evaluating fat mass [42, 56] was $\beta = 0.40$ (95% CI 0.28; 0.52), very similar to the summary estimate obtained for BMI presented in figure 6.1.

Table 6.1.2. Summary estimates for the association between β -HCH and each adiposity measure

	β -HCH			
	Number of included estimates	Summary Estimate*	I ²	95% CI
Body Mass Index	4 ^a	0.44	68.0	0.35; 0.53


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Fat Mass	2 ^b	0.40	0.0	0.28; 0.52
Waist Circumference	1 ^c	0.248 [†]	-	<0.01 [‡]
Waist to Hip Ratio	1 ^c	0.235 [†]	-	<0.001 [‡]

I² available only when meta-analysis was performed.

*Beta coefficient if not otherwise specified; [†]Spearman correlation coefficient; [‡]p value.

Included studies are: ^aPelletier, C et al. (2002)[42], Magnusdottir, E et al. (2005)[43], Hue, O et al. (2006)[44], and Dirinck, E et al. (2011)[56]; ^bPelletier, C et al. (2002)[42] and Dirinck, E et al. (2011)[56]; ^cDirinck, E et al. (2011)[56].

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6.2 Sum of hexachlorocyclohexane compounds


Moon, HB et al. (2012) [7] was the only paper addressing the association between the combination of HCH substances (α -, β - and γ -HCH) and adiposity. In this sample of 53 South Korean women with a diagnosed myoma, the spearman correlation coefficient between the sum of α -, β - and γ -HCH and BMI was -0.33 ($p < 0.05$) (table 6.2.1). This was also the only study presenting exposure levels derived from adipose tissue, while all the previous papers reported exposure levels measured in blood samples.

Table 6.2.1. Description of the only paper assessing the association between the sum of HCH compounds (α -, β - and γ -HCH) and adiposity

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Moon, HB et al. (2012) [52]	KOR	CS	Myoma patients; ♀(n=53)	Adults (40-68)	Adipose Tissue (GC/MS)	BMI [†]	ng/g lipids	$\rho = -0.33$ ($p < 0.05$)	-

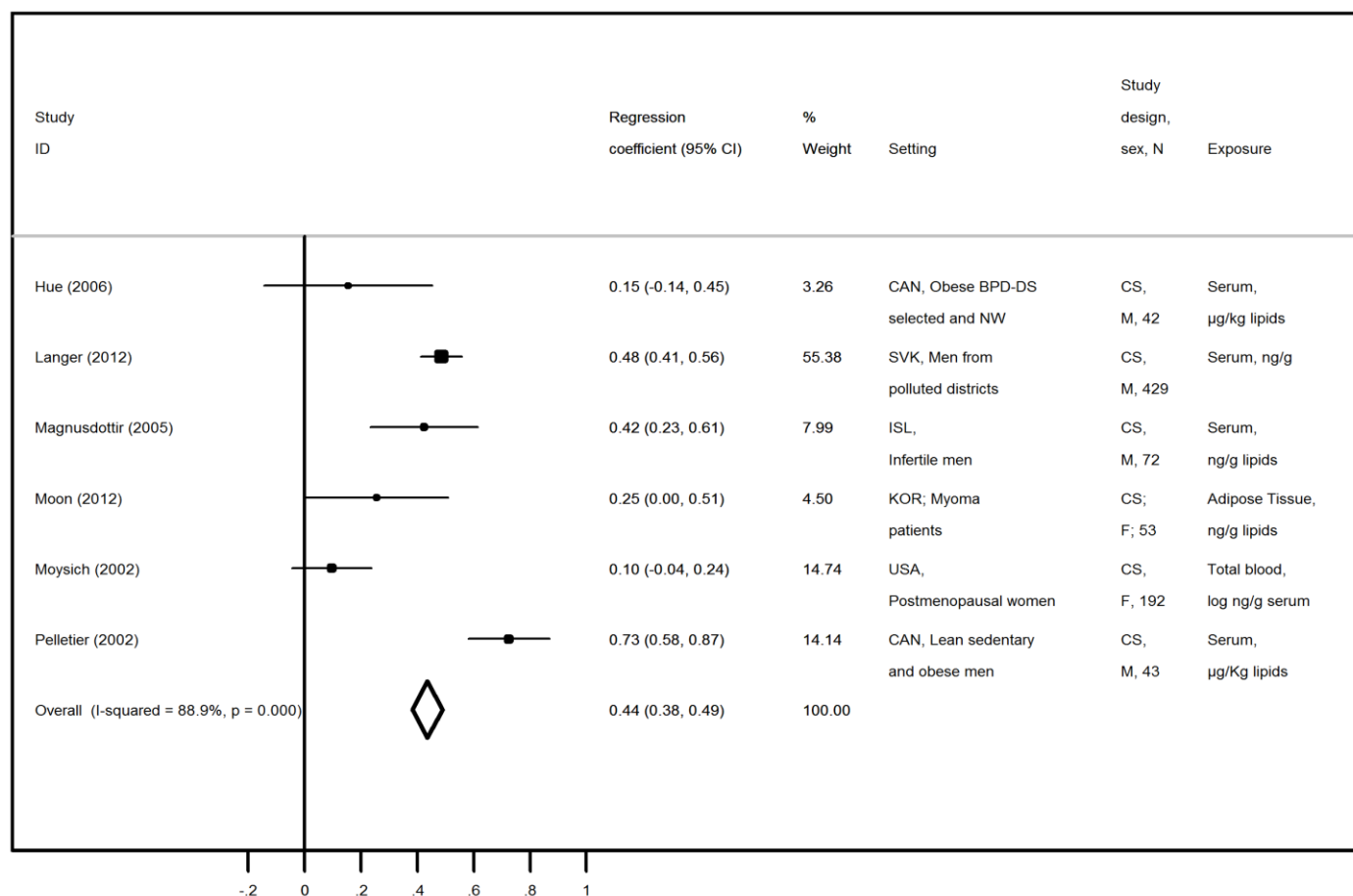
CS: Cross-sectional; GC: Gas Chromatography; MS: Mass Spectrometry; BMI: Body Mass Index; ρ : Spearman correlation coefficient.

[†]No further information.

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7. Hexachlorobenzene (HCB)

Twelve publications [42-44, 49-52, 59-61, 67, 79] were identified evaluating the association between HCB and adiposity. Of the twelve identified publications, six were excluded from the meta-analysis for being performed among children [59] or among cancer patients [61], for presenting association estimates as ORs [50] or for presenting regression coefficients for log transformed variables [49, 51, 79]. This meta-analysis included six publications on the relationship of HCB with adiposity [43, 44, 52, 60, 67, 79]. All publications presented a cross-sectional design. The overall beta coefficient was 0.44 (95% CI 0.38; 0.49), with a heterogeneity of 88.9% (figure 7.1).




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Figure 7.1. Meta-analysis of studies evaluating the association of HCB with BMI in adults. Beta coefficients and corresponding 95% CI (horizontal lines). The size of the black square indicates the study's weight in the analysis (weights are from fixed-effects analysis). The centre of the open diamond indicates the summary estimate and its width represents the 95% CI.

In order to understand if the site of exposure assessment had an impact on the overall estimate, we performed a sensitivity analysis excluding Moysich, KB *et al.* (2002) [67], who measured HCB concentration in whole blood, and Moon, HB *et al.* (2012) [52], who assessed HCB exposure levels in adipose tissue. The overall beta coefficient for the remaining six papers increased to 0.51 (95% CI 0.45; 0.57), but the percentage of variance did not decrease significantly ($I^2=80.4\%$).

Table 7.1.1 shows the description of papers assessing BMI that were not included in the meta-analysis presented in figure 7.1 [59, 61, 79]. In adults, Dhooge, W *et al.* (2010) [79] found positive and statistically significant associations between HCB and BMI. Among nurses from the non-Hodgkin lymphoma study the correlation was also positive ($p= 0.03$, $p>0.05$) [61], but not for nurses from the breast cancer study the correlation was negative ($p= -0.02$, $p>0.05$). Regarding the two publications performed among children, contradictory results were found. Dhooge, W *et al.* (2010) [79] found a positive association in boys but a negative association in girls, both statistical significant. On the contrary, Burns, JS *et al.* (2012) [59] found a negative and significant association in boys. Unlike Burns, JS *et al.* (2012) [59], who presented estimates for BMI z-score calculated from measured weight and height, data in Dhooge, W *et al.* (2010) [79] was self-reported.

Table 7.1.1. Description of papers assessing the association between BMI and HCB not eligible for the meta-analysis

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Adults									
Dhooge, W <i>et al.</i> (2010) [79]	BEL	CS	Gen. Population ♂(n=775)	Adults (50-65)	Serum (GC/ECD)	BMI (Self-reported W&H)	Per 1-unit (ln ng/g fat)	$\beta=1.624$ (1.26; 2.02)	Age, alcohol, education, vegetables, meat intake
Dhooge, W <i>et al.</i> (2010) [79]	BEL	CS	Gen. Population ♀(n=808)	Adults (50-65)	Serum (GC/ECD)	BMI (Self-reported W&H)	Per 1-unit (ln ng/g fat)	$\beta=2.73$ (2.29; 2.17)	Age, alcohol, education, vegetables, meat intake
Wu, H <i>et al.</i> (2013) [61]	USA	PC	Nurses breast cancer study;	Adults	Serum (GC)	BMI (Self-reported)	ng/g lipids	$p= -0.02$ ($p>0.05$)	Age


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Table 7.1.1. Description of papers assessing the association between BMI and HCB not eligible for the meta-analysis

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Wu, H et al. (2013) [61]	USA	PC	♀(n=649) Nurses non-Hodgkin lymphoma study; ♀(n=398)	Adults	Serum (GC)	W&H) BMI (Self-reported W&H)	ng/g lipids	$\rho = 0.03$ ($p > 0.05$)	Age
Children									
Dhooge, W et al. (2010) [79]	BEL	CS	Gen. Population ♂(n=767)	Children (14-15)	Serum (GC/ECD)	BMI (Self-reported W&H)	Per 1-unit (ln ng/g fat)	$\beta = 0.56$ (0.27; 0.85)	Parents' education, height, age, smoking, alcohol
Dhooge, W et al. (2010) [79]	BEL	CS	Gen. Population ♀(n=636)	Children (14-15)	Serum (GC/ECD)	BMI (Self-reported W&H)	Per 1-unit (ln ng/g fat)	$\beta = -0.64$ (-1.23; -0.03)	Parents' education, height, age, smoking, alcohol
Burns, JS et al. (2012) [59]	RUS	PC	Gen. Population; ♂(n=350)	Children (8-9)	Serum (HRGC/HRMS)	BMI z-score (measured W&H)	283-2660 vs. 31-98 (ng/g lipids)	$\beta = -0.84$ (-1.23; -0.46)	Age, BW, gestational age, income, calories, blood lead levels

CS: Cross-sectional; PC: Prospective Cohort; GC: Gas Chromatography; ECD: Electron Capture Detection; HRGC: High Resolution Gas Chromatography; HRMS: High Resolution Mass Spectrometry; BMI: Body Mass Index; W: Weight; H: Height; β : Beta coefficient; ρ : Spearman correlation coefficient.

Table 7.1.2 presents the description of papers addressing the association between HCB and other adiposity measures. Regardless of the measure used, all papers observed positive associations between HCB and adiposity.

Table 7.1.2. Description of papers assessing the association between HCB and other adiposity measures

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Fat Mass									
Pelletier, C et al. (2002) [42]	CAN	CS	Lean sedentary and obese men; ♂(n=43)	Adults (36-58)	Serum (GC)	FM (Siri equation)	$\mu\text{g/Kg}$ lipids	$\rho = 0.58$ ($p < 0.001$)	Age
Ronn, M et al. (2011)	SWE	PC	PIVUS; ♂♀(n=866)	Adults (70y.o.)	Plasma (HRGC/HRMS)	FM (DXA)	Per 1-unit (ln ng/g)	$\beta = 2.29$ (0.91; 3.67)	Sex


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Table 7.1.2. Description of papers assessing the association between HCB and other adiposity measures

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
[49]					HRMS)		lipids)	3.67)	
Waist Circumference									
Lee, DH et al. (2012) [50]	SWE	CS	PIVUS, 2001-2004; ♂(n=490)	Adults (70y.o.)	Plasma (HRGC/HRMS)	WC (measured) >102 cm	229-852 vs. 13.6-82.8 (pg/mL)	OR=3.4 (1.6; 7.5)	Calories, exercise, smoking, TG, TC, alcohol
Lee, DH et al. (2012) [50]	SWE	CS	PIVUS, 2001-2004; ♀(n= 480)	Adults (70y.o.)	Plasma (HRGC/HRMS)	WC (measured) >88 cm	229-852 vs.13.6-82.8 (pg/mL)	OR=1.4 (0.7; 2.9)	Calories, exercise, smoking, TG, TC, alcohol
Lee, DH et al. (2012) [50]	SWE	PC	PIVUS, 2001-2009; ♂(n=306)	Adults (≥75)	Plasma (HRGC/HRMS)	WC (measured) >102 cm	229-852 vs. 13.6-82.8 (pg/mL)	OR=2.6 (0.7; 9.2)	Calories, exercise, smoking, TG, TC, alcohol
Lee, DH et al. (2012) [50]	SWE	PC	PIVUS, 2001-2009; ♀(n= 206)	Adults (≥75)	Plasma (HRGC/HRMS)	WC (measured) >88 cm	229-852 vs. 13.6-82.8) (pg/mL)	OR=2.0 (0.7; 6.0)	Calories, exercise, smoking, TG, TC, alcohol
Visceral Adipose Tissue and Subcutaneous Adipose Tissue									
Roos, V et al. (2013) [51]	SWE	CS	PIVUS; ♂♀(n=287)	Adults (70y.o.)	Plasma (HRGC/HRMS)	VAT (MRI)	Per 1-unit (ln ng/g lipids)	β=24.0 (7.8; 39.0)	Sex, education level, exercise, smoking
Roos, V et al. (2013) [51]	SWE	CS	PIVUS; ♂♀(n=287)	Adults (70y.o.)	Plasma (HRGC/HRMS)	SAT (MRI)	Per 1-unit (ln ng/g lipids)	β=39.0 (13.0; 66.0)	Sex, education level, exercise, smoking

Shading represents studies for which the same samples are already included in the meta-analysis plot.

CS: Cross-sectional; PC: Prospective cohort; PIVUS: Prospective Investigation of the Vasculature in Uppsala Seniors; GC: Gas chromatography; HRGC: High Resolution Gas Chromatography; HRMS: High Resolution Mass Spectrometry; FM: Fat Mass; DXA: Dual X-Ray Absorptiometry; WC: Waist Circumference; VAT: Visceral adipose tissue; MRI: Magnetic Resonance Imaging; SAT: Subcutaneous adipose tissue; p: Spearman coefficient; OR: Odds Ratio; β: Beta coefficient; TG: Triglycerides; TC: Total cholesterol.

Table 7.1.3 summarizes estimates for the relation between HCB and each adiposity measure. It is important to highlight that results from studies with ORs or transformed variables (log) were not considered for the following summary estimates, since it is not possible to combine them with the remaining results. Estimates provided

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for children were also excluded. Furthermore, as we have tried to include as much studies as possible, no sensitivity analysis was taken into account. For these reasons, a high heterogeneity was expected and summary estimates should be carefully considered.

Regardless of the adiposity measure, a positive association between HCB and adiposity was found in adults.


Table 7.1.3. Summary estimates for the association between HCB and each adiposity measure in adults

	HCB			
	Number of included estimates	Summary Estimate*	I ²	95% CI
Body Mass Index	6 ^a	0.44	88.9	0.38; 0.49
Fat Mass	1 ^b	0.58 [†]	-	<0.001 [‡]
Visceral Adipose Tissue	1 ^c	24.0	-	7.8; 39.0
Subcutaneous Adipose Tissue	1 ^c	39.0	-	13.0; 66.0

I² available only when meta-analysis was performed.

*Beta coefficient if not otherwise specified. [†]Spearman correlation coefficient; [‡]p-value.

Included studies are: ^aMoysich, KB et al. (2002)[67], Pelletier, C et al. (2002)[42], Magnusdottir, E *et al.* (2005)[43], Hue, O et al. (2006)[44], Langer, P et al. (2012) [60] and Moon, HB et al. (2012)[52], ^bPelletier, C et al. (2002)[42]; ^cRoos, V et al. (2013)[51].

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8. Organophosphates

We have identified two studies examining the relationship between organophosphate compounds and adiposity [80, 81]. Both publications are cross-sectional and focused on occupational exposure of organophosphates, however each of them studied a different specific compound: Blanco-Munoz, J *et al.* (2010) [80] evaluated diethylthiophosphoric (DETP) and Raafat, N *et al.* (2012) [81] evaluated malathion, so it was not possible to perform a meta-analysis.

Blanco-Munoz, J *et al.* (2010) [80] investigated Mexican male workers involved in the production of flowers and ornamental plants (n=104) and found a negative correlation between urinary levels of diethylthiophosphoric (DETP) and BMI ($\rho = -0.2$, $p = 0.05$). In contrast, Raafat, N *et al.* (2012) [81], observed positive correlations between malathion exposure and both BMI and WC ($r = 0.831$, $p < 0.001$ and $r = 0.510$, $p < 0.001$, respectively), in a sample of 98 Egyptian male farmers who have been mixing and applying pesticides for the past ten years (table 8.1.1).

Table 8.1.1. Description of papers included in the systematic review assessing the association between organophosphates and adiposity

Author, year	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Diethylthiophosphoric acid (DETP)									
BMI									
Blanco-Munoz, J <i>et al.</i> (2010)[80]	MEX	CS	Workers in the production of plants; ♂(n=104)	Adults (18-50)	Urine (GLC)	BMI (measured W&H)	µg/g creatinine	$\rho = -0.2$ ($p = 0.05$)	-
Malathion									
BMI									
Raafat, N <i>et al.</i> (2012)[81]	EGY	CS	Farmers who mix/apply pesticides; ♂(n=98)	Adults (39±12)*	Whole blood (TLC)	BMI (measured W&H)	mg/L	$r = 0.831$ ($p < 0.001$)	-
Waist Circumference									
Raafat, N	EGY	CS	Farmers who	Adults	Whole blood	WC	mg/L	$r = 0.510$	-



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Table 8.1.1. Description of papers included in the systematic review assessing the association between organophosphates and adiposity

Author, year	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
et al. (2012)[81]			mix/apply pesticides; ♂(n=98)	(39±12)*	(TLC)	(Measured)		(p<0.001)	

CS: Cross-sectional; GLC: Gas-liquid Chromatography; TLC: Thin Layer Chromatography; BMI: Body Mass Index; W: Weight; H: Height; WC: Waist circumference; ρ: Spearman coefficient; r: Pearson correlation coefficient. *Mean±sd.

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9. Dioxin-like Polychlorinated Biphenyls

In the systematic review we have identified fourteen papers reporting on the association between dioxin-like PCBs and adiposity [42-44, 46, 49-51, 61, 69, 74, 76, 79, 82, 83]. Ten publications have evaluated the association between PCB 118 and adiposity [42-44, 46, 49-51, 61, 69, 79] and six papers assessed PCB 156 [42-44, 49-51]. PCB 105, 114, 126, 157, 167, 169, 189 were also evaluated but only by a limited number of papers and therefore meta-analysis was not performed. Results on these compounds are presented in the descriptive table. Lastly, four publications have addressed the relation between the sum of dioxin-like PCBs and adiposity [46, 74, 76, 83], which are also presented in the descriptive table.

9.1 Polychlorinated Biphenyl 118 (PCB 118)

Of the ten publications assessing PCB 118 identified in the systematic review, six were excluded from meta-analysis. One publication was excluded for being performed in a sample including among cancer patients [61] and two for not presenting neither correlation nor beta coefficients as the estimation measure [46, 50]. Ronn, M *et al.* (2011) [49], Roos, V *et al.* (2013) [51] and Dhooze, W *et al.* (2010) [79] were also excluded for presenting regression coefficients for log transformed variables.

Four papers were then included in the meta-analysis [42-44, 69]. All the included studies presented a cross-sectional design with positive associations between PCB 118 serum concentration and adiposity. The overall beta coefficient was 0.43 (95% CI 0.33; 0.53). Study heterogeneity was low, with a percentage of variance of 6.1% (figure 9.1).

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	Author(s): V Mendes; I Delgado; B Peleteiro; J Araújo; H Barros; E Ramos; D Sarigiannis; N Baiz; I Annesi-Maesano	Version: 1	82/221

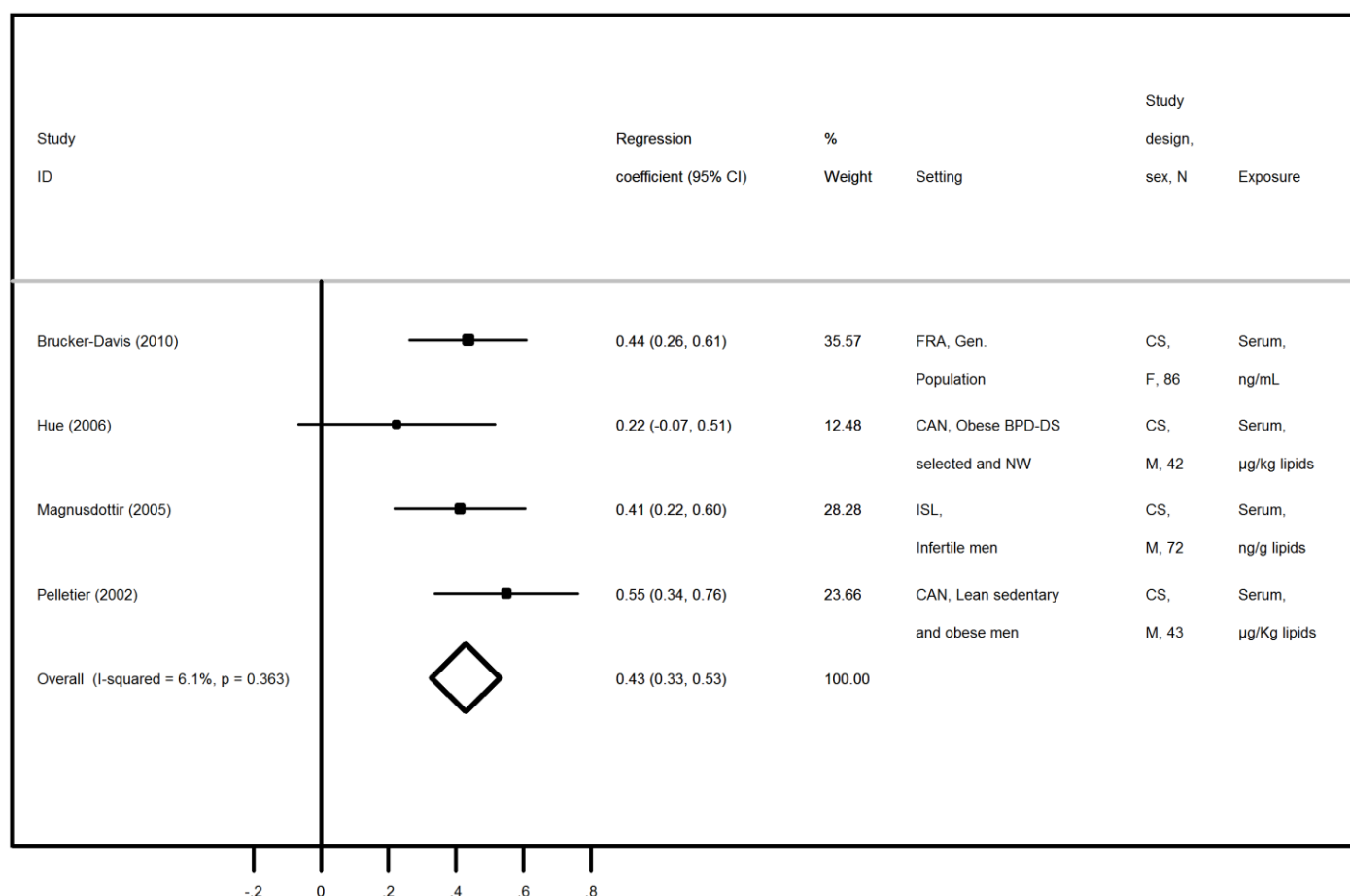


Figure 9.1. Meta-analysis of studies evaluating the association of PCB 118 with BMI in adults. Beta coefficients and corresponding 95% CI (horizontal lines). The size of the black square indicates the study's weight in the analysis (weights are from fixed-effects analysis). The centre of the open diamond indicates the summary estimate and its width represents the 95% CI.


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Table 9.1.1 shows the description of publications that presented results on the association of PCB 118 with BMI but were not included in the meta-analysis presented in figure 9.1.

In adults, Dhooge, W *et al.* (2010) [79] found positive and statistically significant associations in both men and women, while Brucker-Davis, F *et al.* (2010) [69] found a negative correlation between PCB 118 and BMI at delivery ($\rho = -0.43$, $p = 0.037$) among pregnant women. Wu, H *et al.* (2013) [61] has also found conflicting results in nurses from breast cancer ($\rho = -0.01$, $p > 0.05$) study vs. nurses from non-Hodgkin lymphoma study ($\rho = 0.17$, $p < 0.05$).

Among children, Dhooge, W *et al.* (2010) [79] found positive associations with statistical significance between PCB 118 and BMI.

Table 9.1.1. Description of papers assessing the association between PCB 118 and BMI not eligible for the meta-analysis

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Adults									
Dhooge, W <i>et al.</i> (2010) [79]	BEL	CS	Gen. Population; ♂(n=775)	Adults (50-65)	Serum (GC-ECD)	BMI (self-reported W&H)	Per 1-unit (ln ng/g fat)	$\beta = 0.824$ (0.463; 1.185)	Age, alcohol, education, vegetables, meat intake
Dhooge, W <i>et al.</i> (2010) [79]	BEL	CS	Gen. Population; ♀(n=808)	Adults (50-65)	Serum (GC-ECD)	BMI (self-reported W&H)	Per 1-unit (ln ng/g fat)	$\beta = 1.28$ (0.83; 1.72)	Age, alcohol, education, vegetables, meat intake
Brucker-Davis, F <i>et al.</i> (2010) [69]	FRA	CS	Gen. Population; ♀(n=86)	Adults (18-40)	Serum (GC/MS)	BMI at delivery [†]	ng/mL	$\rho = -0.43$ ($p = 0.037$)	-
Wu, H <i>et al.</i> (2013) [61]	USA	PC	Nurses breast cancer study; ♀(n=649)	Adults	Serum (GC)	BMI (self-reported W&H)	ng/g lipids	$\rho = -0.01$ ($p > 0.05$)	Age
Wu, H <i>et al.</i> (2013) [61]	USA	PC	Nurses non-Hodgkin lymphoma study; ♀(n=398)	Adults	Serum (GC)	BMI (self-reported W&H)	ng/g lipids	$\rho = 0.17$ ($p < 0.05$)	Age
Children									
Dhooge, W <i>et al.</i> (2010) [79]	BEL	CS	Gen. Population; ♂(n=767)	Children (14-15)	Serum (GC-ECD)	BMI (self-reported W&H)	Per 1-unit (ln ng/g fat)	$\beta = 0.56$ (0.27; 0.85)	Parents' education, height, age, smoking, alcohol
Dhooge, W <i>et al.</i> (2010) [79]	BEL	CS	Gen. Population; ♀(n=636)	Children (14-15)	Serum (GC-ECD)	BMI (self-reported)	Per 1-unit (ln ng/g)	$\beta = 0.74$ (0.41; 1.07)	Parents' education,


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Table 9.1.1. Description of papers assessing the association between PCB 118 and BMI not eligible for the meta-analysis

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
						W&H)	fat)	1.07)	height, age, smoking, alcohol

Shading represents studies for which the same samples are already included in the meta-analysis plot.

CS: Cross-sectional; PC: Prospective Cohort; GC: Gas Chromatography; MS: Mass Spectrometry; ECD: Electron Capture Detection; BMI: Body Mass Index; W: Weight; H: Height; ρ : Spearman correlation coefficient; β : Beta coefficient.

†No further information

Publications assessing the association between PCB 118 and other adiposity measures are presented in table 9.1.2. All papers observed positive associations between PCB 118 and adiposity, regardless of the measure used. With the exception of Pelletier, C et al. (2002) [42] which is already represented in the meta-analysis plot shown in figure 9.1, and Lee, DH *et al.* (2007) [46] that evaluated non-diabetic individuals from NHANES 1999-2002, all the estimates were obtained from PIVUS individuals.

Table 9.1.2. Description of papers assessing the association between PCB 118 and other adiposity measures

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Fat Mass									
Pelletier, C et al. (2002) [42]	CAN	CS	Lean sedentary and obese men; ♂(n=43)	Adults (36-58)	Serum (GC)	FM (Siri equation)	µg/Kg lipids	$\rho = 0.53$ $p < 0.001$	Age
Ronn, M et al. (2011) [49]	SWE	PC	PIVUS; ♂♀(n=866)	Adults (70y.o.)	Plasma (HRGC/HRMS)	FM (DXA)	Per 1-unit (ln ng/g lipid)	$\beta = 2.93$ (1.95; 3.91)	Sex
Waist Circumference									
Lee, DH et al. (2007) [46]	USA	CS	NHANES Non-diabetic, 1999-2002; ♂♀(n= 721)	Adults (≥ 20)	Total blood (HRGC/HRMS)	WC (measured) ♂ >102 ; ♀ >88 cm	$>75^{\text{th}}$ vs. BDL	OR= 2.2 (1.2; 4.1)	Age, sex, race, PIR, smoking, cotinine, alcohol, exercise
Lee, DH et al. (2012) [50]	SWE	CS	PIVUS, 2001-2004; ♂(n=490)	Adults (70y.o.)	Plasma (HRGC/HRMS)	WC (measured) >102 cm	Qu5 (309-1637) vs. Qu1 (25.0-125) (pg/mL)	OR= 3.1 (1.4; 6.9)	Calorie intake, exercise, smoking, alcohol, TG, TC
Lee, DH et al. (2012) [50]	SWE	CS	PIVUS, 2001-2004; ♀(n= 480)	Adults (70y.o.)	Plasma (HRGC/HRMS)	WC (measured) >88 cm	Qu5 (309-1637) vs. Qu1 (25.0-	OR= 1.2 (0.6; 2.5)	Calorie intake, exercise, smoking,


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Table 9.1.2. Description of papers assessing the association between PCB 118 and other adiposity measures

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Lee, DH et al. (2012) [50]	SWE	PC	PIVUS, 2001-2009; ♂(n=306)	Adults (≥ 75)	Plasma (HRGC/HRMS)	WC (measured) >102 cm	125) (pg/mL) Qu5 (309-1637) vs. Qu1(25.0-125) (pg/mL)	OR= 2.3 (0.6; 8.5)	alcohol, TG, TC Calorie intake, exercise, smoking, alcohol, TG, TC
Lee, DH et al. (2012) [50]	SWE	PC	PIVUS, 2001-2009; ♀(n= 206)	Adults (≥ 75)	Plasma (HRGC/HRMS)	WC (measured) >88 cm	Qu5 (309-1637) vs. Qu1 (25.0-125)(pg/mL)	OR= 1.4 (0.5; 4.5)	Calorie intake, exercise, smoking, alcohol, TG, TC
Visceral Adipose Tissue and Subcutaneous Adipose Tissue									
Roos, V et al. (2013) [51]	SWE	CS	PIVUS; ♂♀(n=287)	Adults (70y.o.)	Plasma (HRGC/HRMS)	VAT (MRI)	Per 1-unit (ln ng/g lipid)	β= 23.0 (10.0; 36.0)	Sex, education level, exercise, smoking
Roos, V et al. (2013) [51]	SWE	CS	PIVUS; ♂♀(n=287)	Adults (70y.o.)	Plasma (HRGC/HRMS)	SAT (MRI)	Per 1-unit (ln ng/g lipid)	β= 37.0 (15.0; 59.0)	Sex, education level, exercise, smoking

Shading represents studies for which the same samples are already included in the meta-analysis plot.


CS: Cross-sectional; PC: Prospective Cohort; NHANES: National Health and Nutrition Examination Survey; PIVUS: Prospective Investigation of the Vasculature in Uppsala Seniors; GC: Gas Chromatography; HRGC: High Resolution Gas Chromatography; HRMS: High Resolution Mass Spectrometry; FM: Fat Mass; WC: Waist Circumference; DXA: Dual-energy X-ray Absorptiometry; VAT: Visceral Adipose Tissue; MRI: Magnetic Resonance Imaging; SAT: Subcutaneous Adipose Tissue; BDL: Below Detected Levels; Qu: Quintile; p: Spearman correlation coefficient; OR: Odds Ratio; β: Beta coefficient; TG: Triglycerides; TC: Total cholesterol.

The results from all adiposity measures support a positive association between PCB 118 and adiposity.

9.2 Polychlorinated Biphenyl 156 (PCB 156)

Six studies assessing PCB 156 were identified in the systematic review [42-44, 49-51]. Three publications were excluded from meta-analysis for presenting ORs as the estimate measure [50] or for presenting regression coefficients for log transformed variables [49, 51]. Three papers were then included in the meta-analysis [42-44].

The overall estimate was positive, though it did not reach statistical significance ($\beta = 0.08$, 95% CI -0.08; 0.24). The percentage of variance between studies was null ($I^2 = 0.0\%$) (figure 9.2). However, it is important to highlight the small sample size of the three included papers.

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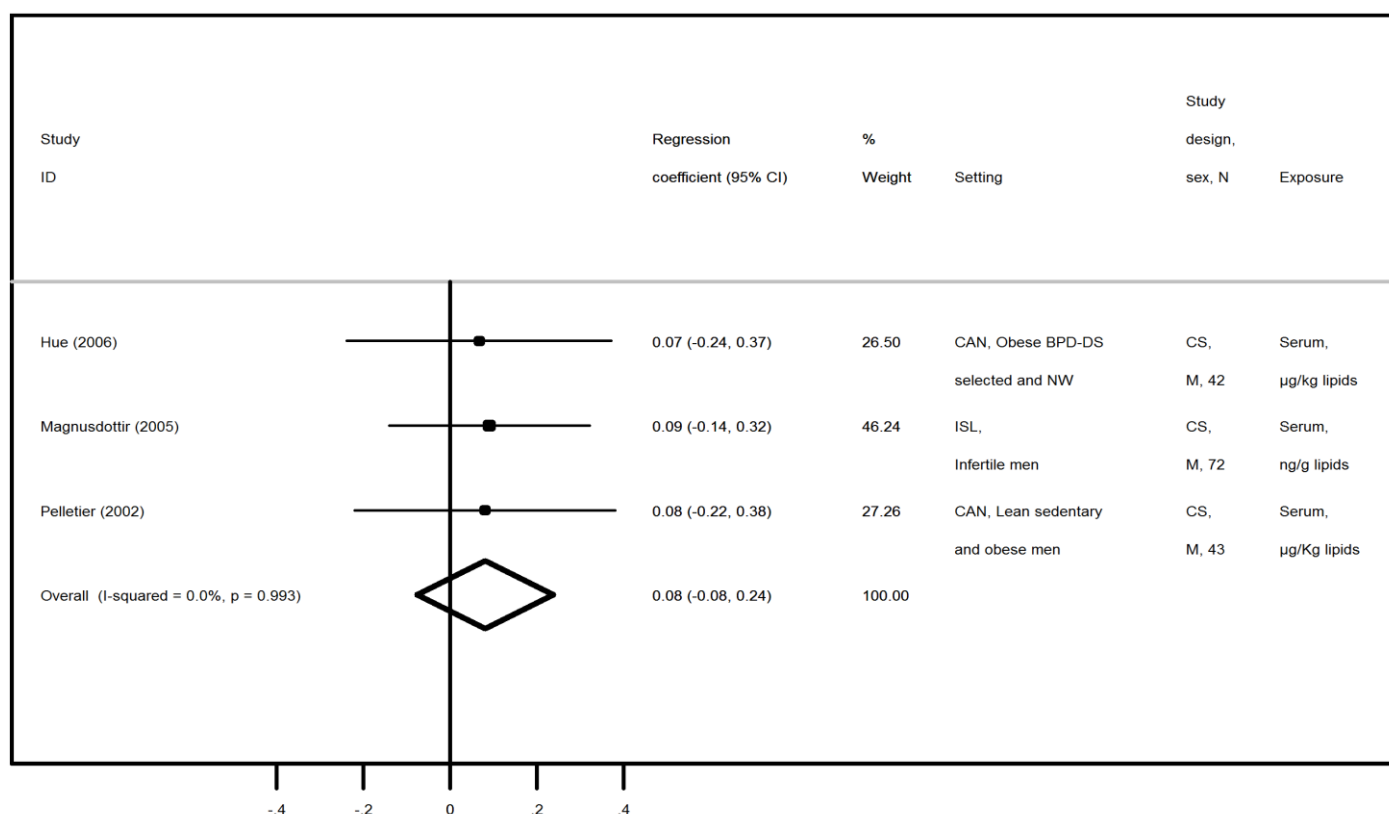



Figure 9.2. Meta-analysis of studies valuating the association of PCB 156 with BMI in adults. Beta coefficients and corresponding 95% CI (horizontal lines). The size of the black square indicates the study's weight in the analysis (weights are from fixed-effects analysis). The centre of the open diamond indicates the summary estimate and its width represents the 95% CI.

The description of publications addressing the association between PCB 156 and other adiposity measures is presented in table 9.2.1. Pelletier, C *et al.* (2002) [42] found a positive correlation with fat mass, but with no statistical significance ($p=0.06$, $p=0.716$). This result is already represented in the meta-analysis plot shown in figure 9.2 with an estimate for BMI.

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All the other papers evaluating other adiposity measures were performed using PIVUS data and found substantially different associations than the one found for BMI in the meta-analysis [49-51]. However, it should be taken into account that all papers assessing BMI had a rather small sample size (ranging from 42 to 72 adult individuals), when compared to those assessing other adiposity measures, and included only men. On the other hand, the consistency of results for other adiposity measures was expected since these results were obtained from the same study (PIVUS).

Table 9.2.1. Description of papers assessing the association between PCB 156 and other adiposity measures

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Fat Mass									
Pelletier, C et al. (2002) [42]	CAN	CS	Lean sedentary and obese men; ♂(n=43)	Adults (36-58)	Serum (GC)	FM (Siri equation)	µg/Kg lipids	ρ= 0.06 (p= 0.716)	Age
Ronn, M et al. (2011) [49]	SWE	PC	PIVUS; ♂♀(n=866)	Adults (70y.o.)	Plasma (HRGC/HRMS)	FM (DXA)	Per 1-unit (ln ng/g lipid)	β= -4.12 (-5.42; -2.83)	Sex
Waist Circumference									
Lee, DH et al. (2012) [50]	SWE	CS	PIVUS, 2001-2004; ♂(n=490)	Adults (70y.o.)	Plasma (HRGC/HRMS)	WC (measured) >102 cm	213-536 vs. Qu1 12.2-111 (pg/mL)	OR= 0.8 (0.4; 1.8)	Calorie intake, exercise, smoking, alcohol, TG, TC
Lee, DH et al. (2012) [50]	SWE	CS	PIVUS, 2001-2004; ♀(n= 480)	Adults (70y.o.)	Plasma (HRGC/HRMS)	WC (measured) >88 cm	213-536 vs. 12.2-111 (pg/mL)	OR= 0.1 (0.0; 0.2)	Calorie intake, exercise, smoking, alcohol, TG, TC
Lee, DH et al. (2012) [50]	SWE	PC	PIVUS, 2001-2009; ♂(n=306)	Adults (≥75)	Plasma (HRGC/HRMS)	WC (measured) >102 cm	213-536 vs.12.2-111 (pg/mL)	OR= 0.5 (0.2; 1.8)	Calorie intake, exercise, smoking, alcohol, TG, TC
Lee, DH et al. (2012) [50]	SWE	PC	PIVUS, 2001-2009; ♀(n= 206)	Adults (≥75)	Plasma (HRGC/HRMS)	WC (measured) >88 cm	213-536 vs. 12.2-111 (pg/mL)	OR= 0.2 (0.1; 0.5)	Calorie intake, exercise, smoking, alcohol, TG, TC
Visceral Adipose Tissue and Subcutaneous Adipose Tissue									
Roos, V et al. (2013) [51]	SWE	CS	PIVUS; ♂♀(n=287)	Adults (70y.o.)	Plasma (HRGC/HRMS)	VAT (MRI)	Per 1-unit (ln ng/g lipid)	β= -20.0 (-36.0; -2.6)	Sex, education, exercise, smoking
Roos, V et al. (2013) [51]	SWE	CS	PIVUS; ♂♀(n=287)	Adults (70y.o.)	Plasma (HRGC/HRMS)	SAT (MRI)	Per 1-unit (ln ng/g lipid)	β= -40.0 (-69.0; -12.0)	Sex, education level, exercise, smoking

Shading represents studies for which the same samples are already included in the meta-analysis plot.

CS: Cross-sectional; PC: Prospective Cohort; PIVUS: Prospective Investigation of the Vasculature in Uppsala Seniors; GC: Gas Chromatography; HRGC: High Resolution Gas Chromatography; HRMS: High Resolution Mass Spectrometry; FM: Fat Mass; WC: Waist Circumference; VAT: Visceral



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Table 9.2.1. Description of papers assessing the association between PCB 156 and other adiposity measures

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Adipose Tissue; MRI: Magnetic Resonance Imaging; SAT: Subcutaneous Adipose Tissue; Qu: Quintile; p: Spearman correlation coefficient; OR: Odds ratio; β : Beta coefficient; TG: Triglycerides; TC: Total cholesterol.									

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	WP16: Obesity and childhood diabetes - link with endocrine disruptors		Security: PU
	Author(s): V Mendes; I Delgado; B Peleteiro; J Araújo; H Barros; E Ramos; D Sarigiannis; N Baiz; I Annesi-Maesano		Version: 1 89/221


9.3 Polychlorinated Biphenyl 105 (PCB 105)

The relationship between PCB 105 and adiposity was evaluated in three papers [49-51], all performed among PIVUS participants thus hindering the meta-analysis. A positive association was reported for all adiposity measures and statistical significance was reached for fat mass [49], waist circumference, among men only [50], and for visceral/ subcutaneous adipose tissue in both sexes [51] (table 9.3.1).

Table 9.3.1. Description of papers included in the systematic review assessing the association between PCB 105 and adiposity

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Fat Mass									
Ronn, M et al. (2011) [49]	SWE	PC	PIVUS; ♂♀(n=866)	Adults (70y.o.)	Plasma (HRGC/HRMS)	FM (DXA)	Per 1-unit (ln ng/g lipid)	β= 3.14 (2.06; 4.23)	Sex
Waist Circumference									
Lee, DH et al. (2012) [50]	SWE	CS	PIVUS, 2001-2004; ♂(n=490)	Adults (70y.o.)	Plasma (HRGC/HRMS)	WC (measured) >102 cm	52.3-376 vs. 5.5-18.8 (pg/mL)	OR= 3.2 (1.5; 7)	Calories, exercise, smoking, alcohol, TG, TC
Lee, DH et al. (2012) [50]	SWE	CS	PIVUS, 2001-2004; ♀(n= 480)	Adults (70y.o.)	Plasma (HRGC/HRMS)	WC (measured) >88 cm	52.3-376 vs. 5.5-18.8 (pg/mL)	OR= 1.3 (0.6;2.5)	Calories, exercise, smoking, alcohol, TG, TC
Lee, DH et al. (2012) [50]	SWE	PC	PIVUS, 2001-2009; ♂(n=306)	Adults (≥75)	Plasma (HRGC/HRMS)	WC (measured) >102 cm	52.3-376 vs. 5.5-18.8 (pg/mL)	OR= 1.3 (0.3;4.8)	Calories, exercise, smoking, alcohol, TG, TC
Lee, DH et al. (2012) [50]	SWE	PC	PIVUS, 2001-2009; ♀(n= 206)	Adults (≥75)	Plasma (HRGC/HRMS)	WC (measured) >88 cm	52.3-376 vs. 5.5-18.8 (pg/mL)	OR= 1.6 (0.5;4.9)	Calories, exercise, smoking, alcohol, TG, TC
Visceral Adipose Tissue and Subcutaneous Adipose Tissue									
Roos, V et al. (2013) [51]	SWE	CS	PIVUS; ♂♀(n=287)	Adults (70y.o.)	Plasma (HRGC/HRMS)	VAT (MRI)	Per 1-unit (ln ng/g lipid)	β= 23.0 (11.0; 34.0)	Sex, education, exercise, smoking
Roos, V et al. (2013) [51]	SWE	CS	PIVUS; ♂♀(n=287)	Adults (70y.o.)	Plasma (HRGC/HRMS)	SAT (MRI)	Per 1-unit (ln ng/g lipid)	β= 37.0 (17.0; 56.0)	Sex, education, exercise, smoking

PC: Prospective Cohort; CS: Cross-sectional; PIVUS: Prospective Investigation of the Vasculature in Uppsala Seniors; HRGC: High Resolution Gas Chromatography; HRMS: High Resolution Mass Spectrometry; FM: Fat Mass; DXA: Dual-energy X-ray Absorptiometry; WC: Waist Circumference; VAT: Visceral Adipose Tissue; MRI: Magnetic Resonance Imaging; SAT: Subcutaneous Adipose Tissue; β: Beta coefficient; OR: Odds ratio; TG: Triglycerides; TC: Total cholesterol.

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	WP16: Obesity and childhood diabetes - link with endocrine disruptors	Security: PU	
	Author(s): V Mendes; I Delgado; B Peleteiro; J Araújo; H Barros; E Ramos; D Sarigiannis; N Baiz; I Annesi-Maesano	Version: 1	90/221

9.4 Polychlorinated Biphenyl 126 (PCB 126)

The association between PCB 126 and adiposity was evaluated in four papers, three including individuals from PIVUS [49-51] and one being performed among NHANES 1999-2002 participants [46] (table 9.4.1).

Reported results were however somewhat contradictory. Ronn, M *et al.* (2011) [49] observed a positive association with fat mass among PIVUS subjects, although with no statistical significance ($\beta = 0.68$, 95% CI -0.64; 2.0). Lee, DH *et al.* (2007) [46] also found a positive and statistically significant association for waist circumference among NHANES 1999-2002 non-diabetic individuals (OR= 2.4, 95% CI 1.4; 4.1), while Lee, DH *et al.* (2012) [50] observed negative associations between this PCB and waist circumference, as well as Roos, V *et al.* (2013) [51] for visceral and subcutaneous adipose tissue, both performed among PIVUS participants.

Table 9.4.1. Description of papers included in the systematic review assessing the association between PCB 126 and adiposity

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Fat Mass									
Ronn, M <i>et al.</i> (2011) [49]	SWE	PC	PIVUS; ♂♀(n=866)	Adults (70y.o.)	Plasma (HRGC/HRMS)	FM (DXA)	Per 1-unit (ln ng/g lipid)	$\beta = 0.68$ (-0.64; 2.0)	Sex
Waist Circumference									
Lee, DH <i>et al.</i> (2007) [46]	USA	CS	NHANES Non-diabetic, 1999-2002; ♂♀(n=721)	Adults (≥ 20)	Whole blood (HRGC/HRMS)	WC (measured) ♂>102 cm; ♀>88 cm	>75 th vs. BDL	OR= 2.4 (1.4; 4.1)	Age, sex, race, PIR, smoking, alcohol, exercise
Lee, DH <i>et al.</i>	SWE	CS	PIVUS, 2001-	Adults	Plasma	WC	83.3-385.8	OR= 0.6	Calories,


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Table 9.4.1. Description of papers included in the systematic review assessing the association between PCB 126 and adiposity

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
(2012) [50]			2004; ♂(n=490)	(70y.o.)	(HRGC/HRMS)	(measured) >102 cm	vs. 0.6-18.3 (pg/mL)	(0.3; 1.2)	exercise, smoking, alcohol, TG, TC
Lee, DH et al. (2012) [50]	SWE	CS	PIVUS, 2001-2004; ♀(n= 480)	Adults (70y.o.)	Plasma (HRGC/HRMS)	WC (measured) >88 cm	83.3-385.8 vs. 0.6-18.3 (pg/mL)	OR= 0.4 (0.2; 0.7)	Calories, exercise, smoking, alcohol, TG, TC
Lee, DH et al. (2012) [50]	SWE	PC	PIVUS, 2001-2009; ♂(n=306)	Adults (≥75)	Plasma (HRGC/HRMS)	WC (measured) >102 cm	83.3-385.8 vs. 0.6-18.3 (pg/mL)	OR= 3.3 (0.8; 13)	Calories, exercise, smoking, alcohol, TG, TC
Lee, DH et al. (2012) [50]	SWE	PC	PIVUS, 2001-2009; ♀(n= 206)	Adults (≥75)	Plasma (HRGC/HRMS)	WC (measured) >88 cm	83.3-385.8 vs. 0.6-18.3 (pg/mL)	OR= 1 (0.4; 2.8)	Calories, exercise, smoking, alcohol, TG, TC

Visceral Adipose Tissue and Subcutaneous Adipose Tissue


Roos, V et al. (2013) [51]	SWE	CS	PIVUS; ♂♀(n=287)	Adults (70y.o.)	Plasma (HRGC/HRMS)	VAT (MRI)	Per 1-unit (ln ng/g lipid)	β= -0.45 (-7.9; 7.0)	Sex, education, exercise, smoking
Roos, V et al. (2013) [51]	SWE	CS	PIVUS; ♂♀(n=287)	Adults (70y.o.)	Plasma (HRGC/HRMS)	SAT (MRI)	Per 1-unit (ln ng/g lipid)	β= -8.5 (-21.0; 3.9)	Sex, education level, exercise, smoking

PC: Prospective Cohort; CS: Cross-sectional; PIVUS: Prospective Investigation of the Vasculature in Uppsala Seniors; NHANES: National Health and Nutrition Examination Survey; HRGC: High Resolution Gas Chromatography; HRMS: High Resolution Mass Spectrometry; FM: Fat Mass; DXA: Dual-energy X-ray Absorptiometry; WC: Waist Circumference; VAT: Visceral Adipose Tissue; MRI: Magnetic Resonance Imaging; SAT: Subcutaneous Adipose Tissue; β: Beta coefficient; OR: Odds ratio; PIR: Poverty Income Ratio; TG: Triglycerides; TC: Total cholesterol.

9.5 Polychlorinated Biphenyl 157 (PCB 157)

Three publications assessed the association between PCB 157 and adiposity [49-51]. All estimates provided were negative regardless of the adiposity measure used, indicating that higher levels of this dioxin-like PCB is associated with lower levels of adiposity. Statistical significance was however only observed for fat mass [49] and subcutaneous adipose tissue [51].

Table 9.5.1. Description of papers included in the systematic review assessing the association between PCB 157 and adiposity


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	Author(s): V Mendes; I Delgado; B Peleteiro; J Araújo; H Barros; E Ramos; D Sarigiannis; N Baiz; I Annesi-Maesano		Version: 1 92/221

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Fat Mass									
Ronn, M et al. (2011) [49]	SWE	PC	PIVUS; ♂♀(n=866)	Adults (70y.o.)	Plasma (HRGC/HRMS)	FM (DXA)	Per 1-unit (ln ng/g lipid)	β= -3.44 (-4.7; -2.2)	Sex
Waist Circumference									
Lee, DH et al. (2012) [50]	SWE	CS	PIVUS, 2001-2004; ♂(n=490)	Adults (70y.o.)	Plasma (HRGC/HRMS)	WC (measured) >102 cm	39.7-239 vs. 5.0-19.6 (pg/mL)	OR= 0.9 (0.4; 2.1)	Calories, exercise, smoking, alcohol, TG, TC
Lee, DH et al. (2012) [50]	SWE	CS	PIVUS, 2001-2004; ♀(n= 480)	Adults (70y.o.)	Plasma (HRGC/HRMS)	WC (measured) >88 cm	39.7-239 vs. 5.0-19.6 (pg/mL)	OR= 0.1 (0.1; 0.3)	Calories, exercise, smoking, alcohol, TG, TC
Lee, DH et al. (2012) [50]	SWE	PC	PIVUS, 2001-2009; ♂(n=306)	Adults (≥75)	Plasma (HRGC/HRMS)	WC (measured) >102 cm	39.7-239 vs. 5.0-19.6 (pg/mL)	OR= 0.9 (0.3; 2.7)	Calories, exercise, smoking, alcohol, TG, TC
Lee, DH et al. (2012) [50]	SWE	PC	PIVUS, 2001-2009; ♀(n= 206)	Adults (≥75)	Plasma (HRGC/HRMS)	WC (measured) >88 cm	39.7-239 vs. 5.0-19.6 (pg/mL)	OR= 0.4 (0.1; 1.2)	Calories, exercise, smoking, alcohol, TG, TC
Visceral Adipose Tissue and Subcutaneous Adipose Tissue									
Roos, V et al. (2013) [51]	SWE	CS	PIVUS; ♂♀(n=287)	Adults (70y.o.)	Plasma (HRGC/HRMS)	VAT (MRI)	Per 1-unit (ln ng/g lipid)	β= -16.0 (-33; 0.6)	Sex, education, exercise, smoking
Roos, V et al. (2013) [51]	SWE	CS	PIVUS; ♂♀(n=287)	Adults (70y.o.)	Plasma (HRGC/HRMS)	SAT (MRI)	Per 1-unit (ln ng/g lipid)	β= -38.0 (-66.0; -10.0)	Sex, education, exercise, smoking

PC: Prospective Cohort; CS: Cross-sectional; PIVUS: Prospective Investigation of the Vasculature in Uppsala Seniors; HRGC: High Resolution Gas Chromatography; HRMS: High Resolution Mass Spectrometry; FM: Fat Mass; DXA: Dual-energy X-ray Absorptiometry; WC: Waist Circumference; VAT: Visceral Adipose Tissue; MRI: Magnetic Resonance Imaging; SAT: Subcutaneous Adipose Tissue; β: Beta coefficient; OR: Odds ratio; TG: Triglycerides; TC: Total cholesterol.

9.6 Polychlorinated Biphenyl 189 (PCB 189)

The relationship between PCB 189 and adiposity was evaluated in three papers [49-51], all performed among PIVUS participants. All estimates provided were negative


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regardless of the adiposity measure used and statistically significant for fat mass [49], waist circumference in women [50] and visceral adipose tissue [51] (table 9.6.1).

Table 9.6.1. Description of papers included in the systematic review assessing the association between PCB 189 and adiposity

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Fat Mass									
Ronn, M et al. (2011) [49]	SWE	PC	PIVUS; ♂♀(n=866)	Adults (70y.o.)	Plasma (HRGC/HRMS)	FM (DXA)	Per 1-unit (ln ng/g lipid)	β= -2.57 (-3.44; -1.71)	Sex
Waist Circumference									
Lee, DH et al. (2012) [50]	SWE	CS	PIVUS, 2001-2004; ♂(n=490)	Adults (70y.o.)	Plasma (HRGC/HRMS)	WC (measured) >102 cm	27.5-1060 vs. 2.0-13.4 (pg/mL)	OR= 0.5 (0.2; 1.1)	Calories, exercise, smoking, alcohol, TG, TC
Lee, DH et al. (2012) [50]	SWE	CS	PIVUS, 2001-2004; ♀(n= 480)	Adults (70y.o.)	Plasma (HRGC/HRMS)	WC (measured) >88 cm	27.5-1060 vs. 2.0-13.4 (pg/mL)	OR= 0.1 (0.1; 0.3)	Calories, exercise, smoking, alcohol, TG, TC
Lee, DH et al. (2012) [50]	SWE	PC	PIVUS, 2001-2009; ♂(n=306)	Adults (≥75)	Plasma (HRGC/HRMS)	WC (measured) >102 cm	27.5-1060 vs. 2.0-13.4 (pg/mL)	OR= 0.3 (0.1; 1.0)	Calories, exercise, smoking, alcohol, TG, TC
Lee, DH et al. (2012) [50]	SWE	PC	PIVUS, 2001-2009; ♀(n= 206)	Adults (≥75)	Plasma (HRGC/HRMS)	WC (measured) >88 cm	27.5-1060 vs. 2.0-13.4 (pg/mL)	OR= 0.2 (0.1; 0.8)	Calories, exercise, smoking, alcohol, TG, TC
Visceral Adipose Tissue and Subcutaneous Adipose Tissue									
Roos, V et al. (2013) [51]	SWE	CS	PIVUS; ♂♀(n=287)	Adults (70y.o.)	Plasma (HRGC/HRMS)	VAT (MRI)	Per 1-unit (ln ng/g lipid)	β= -12.0 (-21.0; -3.6)	Sex, education, exercise, smoking
Roos, V et al. (2013) [51]	SWE	CS	PIVUS; ♂♀(n=287)	Adults (70y.o.)	Plasma (HRGC/HRMS)	SAT (MRI)	Per 1-unit (ln ng/g lipid)	β= -8.1 (-2.3; 6.5)	Sex, education, exercise, smoking

PC: Prospective Cohort; CS: Cross-sectional; PIVUS: Prospective Investigation of the Vasculature in Uppsala Seniors; HRGC: High Resolution Gas Chromatography; HRMS: High Resolution Mass Spectrometry; FM: Fat Mass; DXA: Dual-energy X-ray Absorptiometry; WC: Waist Circumference; VAT: Visceral Adipose Tissue; MRI: Magnetic Resonance Imaging; SAT: Subcutaneous Adipose Tissue; β: Beta coefficient; OR: Odds ratio; TG: Triglycerides; TC: Total cholesterol.

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9.7 Other dioxin-like PCBs

PCB 114 was evaluated by Jackson, LW *et al.* (2010) [82] in children and observed negative associations with weight and weight for length (table 9.7.1).

Among adults, a positive association was found for the association of PCB 167 with BMI in infertile men ($p=0.24$, $p=0.04$) [43]. PCB 169 was evaluated in PIVUS participants results for fat mass and visceral/subcutaneous adipose tissue were all negative and statistically significant [49, 51].

Table 9.7.1. Description of papers included in the systematic review assessing the association between other dioxin-like PCBs and adiposity

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
PCB 114									
Jackson, LW <i>et al.</i> (2010) [82]	USA	CS	CDS, 1998-2002; ♂(n=21), ♀(n=23)	Children (2-2)	Serum (HRGC/HRMS)	Weight z-score (measured)	>0.88 vs. ≤0.88	$\beta = -0.66$ (-1.59; 0.43)	Maternal preconception weight
Jackson, LW <i>et al.</i> (2010) [82]	USA	CS	CDS, 1998-2002; ♂(n=21), ♀(n=23)	Children (2-2)	Serum (HRGC/HRMS)	WfL z-score (measured)	>0.88 vs. ≤0.88	$\beta = -0.39$ (-1.16; 0.38)	Maternal preconception BMI
PCB 167									
Magnusdottir, E <i>et al.</i> (2005) [43]	ISL	CS	Infertile men; ♂(n=72)	Adults (37±5.4)	Serum (GC)	BMI (self-reported W&H)	ng/g lipid	$p = 0.24$ ($p = 0.04$)	-
PCB 169									
Ronn, M <i>et al.</i> (2011) [49]	SWE	PC	PIVUS; ♂♀(n=866)	Adults (70y.o.)	Plasma (HRGC/HRMS)	FM (DXA)	Per 1-unit (ln ng/g lipid)	$\beta = -1.63$ (-3.03; -0.22)	Sex
Roos, V <i>et al.</i> (2013) [51]	SWE	CS	PIVUS; ♂♀(n=287)	Adults (70y.o.)	Plasma (HRGC/HRMS)	VAT (MRI)	Per 1-unit (ln ng/g lipid)	$\beta = -35.0$ (-51.0; -19.0)	Sex, education, exercise, smoking
Roos, V <i>et al.</i> (2013) [51]	SWE	CS	PIVUS; ♂♀(n=287)	Adults (70y.o.)	Plasma (HRGC/HRMS)	SAT (MRI)	Per 1-unit (ln ng/g lipid)	$\beta = -45.0$ (-72.0; -18.0)	Sex, education, exercise, smoking

CS: Cross-sectional; PC: Prospective Cohort; CDS: Child Development Study; PIVUS: Prospective Investigation of the Vasculature in Uppsala Seniors; HRGC: High Resolution Gas Chromatography; HRMS: High Resolution Mass Spectrometry; GC: Gas Chromatography; WfL: Weight for Length; BMI: Body Mass Index; W: Weight; H: Height; FM: Fat Mass; DXA: Dual-energy X-ray Absorptiometry; VAT: Visceral Adipose Tissue; MRI: Magnetic


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Table 9.7.1. Description of papers included in the systematic review assessing the association between other dioxin-like PCBs and adiposity

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Resonance Imaging; SAT: Subcutaneous Adipose Tissue; β : Beta coefficient; ρ : Spearman correlation coefficient.									

9.8 Sum of dioxin-like PCBs

Table 9.8.1 shows the description of publications assessing the association between different sums of dioxin-like PCBs and adiposity [46, 74, 76, 83]. Two publications were performed among adults from NHANES 1999-2002 [46, 76], Uemura, H *et al.* (2009) [74] used data from general population but included both children and adults and Persky, V *et al.* (2011) [83] was based on an occupation sample. Despite methodological differences between these studies, all four papers found positive associations with either BMI or waist circumference.

Table 9.8.1. Description of papers included in the systematic review assessing the association between the sum of dioxin-like PCBs and adiposity

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Sum of dioxin-like PCBs[‡]									
Ha, MH <i>et al.</i> (2007)	USA	CS	NHANES 1999-2002; ♂(n= 889)	Adults (40-85)	Serum (HRGC/ HRMS)	BMI (measured W&H)	ng/g lipid	ρ = 0.1 (p<0.001)	Age
Lee, DH <i>et al.</i> (2007)	USA	CS	NHANES Non-diabetic ; 1999-2002; ♂♀(n=721)	Adults (≥20)	Total blood (HRGC/ HRMS)	WC (measured) ♂>102; ♀>88 cm	>75 th vs. <25 th	OR= 1.6 (0.9; 2.9)	Age, sex, race, PIR, smoking, cotinine, alcohol, exercise



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Table 9.8.1. Description of papers included in the systematic review assessing the association between the sum of dioxin-like PCBs and adiposity

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Persky, V et al. (2011)	USA	CS	Workers in a manufacturing plant; ♂(n=118)	Adults (35-83)	Serum (GC)	BMI [†]	ng/g	ρ= 0.2 (p= 0.034)	-
Persky, V et al. (2011)	USA	CS	Workers in a manufacturing plant; ♂(n=118)	Adults (35-83)	Serum (GC)	BMI [†]	ng/g	ρ= 0.1 (p= 0.283)	-
Sum of TEQ of dioxin-like PCBs									
Uemura, H et al. (2009)	JPN	CS	Gen. Population; ♂(n=627) ♀(n=747)	Children & adults (15-73)	Total blood (GC-MS)	BMI ≥ 25Kg/m2	<4.40 vs. ≥ 12.87	OR= 1.7 (1.1; 2.6)	Age, sex, smoking, drinking, residence, survey year

CS: Cross-sectional; NHANES: National Health and Nutrition Examination Survey; HRGC: High Resolution Gas Chromatography; HRMS: High Resolution Mass Spectrometry; GC: Gas Chromatography; MS: Mass Spectrometry; BMI: Body Mass Index; W: Weight; H: Height; WC: Waist Circumference; ρ: Spearman correlation coefficient; OR: Odds ratio; PIR: Poverty Income Ratio.

†No further information; ‡Sums do not necessarily represent the same combination of substances.


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	Author(s): V Mendes; I Delgado; B Peleteiro; J Araújo; H Barros; E Ramos; D Sarigiannis; N Baiz; I Annesi-Maesano	Version: 1	97/221

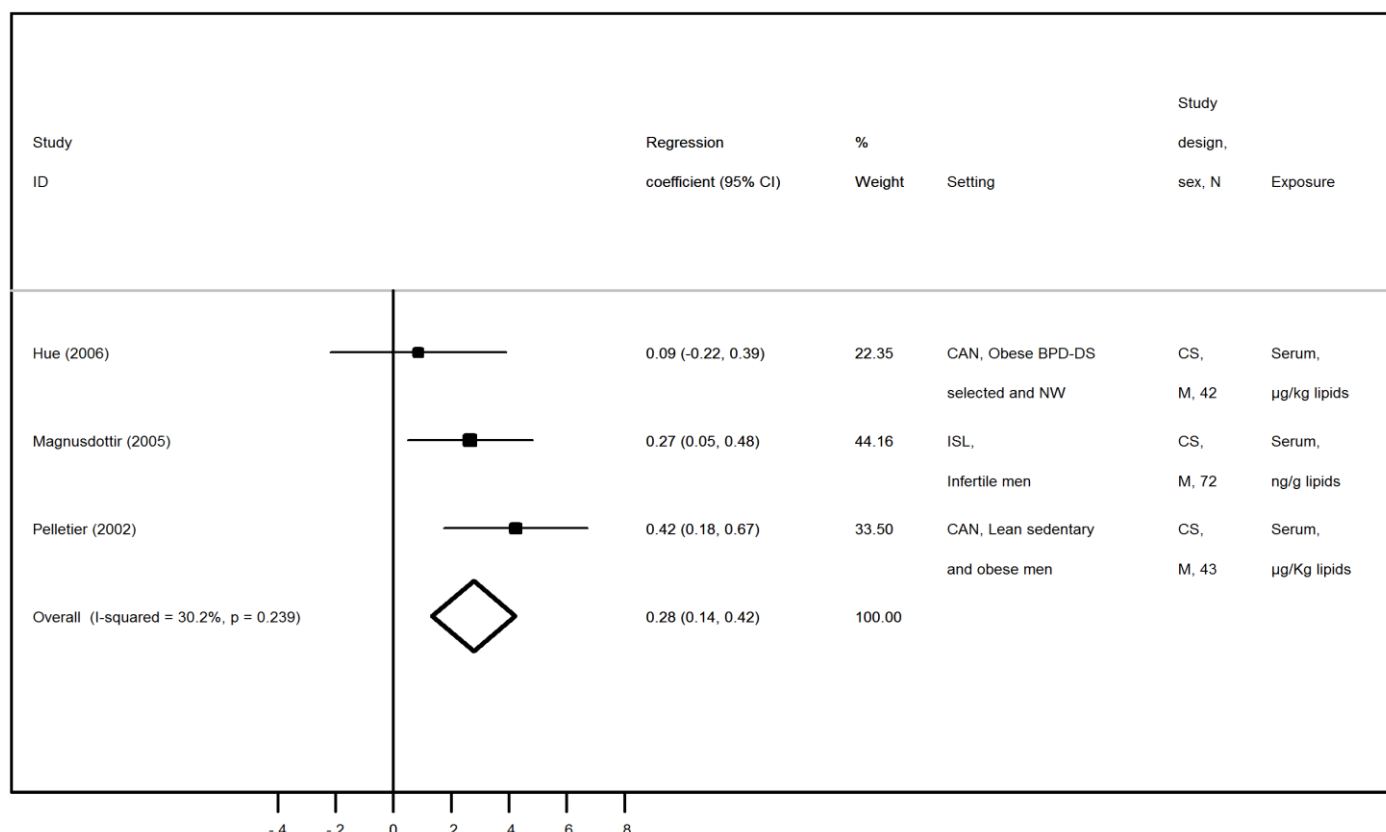
10. Non-dioxin-like Polychlorinated Biphenyls

A total of fourteen non-dioxin-like PCB compounds were evaluated in seventeen papers [42-47, 49-51, 56, 57, 61, 62, 76, 82-84] assessing the association of these substances with adiposity. It was possible to perform a specific meta-analysis for six of these fourteen compounds: PCB 99, 138, 153, 170, 180 and 187.

10.1 Polychlorinated Biphenyl 99 (PCB 99)

Six publications have assessed the relation between PCB 99 and adiposity [42-44, 49-51], but only three were included in the meta-analysis [42-44]. Lee, DH *et al.* (2012) [50] was excluded for presenting ORs as the association estimate, while Ronn, M *et al.* (2011) [49] and Roos, V *et al.* (2013) [51] were excluded for presenting regression coefficients for log transformed variables. The overall estimate for the three included publications was $\beta = 0.28$ (95% CI 0.14; 0.42), with a percentage of variance of 30.2% (figure 10.1). All the three publications presented a cross sectional design, with sample sizes ranging from 42 to 72 adult men.

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	Author(s): V Mendes; I Delgado; B Peleteiro; J Araújo; H Barros; E Ramos; D Sarigiannis; N Baiz; I Annesi-Maesano	Version: 1	98/221



The description of papers with data on the association of PCB 99 with other adiposity measures is presented in table 10.1.1. In general, all the provided estimates were positive, regardless of the adiposity measure used. However, Lee, DH *et al.* (2012) [50] have also observed a positive and statistically significant association between PCB 99 and waist circumference among men from PIVUS study but found an inverse relation among women, though with no statistical significance.

Table 10.1.1. Description of papers assessing the association between PCB 99 and other adiposity measures

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Fat Mass									
Pelletier, C et al. (2002) [42]	CAN	CS	Lean sedentary and obese men; ♂(n=43)	Adults (36-58)	Serum (GC)	FM (Siri equation)	µg/Kg lipids	$\rho = 0.44$ ($p = 0.008$)	Age
Ronn, M et	SWE	PC	PIVUS;	Adults	Plasma	FM (DXA)	Per 1-unit	$\beta = 1.35$	Sex


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	Author(s): V Mendes; I Delgado; B Peleteiro; J Araújo; H Barros; E Ramos; D Sarigiannis; N Baiz; I Annesi-Maesano	Version: 1	99/221

Table 10.1.1. Description of papers assessing the association between PCB 99 and other adiposity measures


Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
al. (2011) [49]			♂♀(n=866)	(70y.o.)	(HRGC/HRMS)		(ln ng/g lipid)	(0.33; 2.36)	
Waist Circumference									
Lee, DH et al. (2012) [50]	SWE	CS	PIVUS, 2001-2004; ♂(n=490)	Adults (70y.o.)	Plasma (HRGC/HRMS)	WC (measured) >102 cm	144-882 vs. 9.0-55.8 (pg/mL)	OR= 2.2 (1.1; 4.6)	Calories, exercise, smoking, TG, TC, alcohol
Lee, DH et al. (2012) [50]	SWE	CS	PIVUS, 2001-2004; ♀(n= 480)	Adults (70y.o.)	Plasma (HRGC/HRMS)	WC (measured) >88 cm	144-882 vs. 9.0-55.8 (pg/mL)	OR= 0.5 (0.3; 1.0)	Calories, exercise, smoking, TG, TC, alcohol
Lee, DH et al. (2012) [50]	SWE	PC	PIVUS, 2001-2009; ♂(n=306)	Adults (≥75)	Plasma (HRGC/HRMS)	WC (measured) >102 cm	144-882 vs. 9.0-55.8 (pg/mL)	OR= 0.9 (0.2; 3.3)	Calories, exercise, smoking, TG, TC, alcohol
Lee, DH et al. (2012) [50]	SWE	PC	PIVUS, 2001-2009; ♀(n= 206)	Adults (≥75)	Plasma (HRGC/HRMS)	WC (measured) >88 cm	144-882 vs. 9.0-55.8 (pg/mL)	OR= 0.4 (0.1; 1.3)	Calories, exercise, smoking, TG, TC, alcohol
Visceral Adipose Tissue and Subcutaneous Adipose Tissue									
Roos, V et al. (2013) [51]	SWE	CS	PIVUS; ♂♀(n=287)	Adults (70y.o.)	Plasma (HRGC/HRMS)	VAT (MRI)	Per 1-unit (ln ng/g lipid)	β= 9.3 (-2.9; 21.0)	Sex, exercise, education, smoking
Roos, V et al. (2013) [51]	SWE	CS	PIVUS; ♂♀(n=287)	Adults (70y.o.)	Plasma (HRGC/HRMS)	SAT (MRI)	Per 1-unit (ln ng/g lipid)	β= 18.0 (-2.1; 39.0)	Sex, exercise, education, smoking

Shading represents papers for which the same samples were already described in the previous meta-analysis plot.

CS: Cross-sectional; PC: Prospective Cohort; PIVUS: Prospective Investigation of the Vasculature in Uppsala Seniors; GC: Gas Chromatography; HRGC: High Resolution Gas Chromatography; HRMS: High Resolution Mass Spectrometry; FM: Fat Mass; DXA: Dual-energy X-ray Absorptiometry; WC: Waist Circumference; VAT: Visceral Adipose Tissue; MRI: Magnetic Resonance Imaging; SAT: Subcutaneous Adipose Tissue; Qu: Quintile; p: Spearman correlation coefficient; β: Beta coefficient; OR: Odds ratio; TG: Triglycerides; TC: Total Cholesterol.

10.2 Polychlorinated Biphenyl 138 (PCB 138)

Twelve papers evaluating the association between PCB 138 and adiposity were identified in the systematic review [42-44, 46, 47, 49, 51, 56, 57, 61, 62, 84]. Two

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publications were excluded from meta-analysis for presenting regression coefficients for log transformed variables [49, 51]. Two other papers were also excluded, one for presenting ORs as the association estimate [46] and the other for being performed among cancer patients [61]. Eight papers were included in the meta-analysis providing a total of twelve estimates.

Most of studies assessed BMI as the adiposity measure, with the exception of Cho, MR *et al.* (2011) [47] which evaluated fat mass. The overall beta coefficient was 0.03 (95% CI -0.00; 0.06), with a percentage of variance of 93.5%, indicating no association between PCB 138 and adiposity (figure 10.2).

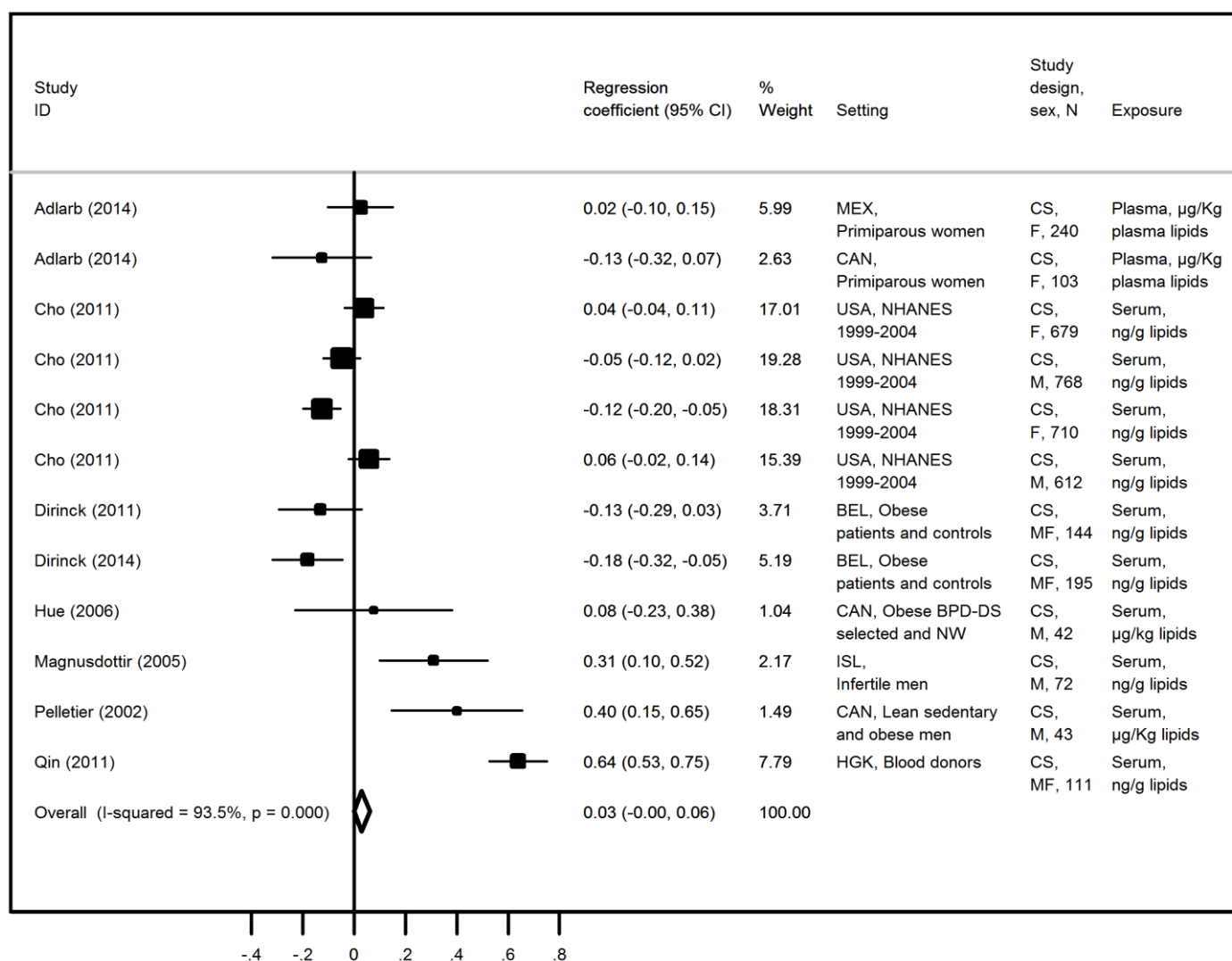



Figure 10.2. Meta-analysis of studies evaluating the association of PCB 138 with adiposity in adults. Beta coefficients and corresponding 95% CI (horizontal lines). The size of the black square indicates the study's weight in the analysis (weights are from fixed-effects analysis). The centre of the open diamond indicates the summary estimate and its width represents the 95% CI.

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The sensitivity analysis including only papers assessing BMI (i.e. excluding Cho, MR *et al.* (2011) [47]) did not improve significantly the estimate quality [$\beta = 0.16$ (0.10; 0.21), $I^2 = 94.5\%$]. Since the heterogeneity between the included studies is very high, these results should be carefully considered.

Table 10.2.1 presents the description of papers addressing the association between PCB 138 and adiposity measures.

The only paper assessing BMI that was not included in the meta-analysis presented in figure 10.2 [61], for including cancer patients, found different results for patients with breast cancer (negative and statistically significant) and for the study on non-Hodgkin lymphoma (positive but not statistically significant). Regarding other adiposity measures, mixed results were found across the twelve different estimates provided in these six papers. Dirinck, E *et al.* (2014) [62] was the only evaluating weight and found a marginal negative association but not statistically significant ($r = -0.1$, $p = 0.143$). Regarding fat mass, while Pelletier, C *et al.* (2002) [42] found a positive and significant correlation ($p = 0.37$, $p = 0.014$), Dirinck, E *et al.* (2011) [56], Ronn, M *et al.* (2011) [49] and Dirinck, E *et al.* (2014) [62] found negative estimates, but only statistically significant in these last two papers. On the other hand, considering waist circumference and waist to hip ratio, Dirinck, E *et al.* (2014) [62] found a positive and statistically significant association, while in Dirinck, E *et al.* (2011) [56] the estimate was negative. Roos, V *et al.* (2013) [51] observed positive associations with both visceral and subcutaneous adipose tissue.

It is important to highlight that in general, the evaluated sample sizes are small and most of them address specific settings such as weight management clinics which may lead to biased results.


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Table 10.2.1. Description of papers assessing the association between PCB 138 and adiposity measures

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
BMI									
Wu, H et al. (2013) [61]	USA	PC	Nurses breast cancer study; ♀(n=649)	Adults	Serum (GC)	BMI (self-reported W&H)	ng/g lipids	$\rho = -0.11$ ($p < 0.05$)	Age
Wu, H et al. (2013) [61]	USA	PC	Nurses non-Hodgkin lymphoma study; ♀(n=398)	Adults	Serum (GC)	BMI (self-reported W&H)	ng/g lipids	$\rho = 0.001$ ($p > 0.05$)	Age
Weight									
Dirinck, E. et al. (2014) [62]	BEL	CS	Patients weight management clinic; ♂♀(n=195)	Adults (18-84)	Serum [†]	Weight (measured)	ng/g lipids	$r = -0.1$ ($p = 0.143$)	-
Fat Mass									
Pelletier, C et al. (2002) [42]	CAN	CS	Lean sedentary and obese men; ♂(n=43)	Adults (36-58)	Serum (GC)	FM (Siri equation)	µg/Kg lipids	$\rho = 0.37$ ($p = 0.014$)	Age
Dirinck, E et al. (2011) [56]	BEL	CS	Obese patients and controls; ♂n=73, ♀n=71	Adults (21-60)	Serum (GC/MS)	FM (BIA)	ng/g lipids	$\rho = -0.094$ ($p > 0.05$)	-
Ronn, M et al. (2011) [49]	SWE	PC	PIVUS; ♂♀(n=866)	Adults (70y.o.)	Plasma (HRGC/HRMS)	FM (DXA)	Per 1-unit (ln ng/g lipid)	$\beta = -5.27$ (-6.69; -3.84)	Sex
Dirinck, E. et al. (2014) [62]	BEL	CS	Patients weight management clinic; ♂♀(n=195)	Adults (18-84)	Serum [†]	FM (BIA)	ng/g lipids	$r = -0.22$ ($p = 0.0002$)	-
Waist Circumference									
Lee, DH et al. (2007) [46]	USA	CS	NHANES Non-diabetic, 1999-2002; ♂♀(n=721)	Adults (≥ 20)	Whole blood (HRGC/HRMS)	WC (measured) ♂ >102 ; ♀ >88 cm	$>75^{\text{th}}$ vs. BDL	OR= 1.0 (0.6; 1.18)	Age, sex, race, PIR, smoking, alcohol, exercise
Dirinck, E et al. (2011) [56]	BEL	CS	Obese patients and controls; ♂n=73, ♀n=71	Adults (21-60)	Serum (GC/MS)	WC (measured)	ng/g lipids	$\rho = -0.128$ ($p > 0.05$)	-
Dirinck, E. et al. (2014) [62]	BEL	CS	Patients weight management clinic; ♂♀(n=195)	Adults (18-84)	Serum [†]	WC (measured)	ng/g lipids	$r = 0.19$ ($p = 0.006$)	-
Waist to Hip Ratio									
Dirinck, E et al.	BEL	CS	Obese patients	Adults	Serum	WtHR	ng/g lipids	$\rho = -0.037$	-


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Table 10.2.1. Description of papers assessing the association between PCB 138 and adiposity measures

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
al. (2011) [56]	BEL	CS	and controls; ♂n=73, ♀n=71	(21-60)	(GC/MS)	(measured)		(p>0.05)	
Dirinck, E. et al. (2014) [62]			Patients weight management clinic; ♂♀(n=195)	Adults (18-84)	Serum [†]	WtHR (measured)	ng/g lipids	r=0.001 (p=0.986)	-
Visceral Adipose Tissue and Subcutaneous Adipose Tissue									
Roos, V et al. (2013) [51]	SWE	CS	PIVUS; ♂♀(n=287)	Adults (70y.o.)	Plasma (HRGC/HRMS)	VAT (MRI)	Per 1-unit (ln ng/g lipid)	β= 8.6 (-7.3; 24.0)	Sex, exercise, education, smoking
Roos, V et al. (2013) [51]	SWE	CS	PIVUS; ♂♀(n=287)	Adults (70y.o.)	Plasma (HRGC/HRMS)	SAT (MRI)	Per 1-unit (ln ng/g lipid)	β= 11.0 (-15.0; 38.0)	Sex, exercise, education, smoking

Shading represents studies for which the same samples were already described in the meta-analysis plot. PC: Prospective Cohort; CS: Cross-sectional; PIVUS: Prospective Investigation of the Vasculature in Uppsala Seniors; NHANES: National Health and Nutrition Examination Survey; GC: Gas Chromatography; MS: Mass Spectrometry; HRGC: High Resolution Gas Chromatography; HRMS: High Resolution Mass Spectrometry; BMI: Body Mass Index; W: Weight; H : Height; FM: Fat Mass; BIA: Bioelectrical Impedance Analysis; DXA: Dual X-ray Absortriometry WC: Waist Circumference; WtHR: Waist to Hip Ratio; VAT: Visceral Adipose Tissue; MRI: Magnetic Resonance Imaging; SAT: Subcutaneous Adipose Tissue; BDL: Below Detected Levels; p: Spearman correlation coefficient; r: Pearson correlation coefficient; β: Beta coefficient; OR: Odds Ratio; PIR: Poverty Income Ratio. [†]No further information.

Table 10.2.2 summarizes the available data on the association of PCB 138 with each adiposity measure. It is important to highlight that results from studies with ORs or transformed variables (log) were not considered for the following summary estimates, since it is not possible to combine them with the remaining results. Furthermore, as we have tried to include as much studies as possible, no sensitivity analysis was taken into account, and a high heterogeneity is expected. These summary estimates should be carefully considered. Beyond the overall estimate obtained for BMI, seven estimates derived from 4 publications assessing the relation between PCB 138 and fat mass were obtained. Unlike results observed for BMI, the overall estimate was negative but also with no statistical significance $\beta = -0.03$ (95% CI -0.07; 0.00) and with a very high percentage of variance between publications $I^2 = 82.1\%$. Summary estimates for waist circumference and waist to hip ratio were also performed and also no consensual results were observed.

Table 10.2.2. Summary estimates for the association between PCB 138 and each

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adiposity measure

	PCB 138			
	Number of included estimates	Summary Estimate*	I ² (%)	95% CI
Body Mass Index	8 ^a	0.16	94.5	0.10; 0.21
Weight	1 ^b	-0.1 [†]	-	0.143 [‡]
Fat Mass	7 ^c	-0.03	82.1	-0.07; 0.00
Waist Circumference	2 ^d	-0.06	28.1	-0.1; 0.05
Waist to Hip Ratio	2 ^d	0.10	77.7	-0.01; 0.20
Visceral Adipose Tissue	1 ^e	9.3	-	-2.9; 21.0
Subcutaneous Adipose Tissue	1 ^e	18.0	-	-2.1; 39.0

I² available only when meta-analysis was performed.


*Beta coefficient if not otherwise specified; [†]Pearson correlation coefficient; [‡]p value.

Included studies are: ^aPelletier, C *et al.* (2002)[42], Magnusdottir, E *et al.* (2005)[43], Hue, O *et al.* (2006)[44], Dirinck, E *et al.* (2011)[56], Qin, YY *et al.* (2011)[57], Adlarb, B *et al.* (2014)[84] and Dirinck, E *et al.* (2014)[62]; ^bDirinck, E *et al.* (2014)[62]; ^cPelletier, C *et al.* (2002)[42], Cho, MR *et al.* (2011)[47], Dirinck, E *et al.* (2011)[56], and Dirinck, E *et al.* (2014)[62]; ^dDirinck, E *et al.* (2011)[56] and Dirinck, E *et al.* (2014)[62]; ^eRoos, V *et al.* (2013)[51].

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	WP16: Obesity and childhood diabetes - link with endocrine disruptors	Security: PU	
	Author(s): V Mendes; I Delgado; B Peleteiro; J Araújo; H Barros; E Ramos; D Sarigiannis; N Baiz; I Annesi-Maesano	Version: 1	105/221

10.3 Polychlorinated Biphenyl 153 (PCB 153)

Fourteen publications assessing the relationship between PCB 153 and adiposity were identified in the systematic review [42-47, 49-51, 56, 61, 62, 82, 84]. Lee, DH *et al.* (2006) [45], Lee, DH *et al.* (2007) [46] and Cho, MR *et al.* (2011) [47] were performed using NHANES 1999-2002 dataset. Lee, DH *et al.* (2006) [45] was selected to be included in the meta-analysis for being the only among the three presenting beta/correlation coefficients and assessing BMI. Two papers were excluded from meta-analysis for presenting regression coefficients for log transformed variables [49, 51] and one for presenting only ORs as the association estimate. Jackson, LW *et al.* (2010) [82] and Wu, H *et al.* (2013) [61] were excluded for being performed among children and cancer patients, respectively. A total of seven papers providing nine different estimates were then included in the meta-analysis [42-45, 56, 62, 84]. The overall beta coefficient was negative but it did not reach statistical significance ($\beta = -0.10$, 95% CI -0.14; -0.07) and the heterogeneity among the included studies was high ($I^2 = 79.7\%$) (figure 10.3).

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	WP16: Obesity and childhood diabetes - link with endocrine disruptors	Security: PU	
	Author(s): V Mendes; I Delgado; B Peleteiro; J Araújo; H Barros; E Ramos; D Sarigiannis; N Baiz; I Annesi-Maesano	Version: 1	106/221

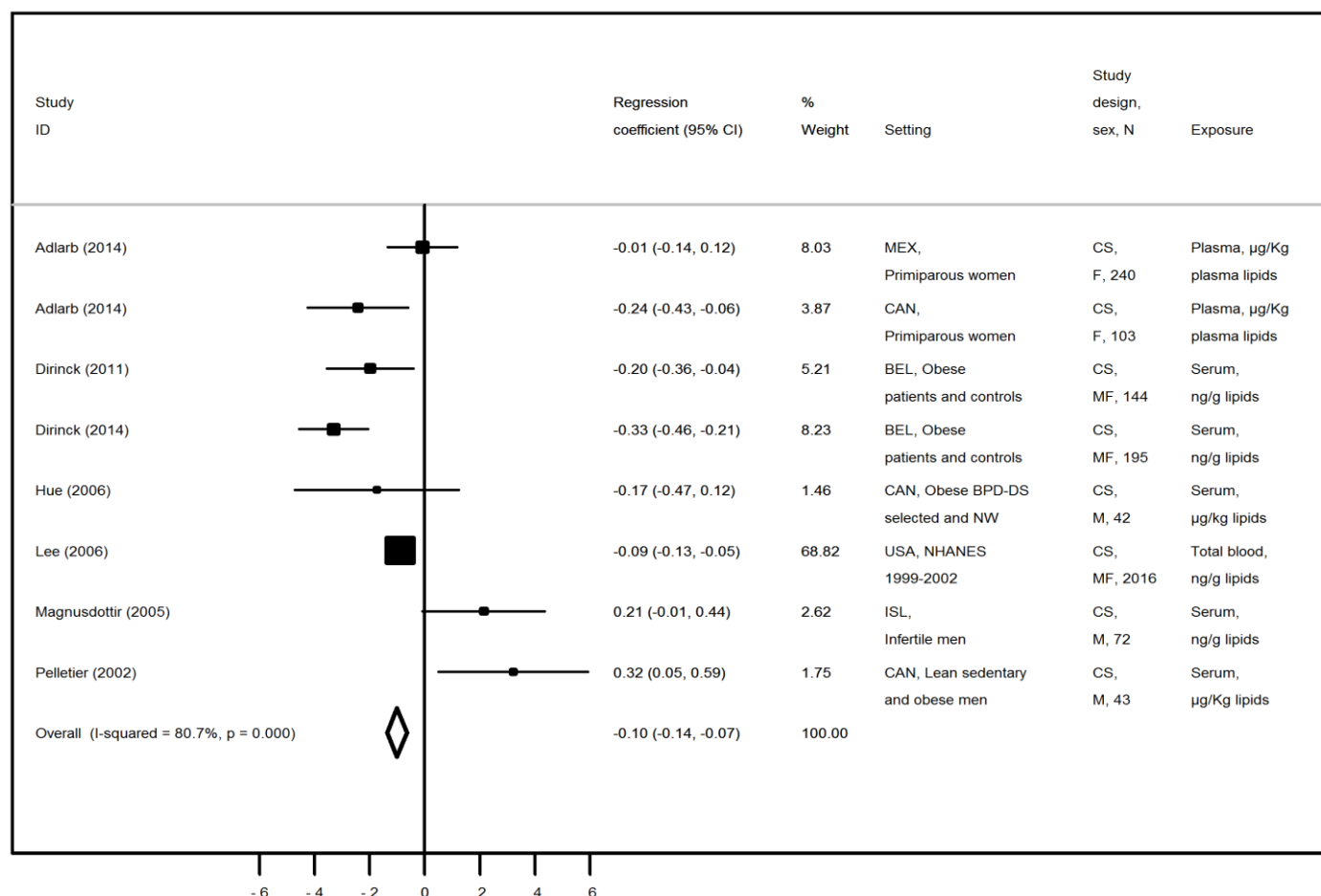



Table 10.3.1 presents the description of papers addressing the association between PCB 153 and adiposity measures.

The only publication assessing BMI that was not considered in the meta-analysis presented in figure 10.3. [61] focused on cancer patients and found a negative association, statistically significant in a sample including breast cancer but not among those with non-Hodgkin lymphoma. Regarding other adiposity measures, in general, negative associations were found. Exceptions were observed for fat mass in Pelletier, C *et al.* (2002) [42] and in Cho, MR *et al.* (2011) [47] among women aged ≥ 50 y.o. from NHANES 1999-2004, and for waist circumference among PIVUS males in Lee, DH *et al.* (2012) [50]. Nevertheless, none of these estimates was statistically significant and

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	Author(s): V Mendes; I Delgado; B Peleteiro; J Araújo; H Barros; E Ramos; D Sarigiannis; N Baiz; I Annesi-Maesano	Version: 1	107/221

all of them are derived from population samples already represented in the meta-analysis plot presented in figure 10.3.

Jackson, LW *et al.* (2010) [82] was the only paper including children and also has described negative associations, however with no statistical significance.

Table 10.3.1. Description of papers assessing the association between PCB 153 and adiposity measures

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Adults									
BMI									
Wu, H et al. (2013) [61]	USA	PC	Nurses breast cancer study; ♀(n=649)	Adults†	Serum (GC)	BMI (self-reported W&H)	ng/g lipid	$\rho = -0.21$ ($p < 0.05$)	Age
Wu, H et al. (2013) [61]	USA	PC	Nurses non-Hodgkin lymphoma study; ♀(n=398)	Adults†	Serum (GC)	BMI (self-reported W&H)	ng/g lipid	$\rho = -0.1$ ($p > 0.05$)	Age
Fat Mass									
Pelletier, C et al. (2002) [42]	CAN	CS	Lean sedentary and obese men; ♂(n=43)	Adults (36-58)	Serum (GC)	FM (Siri equation)	µg/Kg lipids	$\rho = 0.29$ ($p = 0.056$)	Age
Cho, MR et al. (2011) [47]	USA	CS	NHANES, 1999-2004; ♂(n=768)	Adults (<50)	Serum (HRGC/IDHRMS)	FM (BIA)	ng/g lipid	$r = -0.19$ ($p < 0.001$)	Age, race, PIR, smoking, PA, height
Cho, MR et al. (2011) [47]	USA	CS	NHANES, 1999-2004; ♂(n=612)	Adults (≥50)	Serum (HRGC/IDHRMS)	FM (BIA)	ng/g lipid	$r = -0.05$ ($p > 0.05$)	Age, race, PIR, smoking, PA, height
Cho, MR et al. (2011) [47]	USA	CS	NHANES, 1999-2004; ♀(n=710)	Adults (<50)	Serum (HRGC/IDHRMS)	FM (BIA)	ng/g lipid	$r = -0.14$ ($p < 0.001$)	Age, race, PIR, smoking, PA, height
Cho, MR et al. (2011) [47]	USA	CS	NHANES, 1999-2004; ♀(n=679)	Adults (≥50)	Serum (HRGC/IDHRMS)	FM (BIA)	ng/g lipid	$r = 0.02$ ($p > 0.05$)	Age, race, PIR, smoking, PA, height
Dirinck, E et al. (2011) [56]	BEL	CS	Obese patients and controls; ♂n=73, ♀n=71	Adults (21-60)	Serum (GC/MS)	FM (BIA)	ng/g lipids	$\rho = -0.198$ ($p < 0.05$)	-
Ronn, M et al. (2011) [49]	SWE	PC	PIVUS; ♂♀(n=866)	Adults (70y.o.)	Plasma (HRGC/HRMS)	FM (DXA)	Per 1-unit (ln ng/g lipid)	$\beta = -0.672$ (-1.31; -0.034)	Sex
Dirinck, E. et al. (2014) [62]	BEL	CS	Patients weight management clinic; ♂♀n= 195	Adults (18-84)	Serum†	FM (BIA)	ng/g lipids	$r = -0.36$ ($p < 0.01$)	-
Weight									
Dirinck, E. et al. (2014) [62]	BEL	CS	Patients weight management clinic; ♂♀n= 195	Adults (18-84)	Serum†	Weight (measured)	ng/g lipids	$r = -0.24$ ($p = 0.0002$)	-
Waist Circumference									
Lee, DH et	USA	CS	NHANES 1999-	Adults	Whole blood;	WC	ng/g of	$\rho = -0.08$	-


	D16.1 - Report on overview of cohorts/studies relating adverse health outcomes related to adiposity as an intermediate phenotypes of overweight, obesity, diabetes and metabolic disorders to environmental exposures of endocrine disruptors		
	WP16: Obesity and childhood diabetes - link with endocrine disruptors		Security: PU
	Author(s): V Mendes; I Delgado; B Peleteiro; J Araújo; H Barros; E Ramos; D Sarigiannis; N Baiz; I Annesi-Maesano		Version: 1 108/221

Table 10.3.1. Description of papers assessing the association between PCB 153 and adiposity measures

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
al. (2006) [45]	USA	CS	2002; ♂(n=903), ♀(n=1113)	(≥20)	(HRGC/HRMS)	(measured)	lipid	(p<0.01)	
Lee, DH et al. (2007) [46]			NHANES Non-diabetic, 1999-2002; ♂♀(n=721)	Adults (≥20)	Whole blood; (HRGC/HRMS)	WC (measured) ♂>102; ♀>88 cm	>75 th vs. BDL	OR= 0.8 (0.4; 1.4)	Age, sex, race, PIR, smoking, alcohol, exercise
Dirinck, E et al. (2011) [56]	BEL	CS	Obese patients and controls; ♂n=73, ♀n=71	Adults (21-60)	Serum (GC/MS)	WC (measured)	ng/g lipids	p= -0.184 (p<0.05)	-
Lee, DH et al. (2012) [50]	SWE	CS	PIVUS, 2001-2004; ♂(n=490)	Adults (70y.o.)	Plasma (HRGC/HRMS)	WC (measured) >102 cm	1957-4672 vs. 117-1007 (pg/mL)	OR= 1.1 (0.5; 2.3)	Calories, exercise, smoking, TG, TC, alcohol
Lee, DH et al. (2012) [50]	SWE	CS	PIVUS, 2001-2004; ♀(n= 480)	Adults (70y.o.)	Plasma (HRGC/HRMS)	WC (measured) >88 cm	1957-4672 vs. 117-1007 (pg/mL)	OR= 0.2 (0.1;0.4)	Calories, exercise, smoking, TG, TC, alcohol
Lee, DH et al. (2012) [50]	SWE	PC	PIVUS, 2001-2009; ♂(n=306)	Adults (≥75)	Plasma (HRGC/HRMS)	WC (measured) >102 cm	1957-4672 vs. 117-1007 (pg/mL)	OR= 0.6 (0.2; 2.1)	Calories, exercise, smoking, TG, TC, alcohol
Lee, DH et al. (2012) [50]	SWE	PC	PIVUS, 2001-2009; ♀(n= 206)	Adults (≥75)	Plasma (HRGC/HRMS)	WC (measured) >88 cm	1957-4672 vs. 117-1007 (pg/mL)	OR= 0.3 (0.1; 1.1)	Calories, exercise, smoking, TG, TC, alcohol
Dirinck, E. et al. (2014) [62]	BEL	CS	Patients weight management clinic; ♂♀n= 195	Adults (18-84)	Serum†	WC (measured)	ng/g lipids	r= -0.13 (p=0.062)	

Waist to Hip Ratio

Dirinck, E et al. (2011) [56]	BEL	CS	Obese patients and controls; ♂n=73, ♀n=71	Adults (21-60)	Serum (GC/MS)	WtHR (measured)	ng/g lipids	p= -0.076 (p>0.05)	-
Dirinck, E. et al. (2014) [62]	BEL	CS	Patients weight management clinic; ♂♀n= 195	Adults (18-84)	Serum†	WtHR (measured)	ng/g lipids	r= -0.13 (p=0.062)	-

Visceral Adipose Tissue and Subcutaneous Adipose Tissue

Roos, V et al. (2013) [51]	SWE	CS	PIVUS; ♂♀(n=287)	Adults (70y.o.)	Plasma (HRGC/HRMS)	VAT (MRI)	Per 1-unit (ln ng/g lipid)	β= -6.4 (-24.0; 12.0)	Sex, exercise, education, smoking
Roos, V et al. (2013) [51]	SWE	CS	PIVUS; ♂♀(n=287)	Adults (70y.o.)	Plasma (HRGC/HRMS)	SAT (MRI)	Per 1-unit (ln ng/g lipid)	β= -13.0 (-43.0; 17.0)	Sex, exercise, education, smoking

Children

Weight

Jackson, LW et al. (2010) [82]	USA	CS	CDS, 1998-2002; ♂(n=21), ♀(n=23)	Children (2-2)	Serum (HRGC/HRMS)	Weight z-score (measured)	>0.88 vs. ≤0.88	β= -0.57 (-1.58; 0.43)	Maternal preconception weight
Jackson, LW et al. (2010) [82]	USA	CS	CDS, 1998-2002; ♂(n=21), ♀(n=23)	Children (2-2)	Serum (HRGC/HRMS)	WfL z-score (measured)	>0.88 vs. ≤0.89	β= -0.38 (-1.19; 0.44)	Maternal preconception BMI

Shading represents studies for which the same samples were already described in the meta-analysis plot.

PC: Prospective Cohort; CS: Cross-sectional; NHANES: National Health and Nutrition Examination Survey; PIVUS: Prospective Investigation of the Vasculature in Uppsala Seniors; CDS: Child Development Study; GC: Gas Chromatography; HRGC: High Resolution Gas Chromatography; IDHRMS:


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	WP16: Obesity and childhood diabetes - link with endocrine disruptors	Security: PU	
	Author(s): V Mendes; I Delgado; B Peleteiro; J Araújo; H Barros; E Ramos; D Sarigiannis; N Baiz; I Annesi-Maesano	Version: 1	109/221

Table 10.3.1. Description of papers assessing the association between PCB 153 and adiposity measures


Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Isotope Dilution High Resolution Mass Spectrometry; HRMS: High Resolution Mass Spectrometry; BMI: Body Mass Index; W: Weight; H: Height; FM: Fat Mass; BIA: Bioelectrical Impedance Analysis; DXA: Dual-energy X-ray Absorptiometry; WC: Waist Circumference; WtHR: Waist to Hip Ratio; VAT: Visceral Adipose Tissue; MRI: Magnetic Resonance Imaging; SAT: Subcutaneous Adipose Tissue; WfL: Weight for length; BDL: Below Detected Levels; ρ : Spearman correlation coefficient; r : Pearson correlation coefficient; β : Beta coefficient; OR: Odds ratio; PIR: Poverty Income Ratio; PA: Physical Activity; TG: Triglycerides; TC: Total Cholesterol. †No further information.									

Available data on the association of PCB 153 with each adiposity measure is summarized in table 10.3.2. Seven estimates focusing on the relation between PCB 153 and fat mass were provided by four publications [42, 47, 56, 62] with an overall estimate of $\beta = -0.12$ (95% CI -0.15; -0.08), but with a very high heterogeneity ($I^2 = 86.9\%$). Regarding waist circumference, three estimates were provided by three publications [45, 56, 62], with an overall beta coefficient of -0.09 (95% CI -0.13; -0.05). In general, negative associations were found but only those for fat mass and waist circumference reached statistical significance. Due to the limited number of included estimates and to the high percentage of variance between studies, this result should be carefully considered.

Table 10.3.2. Summary estimates for the association between PCB 153 and each adiposity measure in adults


	PCB 153			
	Number of included estimates	Summary Estimate*	I^2 (%)	95% CI
Body Mass Index	8 ^a	-0.08	80.7	-0.20; 0.03
Weight	1 ^b	-0.24 [†]	-	0.0002 [‡]
Fat Mass	7 ^c	-0.12	86.9	-0.15; -0.08
Waist Circumference	3 ^d	-0.09	0.0	-0.13; -0.05
Waist to Hip Ratio	2 ^e	0.02	56.7	-0.09; 0.13
Visceral Adipose Tissue	1 ^f	-6.4	-	-24.0; 12.0
Subcutaneous Adipose Tissue	1 ^f	-13.0	-	-43.0; 17.0

^a I^2 available only when meta-analysis was performed. *Beta coefficient if not otherwise specified; [†]Pearson correlation coefficient; [‡]p value. Included studies are: ^aPelletier, C *et al.* (2002)[42], Magnusdottir, E *et al.* (2005)[43], Hue, O *et al.* (2006)[44], Lee, DH *et al.* (2006)[45], Dirinck, E *et al.* (2011)[56], Adlarb, B *et al.* (2014)[84] and Dirinck, E *et al.* (2014)[62]; ^bDirinck, E *et al.* (2014)[62]; ^cPelletier, C *et al.* (2002)[42], Cho, MR *et al.* (2011)[47], Dirinck, E *et al.* (2011)[56] and Dirinck, E *et al.* (2014)[62]; ^dLee, DH *et al.* (2006)[45], Dirinck, E *et al.* (2011)[56] and Dirinck, E *et al.* (2014)[62]; ^eDirinck, E *et al.* (2011)[56] and Dirinck, E *et al.* (2014)[62]; ^fRoos, V *et al.* (2013)[51].

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	WP16: Obesity and childhood diabetes - link with endocrine disruptors	Security: PU	
	Author(s): V Mendes; I Delgado; B Peleteiro; J Araújo; H Barros; E Ramos; D Sarigiannis; N Baiz; I Annesi-Maesano	Version: 1	110/221

10.4 Polychlorinated Biphenyl 170 (PCB 170)

Eight papers evaluated the association between PCB 170 and adiposity [42-44, 46, 49-51, 56]. Lee, DH *et al.* (2007) [46] and Lee, DH *et al.* (2012) [50] were excluded for presenting only ORs, while Roos, V *et al.* (2013) [51] and Ronn, M *et al.* (2011) [49] were excluded for presenting regression coefficients for log transformed variables. A total of four papers were included in this meta-analysis [42-44, 56]. Dirinck, E *et al.* (2011) [56] was the only describing a clearly negative association. However, the other three results were reported from studies with a very small sample size and presenting large CIs, resulting in a smaller weight for the summary measure. The overall beta coefficient was -0.19 (95% CI -0.29; -0.08), with a percentage of variance of 68.7%. (figure 10.4).

	D16.1 - Report on overview of cohorts/studies relating adverse health outcomes related to adiposity as an intermediate phenotypes of overweight, obesity, diabetes and metabolic disorders to environmental exposures of endocrine disruptors		
	WP16: Obesity and childhood diabetes - link with endocrine disruptors	Security: PU	
	Author(s): V Mendes; I Delgado; B Peleteiro; J Araújo; H Barros; E Ramos; D Sarigiannis; N Baiz; I Annesi-Maesano	Version: 1	111/221

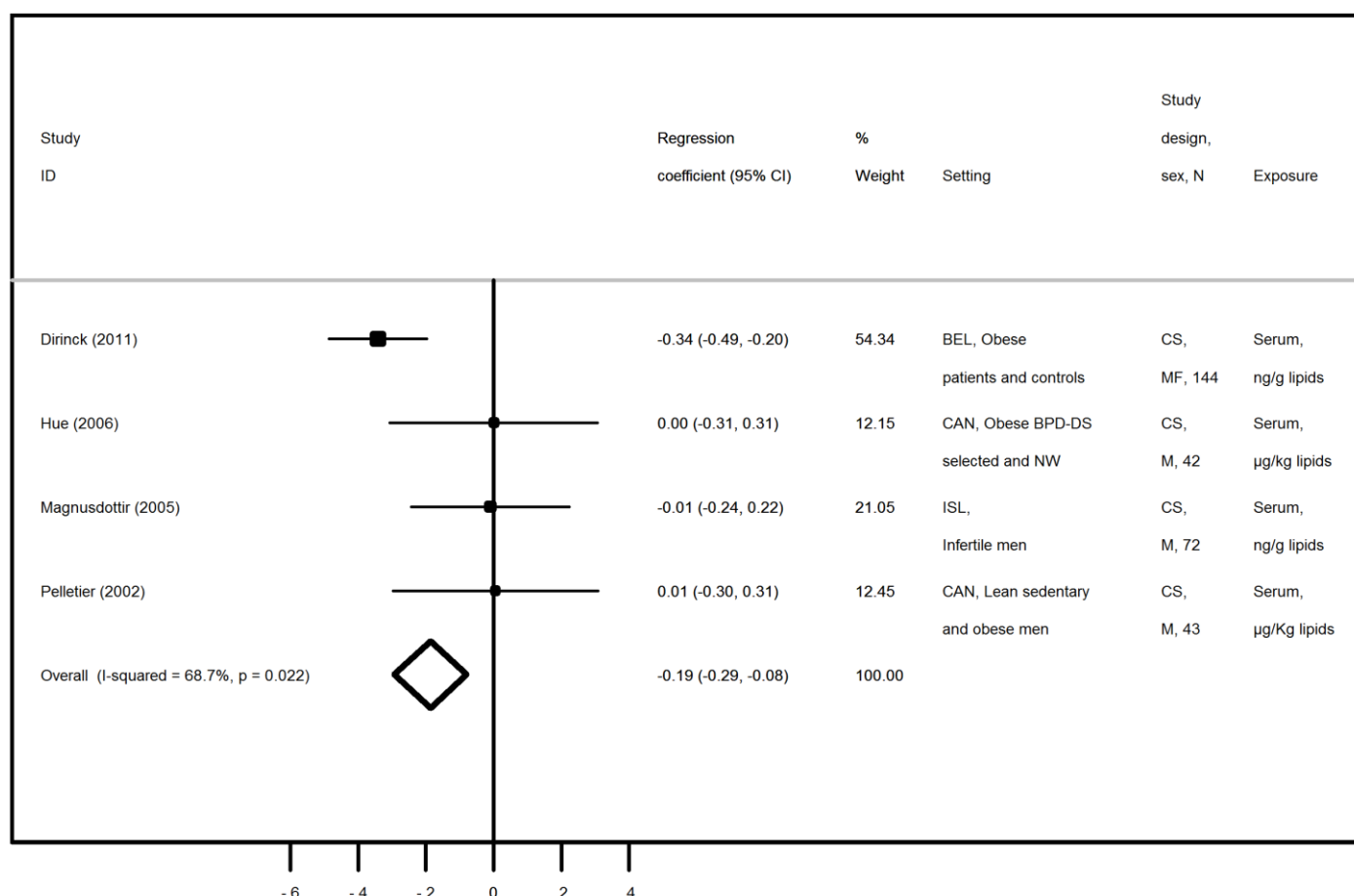


Figure 10.4. Meta-analysis of studies evaluating the association of PCB 170 with BMI in adults. Beta coefficients and corresponding 95% CI (horizontal lines). The size of the black square indicates the study's weight in the analysis (weights are from fixed-effects analysis). The centre of the open diamond indicates the summary estimate and its width represents the 95% CI.

Table 10.4.1 shows the description of papers assessing the association between PCB 170 and other adiposity measures. Four of the presented estimates were obtained from populations already included in the meta-analysis represented in figure 10.4. In general, all the provided estimates were negative and statistically significant, regardless of the adiposity measure used.


	D16.1 - Report on overview of cohorts/studies relating adverse health outcomes related to adiposity as an intermediate phenotypes of overweight, obesity, diabetes and metabolic disorders to environmental exposures of endocrine disruptors		
	WP16: Obesity and childhood diabetes - link with endocrine disruptors		Security: PU
	Author(s): V Mendes; I Delgado; B Peleteiro; J Araújo; H Barros; E Ramos; D Sarigiannis; N Baiz; I Annesi-Maesano		Version: 1 112/221

Table 10.4.1. Description of papers assessing the associations between PCB 170 and other adiposity measures

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Fat Mass									
Pelletier, C et al. (2002) [42]	CAN	CS	Lean sedentary and obese men; ♂(n=43)	Adults (36-58)	Serum (GC)	FM (Siri equation)	µg/Kg lipids	ρ= -0.08 (p= 0.597)	Age
Dirinck, E et al. (2011) [56]	BEL	CS	Obese patients and controls; ♂(n=73), ♀(n=71)	Adults (21-60)	Serum (GC/MS)	FM (BIA)	ng/g lipids	ρ= -0.258 (p<0.001)	-
Ronn, M et al. (2011) [49]	SWE	PC	PIVUS; ♂♀(n=866)	Adults (70y.o.)	Plasma (HRGC/HRMS)	FM (DXA)	Per 1-unit (ln ng/g lipid)	β= -7.01 (-8.45; -5.57)	Sex
Waist Circumference									
Lee, DH et al. (2007) [46]	USA	CS	NHANES Non-diabetic, 1999-2002; ♂♀(n=721)	Adults (≥20)	Total blood (HRGC/HRMS)	WC (measured) ♂>102; ♀>88 cm	>75 th vs. BDL	OR= 0.4 (0.2; 0.8)	Age, sex, race, PIR, smoking, alcohol, exercise
Dirinck, E et al. (2011) [56]	BEL	CS	Obese patients and controls; ♂n=73, ♀n=71	Adults (21-60)	Serum (GC/MS)	WC (measured)	ng/g lipids	ρ= -0.265 (p<0.01)	-
Lee, DH et al. (2012) [50]	SWE	CS	PIVUS, 2001-2004; ♂(n=490)	Adults (70y.o.)	Plasma (HRGC/HRMS)	WC (measured) >102 cm	670-1852 vs 62.8-363 (pg/mL)	OR= 0.6 (0.3; 1.3)	Calories, exercise, smoking, TC, TG, alcohol
Lee, DH et al. (2012) [50]	SWE	CS	PIVUS, 2001-2004; ♀(n= 480)	Adults (70y.o.)	Plasma (HRGC/HRMS)	WC (measured) >88 cm	670-1852 vs 62.8-363 (pg/mL)	OR= 0.1 (0.0;0.1)	Calories, exercise, smoking, TC, TG, alcohol
Lee, DH et al. (2012) [50]	SWE	PC	PIVUS, 2001-2009; ♂(n=306)	Adults (≥75)	Plasma (HRGC/HRMS)	WC (measured) >102 cm	670-1852 vs 62.8-363 (pg/mL)	OR= 0.5 (0.1;1.9)	Calories, exercise, smoking, TC, TG, alcohol
Lee, DH et al. (2012) [50]	SWE	PC	PIVUS, 2001-2009; ♀(n= 206)	Adults (≥75)	Plasma (HRGC/HRMS)	WC (measured) >88 cm	670-1852 vs 62.8-363 (pg/mL)	OR= 0.2 (0.1; 0.7)	Calories, exercise, smoking, TC, TG, alcohol
Waist to Hip Ratio									
Dirinck, E et al. (2011) [56]	BEL	CS	Obese patients and controls; ♂n=73, ♀n=71	Adults (21-60)	Serum (GC/MS)	WtHR (measured)	ng/g lipids	ρ= -0.141 (p>0.05)	-
Visceral Adipose Tissue and Subcutaneous Adipose Tissue									
Roos, V et al. (2013) [51]	SWE	CS	PIVUS; ♂♀(n=287)	Adults (70y.o.)	Plasma (HRGC/HRMS)	VAT (MRI)	Per 1-unit (ln ng/g lipid)	β= -43.0 (-63.0; -23.0)	Sex, exercise, education, smoking
Roos, V et al. (2013) [51]	SWE	CS	PIVUS; ♂♀(n=287)	Adults (70y.o.)	Plasma (HRGC/HRMS)	SAT (MRI)	Per 1-unit (ln ng/g lipid)	β= -76.0 (-110.0; -42.0)	Sex, exercise, education, smoking

Shading represents studies for which the same samples were already described in the meta-analysis plot. CS: Cross-sectional; PC: Prospective Cohort; NHANES: National Health and Nutrition Examination Survey; PIVUS: Prospective Investigation of the Vasculature in Uppsala Seniors; GC: Gas Chromatography; HRGC: High Resolution Gas Chromatography; HRMS: High Resolution Mass Spectrometry; MS: Mass Spectrometry; FM: Fat Mass; WC: Waist Circumference; BIA: Bioelectrical Impedance Analysis; WtHR: Waist to Hip Ratio; DXA: Dual-energy X-ray Absorptiometry; VAT: Visceral Adipose Tissue; MRI: Magnetic Resonance Imaging; SAT: Subcutaneous Adipose Tissue; BDL: Below Detected Levels, Qu: Quintile; p:


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	WP16: Obesity and childhood diabetes - link with endocrine disruptors	Security: PU	
	Author(s): V Mendes; I Delgado; B Peleteiro; J Araújo; H Barros; E Ramos; D Sarigiannis; N Baiz; I Annesi-Maesano	Version: 1	113/221

Table 10.4.1. Description of papers assessing the associations between PCB 170 and other adiposity measures

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
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Spearman correlation coefficient; OR: Odds ratio; β : Beta coefficient; PIR: Poverty Income Ratio; TG: Triglycerides; TC: Total Cholesterol.

Available data on the association between PCB 170 and each adiposity measure is summarized in table 10.4.2. Results were consistent, showing and inverse association for all adiposity measures. Three publications provided estimates for fat mass with an overall beta coefficient of **-0.23 (95% CI -0.36, -0.09)**. However, the percentage of variance between studies was very high ($I^2 = 12.5\%$).


Table 10.4.2. Summary estimates for the association between PCB 170 with each adiposity measure

	PCB 170			
	Number of included estimates	Summary Estimate*	I^2 (%)	95% CI
Body Mass Index	4 ^a	-0.19	68.7	-0.29; -0.08
Fat Mass	2 ^b	-0.23	12.5	-0.36; -0.09
Waist Circumference	1 ^c	-0.265 [†]	-	<0.01 [‡]
Waist to Hip Ratio	1 ^c	-0.141 [†]	-	>0.05 [‡]
Visceral Adipose Tissue	1 ^d	-43.0	-	-63.0; -23.0
Subcutaneous Adipose Tissue	1 ^d	-76.0	-	-110.0; -42.0

I^2 available only when meta-analysis was performed.

*Beta coefficient if not otherwise specified; [†]Spearman correlation coefficient; [‡]p value.


Included studies are: ^aPelletier, C *et al.* (2002)[42], Magnusdottir, E *et al.* (2005)[43], Hue, O *et al.* (2006)[44] and Dirinck, E *et al.* (2011)[56]; ^bPelletier, C *et al.* (2002)[42] and Dirinck, E *et al.* (2011)[56]; ^cDirinck, E *et al.* (2011); ^dRoos, V *et al.* (2013)[51].

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	WP16: Obesity and childhood diabetes - link with endocrine disruptors	Security: PU	
	Author(s): V Mendes; I Delgado; B Peleteiro; J Araújo; H Barros; E Ramos; D Sarigiannis; N Baiz; I Annesi-Maesano	Version: 1	114/221

10.5 Polychlorinated Biphenyl 180 (PCB 180)

Eleven papers were identified in the systematic review assessing the association between PCB 180 and adiposity [42-44, 46, 49-51, 56, 61, 62, 84]. Lee, DH *et al.* (2007) [46] and Lee, DH *et al.* (2012) [50] were excluded for presenting ORs and Ronn, M *et al.* (2011) [49], and Roos, V *et al.* (2013) [51] were excluded for presenting estimates for log transformed variables. Wu, H *et al.* (2013) [61] was also excluded from meta-analysis for being performed in samples including cancer patients.

Five papers were included in this meta-analysis [42-44, 56, 62, 84], providing seven estimates. The overall estimate on the association between PCB 180 and adiposity was $\beta = -0.23$ (95% CI -0.29; -0.17), with a percentage of variance of 79.5% (figure 10.5).

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	WP16: Obesity and childhood diabetes - link with endocrine disruptors	Security: PU	
	Author(s): V Mendes; I Delgado; B Peleteiro; J Araújo; H Barros; E Ramos; D Sarigiannis; N Baiz; I Annesi-Maesano	Version: 1	115/221

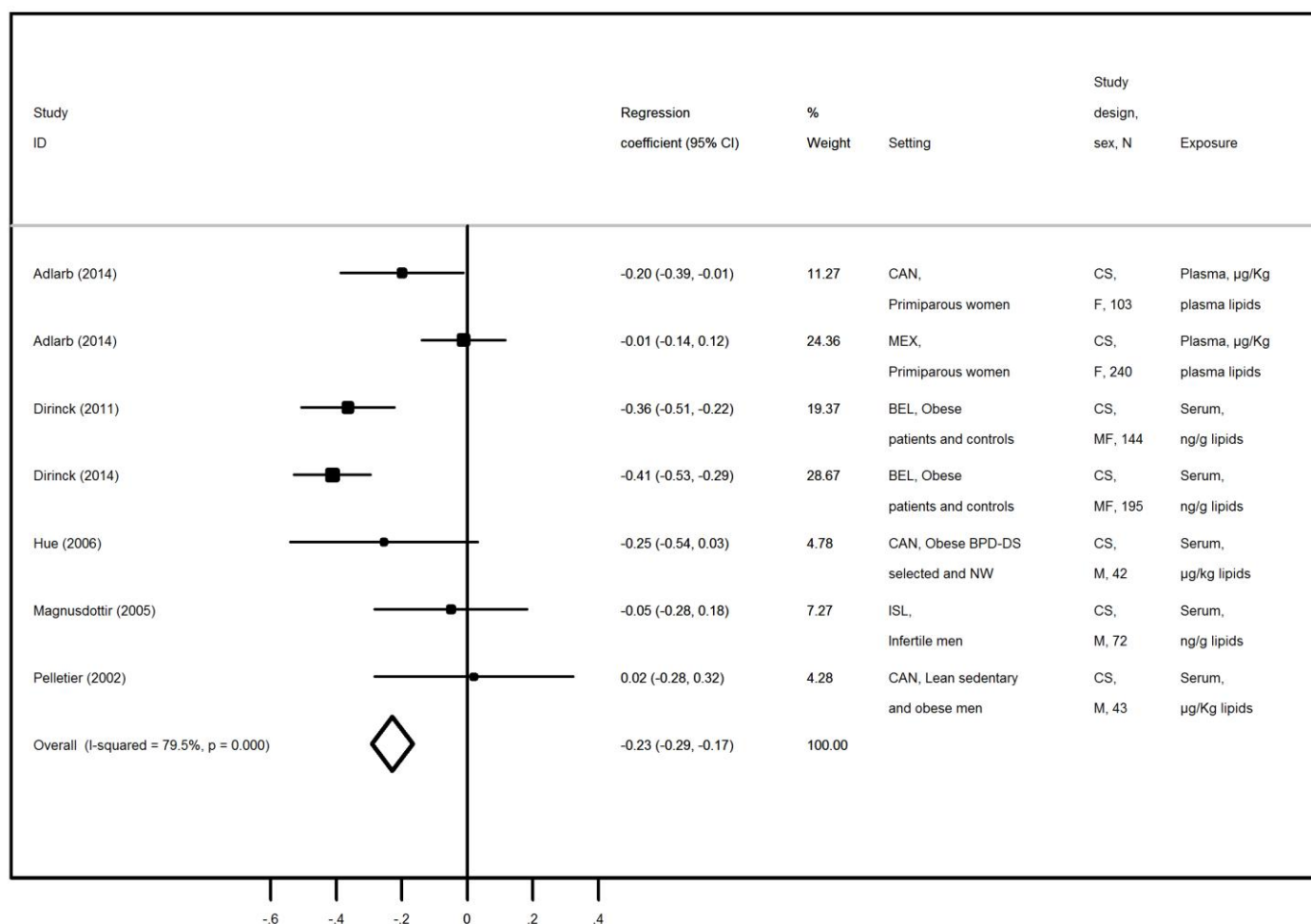


Figure 10.5. Meta-analysis of studies evaluating the association of PCB 180 with BMI in adults. Beta coefficients and corresponding 95% CI (horizontal lines). The size of the black square indicates the study's weight in the analysis (weights are from fixed-effects analysis). The centre of the open diamond indicates the summary estimate and its width represents the 95% CI.

Table 10.5.1 presents the description of papers addressing the association between PCB 180 and adiposity measures. The only paper assessing BMI that was not eligible for meta-analysis has found negative correlations among nurses from breast cancer study and from non-Hodgkin lymphoma study [61]. Regarding other adiposity measures, all the results observed also indicated a negative association with adiposity.


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	Author(s): V Mendes; I Delgado; B Peleteiro; J Araújo; H Barros; E Ramos; D Sarigiannis; N Baiz; I Annesi-Maesano		Version: 1 116/221

Table 10.5.1. Description of papers assessing the association between PCB 180 and adiposity measures

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
BMI									
Wu, H et al. (2013)[61]	USA	PC	Nurses breast cancer study; ♀(n=649)	Adults	Serum (GC)	BMI (self-reported W&H)	ng/g lipid	$\rho = -0.26$ (p<0.05)	Age
Wu, H et al. (2013)[61]	USA	PC	Nurses non-Hodgkin lymphoma study; ♀(n=398)	Adults	Serum (GC)	BMI (self-reported W&H)	ng/g lipid	$\rho = -0.02$ (p<0.05)	Age
Weight									
Dirinck, E. et al. (2014)[62]	BEL	CS	Patients weight management clinic; ♂♀(n=195)	Adults (18-84)	Serum [†]	Weight (measured)	ng/g lipids	$r = -0.3$ (p<0.001)	-
Fat Mass									
Pelletier, C et al. (2002) [42]	CAN	CS	Lean sedentary and obese men; ♂(n=43)	Adults (36-58)	Serum (GC)	FM (Siri equation)	µg/Kg lipids	$\rho = -0.1$ (p= 0.523)	Age
Dirinck, E et al. (2011)[56]	BEL	CS	Obese patients and controls; ♂(n=73), ♀(n=71)	Adults (21-60)	Serum (GC/MS)	FM (BIA)	ng/g lipids	$\rho = -0.324$ (p<0.001)	-
Ronn, M et al. (2011)[49]	SWE	PC	PIVUS; ♂♀(n=866)	Adults (70y.o.)	Plasma (HRGC/HRMS)	FM (DXA)	Per 1-unit (ln ng/g lipid)	$\beta = -6.54$ (-8.02; -5.05)	Sex
Dirinck, E. et al. (2014)[62]	BEL	CS	Patients weight management clinic; ♂♀(n=195)	Adults (18-84)	Serum [†]	FM (BIA)	ng/g lipids	$r = -0.43$ (p<0.001)	-
Waist Circumference									
Lee, DH et al. (2007)[46]	USA	CS	NHANES Non-diabetic 1999-2002; ♂♀(n= 721)	Adults (≥20)	Whole blood (HRGC/HRMS)	WC (measured) ♂>102; ♀>88 cm	>75 th vs. BDL	OR= 0.4 (0.2; 0.7)	Age, sex, race, PIR, smoking, alcohol, exercise
Dirinck, E et al. (2011)[56]	BEL	CS	Obese patients and controls; ♂(n=73), (n=71)	Adults (21-60)	Serum (GC/MS)	WC (measured)	ng/g lipids	$\rho = -0.325$ (p<0.01)	-
Lee, DH et al. (2012)[50]	SWE	CS	PIVUS, 2001-2004; ♂(n=490)	Adults (70y.o.)	Plasma (HRGC/HRMS)	WC (measured) >102 cm	1585-7865 vs. 153-858 (pg/mL)	OR= 0.5 (0.2; 1.1)	Calories, exercise, smoking, TG, TC, alcohol
Lee, DH et al. (2012)[50]	SWE	CS	PIVUS, 2001-2004; ♀(n= 480)	Adults (70y.o.)	Plasma (HRGC/HRMS)	WC (measured) >88 cm	1585-7865 vs. 153-858 (pg/mL)	OR= 0.1 (0;0.2)	Calories, exercise, smoking, TG, TC, alcohol
Lee, DH et al. (2012)[50]	SWE	PC	PIVUS, 2001-2009; ♂(n=306)	Adults (≥75)	Plasma (HRGC/HRMS)	WC (measured) >102 cm	1585-7865 vs. 153-858 (pg/mL)	OR= 0.3 (0.1;1.1)	Calories, exercise, smoking, TG, TC, alcohol
Lee, DH et al. (2012)[50]	SWE	PC	PIVUS, 2001-2009; ♀(n= 206)	Adults (≥75)	Plasma (HRGC/HRMS)	WC (measured) >88 cm	1585-7865 vs. 153-858 (pg/mL)	OR= 0.2 (0.1; 0.6)	Calories, exercise, smoking, TG, TC, alcohol
Dirinck, E. et	BEL	CS	Patients weight	Adults	Serum [†]	WC	ng/g lipids	$r = 0.04$	-


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	Author(s): V Mendes; I Delgado; B Peleteiro; J Araújo; H Barros; E Ramos; D Sarigiannis; N Baiz; I Annesi-Maesano	Version: 1	117/221

Table 10.5.1. Description of papers assessing the association between PCB 180 and adiposity measures

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
al. (2014)[62]			management clinic; ♂♀(n=195)	(18-84)		(measured)		(p= 0.598)	
Waist to Hip Ratio									
Dirinck, E et al. (2011)[56]	BEL	CS	Obese patients and controls; ♂(n=73), ♀(n=71)	Adults (21-60)	Serum (GC/MS)	WtHR (measured)	ng/g lipids	ρ= -0.189 (p<0.05)	-
Dirinck, E. et al. (2014)[62]	BEL	CS	Patients weight management clinic; ♂♀(n=195)	Adults (18-84)	Serum†	WtHR (measured)	ng/g lipids	r= -0.2 (p=0.005)	-
Visceral Adipose Tissue and Subcutaneous Adipose Tissue									
Roos, V et al. (2013)[51]	SWE	CS	PIVUS; ♂♀(n=287)	Adults (70y.o.)	Plasma (HRGC/HRMS)	VAT (MRI)	Per 1-unit (ln ng/g lipid)	β= -42.0 (-61.0;-22.0)	Sex, exercise, education, smoking
Roos, V et al. (2013)[51]	SWE	CS	PIVUS; ♂♀(n=287)	Adults (70y.o.)	Plasma (HRGC/HRMS)	SAT (MRI)	Per 1-unit (ln ng/g lipid)	β= -78.0 (-111.0;-46.0)	Sex, exercise, education, smoking

Shading represents studies for which the same samples were already described in the meta-analysis plot.


PC: Prospective Cohort; CS: Cross-sectional; PIVUS: Prospective Investigation of the Vasculature in Uppsala Seniors; NHANES: National Health and Nutrition Examination Survey; HRGC: High Resolution Gas Chromatography; HRMS: High Resolution Mass Spectrometry; GC: Gas Chromatography; MS: Mass Spectrometry; BMI: Body Mass Index; W: Weight; H: Height; FM: Fat Mass; BIA: Bioelectrical Impedance Analysis; DXA: Dual X-ray Absorptiometry; WC: Waist Circumference; WtHR: Waist to Hip Ratio; VAT: Visceral Adipose Tissue; MRI: Magnetic Resonance Imaging; SAT: Subcutaneous Adipose Tissue; BDL: Below Detected Levels; ρ: Spearman correlation coefficient; r: Pearson correlation coefficient; β: Beta coefficient; OR: Odds ratio; PIR: Poverty Income Ratio; TG: Triglycerides; TC: Total Cholesterol.

†No further information.

Table 10.5.2 summarizes the available results on the association between PCB 180 and each adiposity measure. Despite the high heterogeneity observed for all the summary estimates, there is consistency between results for all the adiposity measures, indicating that higher blood levels of PCB 180 were associated with lower levels of adiposity.

Table 10.5.2. Summary estimates for the association between PCB 180 and each adiposity measure

	PCB 180			
	Number of included estimates	Summary Estimate*	I ² (%)	95% CI
Body Mass Index	7 ^a	-0.23	79.5	-0.29; -0.17

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Weight	1 ^b	0.03 [†]	-	<0.001 [‡]
Fat Mass	3 ^c	-0.39	64.6	-0.47; -0.30
Waist Circumference	2 ^d	-0.27	43.4	-0.36; -0.17
Waist to Hip Ratio	2 ^d	0.02	56.7	-0.09; 0.13
Visceral Adipose Tissue	1 ^e	-42.0	-	-61.0; -22.0
Subcutaneous Adipose Tissue	1 ^e	-78.0	-	-111.0; -46.0

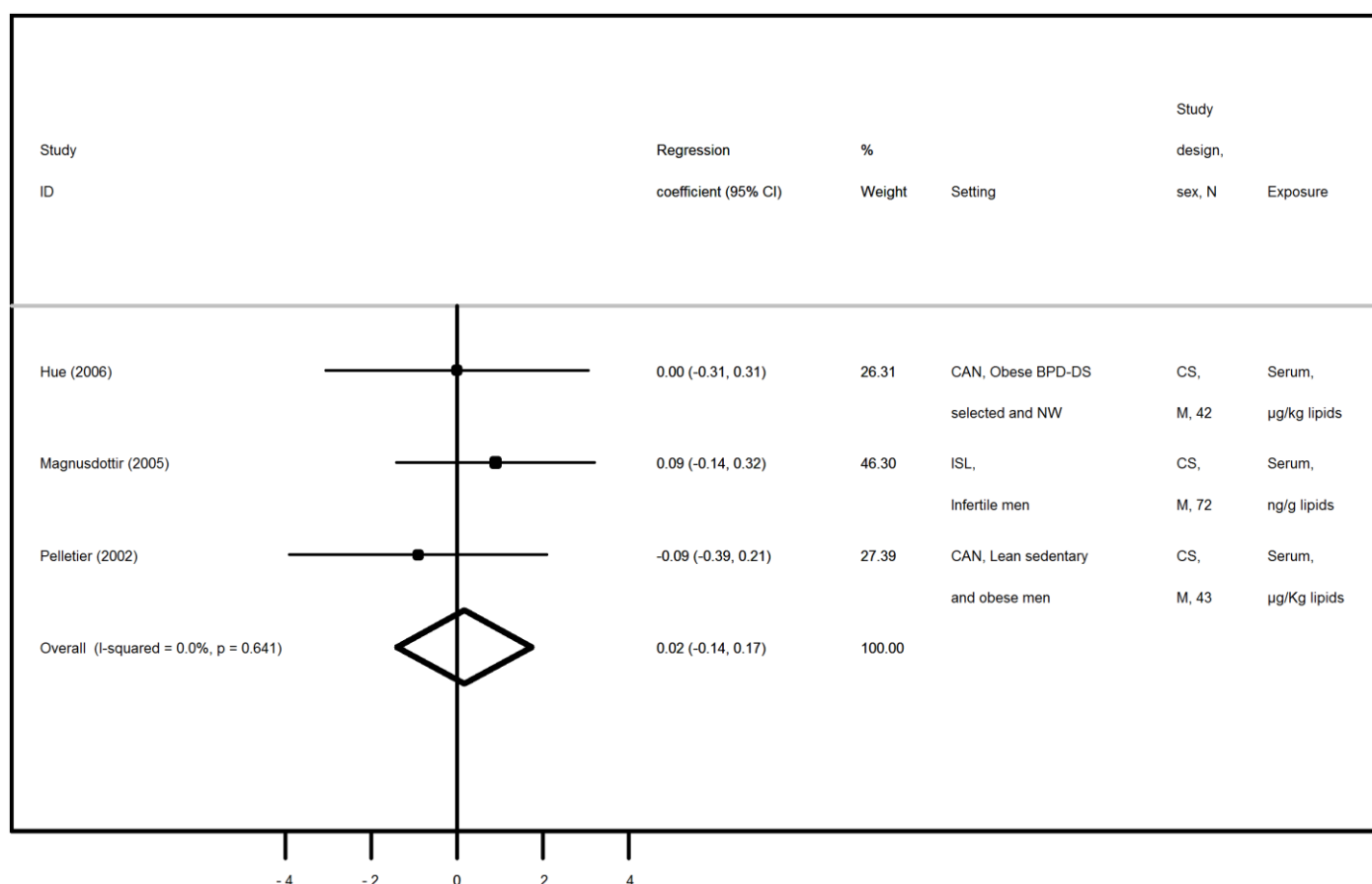
[†] available only when meta-analysis was performed.

*Beta coefficient if not otherwise specified; [†]Pearson correlation coefficient; [‡]p value.

Included studies are: ^aPelletier, C *et al.* (2002)[42], Magnusdottir, E *et al.* (2005)[43], Hue, O *et al.* (2006)[44], Dirinck, E *et al.* (2011)[56], Adlard, B *et al.* (2014)[84] and Dirinck, E *et al.* (2014)[62]; ^bDirinck, E *et al.* (2014)[62]; ^cPelletier, C *et al.* (2002)[42], Dirinck, E *et al.* (2011)[56] and Dirinck, E *et al.* (2014)[62]; ^dDirinck, E *et al.* (2011)[56] and Dirinck, E *et al.* (2014)[62]; ^eRoos, V *et al.* (2013)[51].

10.6 Polychlorinated Biphenyl 187 (PCB 187)

Only four publications have investigated the association between PCB 187 and adiposity outcomes [42-44, 46]. Lee, DH *et al.* (2007) [46] was excluded from meta-analysis for presenting ORs. All the included studies had a cross-sectional design and the sample sizes ranged from 42 to 72 adult men. The overall beta-coefficient was 0.02 (95% CI -0.14; 0.17), indicating no association between PCB 187 and BMI (figure 10.6).




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	WP16: Obesity and childhood diabetes - link with endocrine disruptors	Security: PU	
	Author(s): V Mendes; I Delgado; B Peleteiro; J Araújo; H Barros; E Ramos; D Sarigiannis; N Baiz; I Annesi-Maesano	Version: 1	119/221


Figure 10.6. Meta-analysis of studies evaluating the association of PCB 187 with BMI in adults. Beta coefficients and corresponding 95% CI (horizontal lines). The size of the black square indicates the study's weight in the analysis (weights are from fixed-effects analysis). The centre of the open diamond indicates the summary estimate and its width represents the 95% CI.

Table 10.6.1 presents the description of studies assessing other adiposity measures. While Pelletier, C et al. (2002) found a negative, although not statistically significant, association with fat mass ($p = -0.21$, $p = 0.171$), Lee, DH et al. (2007) found no association between PCB 187 and waist circumference in NHANES non-diabetic individuals (OR= 1.0, 95% CI 0.5; 1.8).

Table 10.6.1. Description of papers assessing the association between PCB 187 and other adiposity measures

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Fat Mass									
Pelletier, C et al. (2002) [42]	CAN	CS	Lean sedentary and obese men; ♂(n=43)	Adults (36-58)	Serum (GC)	FM (Siri equation)	µg/Kg lipids	$\rho = -0.21$ ($p = 0.171$)	Age
Waist Circumference									
Lee, DH et al. (2007) [46]	USA	CS	NHANES Non-diabetic; 1999-2002; ♂♀(n=721)	Adults (≥20)	Total blood (HRGC/HRMS)	WC (measured) ♂>102; ♀>88 cm	>75 th vs. BDL	OR=1.0 (0.5;1.8)	Age, sex, race, PIR, smoking, alcohol, exercise

Shading represents studies for which the same samples were already described in the meta-analysis plot. CS: Cross-sectional; NHANES: National Health and Nutrition Examination Survey; GC: Gas Chromatography; HRGC: High Resolution Gas Chromatography; HRMS: High Resolution Mass Spectrometry; FM: Fat Mass; WC: Waist Circumference; BDL: Below Detected Levels; ρ : Spearman correlation coefficient; OR: Odds ratio; PIR: Poverty Income Ratio.

	D16.1 - Report on overview of cohorts/studies relating adverse health outcomes related to adiposity as an intermediate phenotypes of overweight, obesity, diabetes and metabolic disorders to environmental exposures of endocrine disruptors		
	WP16: Obesity and childhood diabetes - link with endocrine disruptors	Security: PU	
	Author(s): V Mendes; I Delgado; B Peleteiro; J Araújo; H Barros; E Ramos; D Sarigiannis; N Baiz; I Annesi-Maesano	Version: 1	120/221

10.7 Polychlorinated Biphenyl 74 (PCB 74)

Five papers evaluated the association between PCB 74 and adiposity. Meta-analysis was not possible to perform due to the limited number of studies identified (most results were based on PIVUS participants).

In general, all results reported positive and statistically significant associations, with the exception of women from PIVUS in Lee, DH *et al.* (2012) [50] that found a non-statistical significant inverse association (OR= 0.5, 95% CI 0.3; 1.1) (table 10.7.1).

Table 10.7.1. Description of papers included in the systematic review assessing the association between PCB 74 and adiposity

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
BMI									
Magnusdottir E <i>et al.</i> (2005) [43]	ISL	CS	Infertile men; ♂(n=72)	Adults (37±5.4)*	Serum (GC)	BMI (self-reported W&H)	ng/g lipids	ρ= 0.38 p= 0.0009	-
Fat Mass									
Ronn, M <i>et al.</i> (2011) [49]	SWE	PC	PIVUS; ♂♀(n=866)	Adults (70y.o.)	Plasma (HRGC/HRMS)	FM (DXA)	Per 1-unit (ln ng/g lipid)	β= 1.54 (0.35; 2.73)	Sex
Waist Circumference									
Lee, DH <i>et al.</i> (2007) [46]	USA	CS	NHANES Non-diabetic, 1999-2002; ♂♀(n=721)	Adults (≥20)	Total blood (HRGC/HRMS)	WC (measured) ♂>102; ♀>88cm	>75 th vs. BDL	OR= 1.3 (0.7; 2.4)	Age, sex, race, PIR, smoking, alcohol, exercise
Lee, DH <i>et al.</i> (2012) [50]	SWE	CS	PIVUS, 2001-2004; ♂(n=490)	Adults (70y.o.)	Plasma (HRGC/HRMS)	WC (measured) >102 cm	139-418 vs. 8.6-57.4 (pg/mL)	OR= 3.0 (1.3; 6.5)	Calories, exercise, smoking, TG, TC alcohol
Lee, DH <i>et al.</i> (2012) [50]	SWE	CS	PIVUS, 2001-2004; ♀(n= 480)	Adults (70y.o.)	Plasma (HRGC/HRMS)	WC (measured) >88 cm	139-418 vs. 8.6-57.4 (pg/mL)	OR= 0.5 (0.3; 1.1)	Calories, exercise, smoking, TG, TC alcohol
Lee, DH <i>et al.</i> (2012) [50]	SWE	PC	PIVUS, 2001-2009; ♂(n=306)	Adults (≥75)	Plasma (HRGC/HRMS)	WC (measured) >102 cm	139-418 vs. 8.6-57.4 (pg/mL)	OR= 0.9 (0.2; 3.3)	Calories, exercise, smoking, TG, TC alcohol
Lee, DH <i>et al.</i> (2012) [50]	SWE	PC	PIVUS, 2001-2009; ♀(n= 206)	Adults (≥75)	Plasma (HRGC/HRMS)	WC (measured) >88 cm	139-418 vs. 8.6-57.4 (pg/mL)	OR= 0.7 (0.5; 2.5)	Calories, exercise, smoking, TG, TC alcohol
Visceral Adipose Tissue and Subcutaneous Adipose Tissue									
Roos, V <i>et</i>	SWE	CS	PIVUS;	Adults	Plasma	VAT (MRI)	Per 1-unit	β= 21.0	Sex,


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	Author(s): V Mendes; I Delgado; B Peleteiro; J Araújo; H Barros; E Ramos; D Sarigiannis; N Baiz; I Annesi-Maesano		Version: 1 121/221

Table 10.7.1. Description of papers included in the systematic review assessing the association between PCB 74 and adiposity

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
al. (2013) [51]			♂♀(n=287)	(70y.o.)	(HRGC/HRMS)		(ln ng/g lipid)	(6.3; 35.0)	education, exercise, smoking
Roos, V et al. (2013) [51]	SWE	CS	PIVUS; ♂♀(n=287)	Adults (70y.o.)	Plasma (HRGC/HRMS)	SAT (MRI)	Per 1-unit (ln ng/g lipid)	β= 24.0 (0.068; 49.0)	Sex, education, exercise, smoking

CS: Cross-sectional; PC: Prospective Cohort; NHANES: National Health and Nutrition Examination Survey; PIVUS: Prospective Investigation of the Vasculature in Uppsala Seniors; GC: Gas Chromatography; HRGC: High Resolution Gas Chromatography; HRMS: High Resolution Mass Spectrometry; BMI: Body Mass Index; W: Weight; H: Height; FM: Fat Mass; DXA: Dual-energy X-ray Absorptiometry; WC: Waist Circumference; VAT: Visceral Adipose Tissue; MRI: Magnetic Resonance Imaging; SAT: Subcutaneous Adipose Tissue; BDL: Below Detected Level; ρ: Spearman correlation coefficient; OR: Odds ratio; β: Beta coefficient; TG: Triglycerides; TC: Total Cholesterol. *Mean±sd.

10.8 Polychlorinated Biphenyl 194 (PCB 194)

The association between PCB 194 and adiposity was evaluated in four publications: one was performed among infertile adult men [43] and three among PIVUS participants [49-51] (table 10.8.1).

All results provided presented negative estimates, indicating that higher levels of PCB 194 are associated with lower levels of adiposity. Results regarding PIVUS participants have shown strong and statistically significant inverse associations, regardless of the adiposity measure used [49-51].

Table 10.8.1. Description of papers included in the systematic review assessing the association between PCB 194 and adiposity

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
BMI									
Magnusdottir E et al. (2005) [43]	ISL	CS	Infertile men; ♂(n=72)	Adults (37±5.4)*	Serum (GC)	BMI (self-reported W&H)	ng/g lipid	ρ= -0.15 (ρ=0.2)	-
Fat Mass									
Ronn, M et al. (2011) [49]	SWE	PC	PIVUS; ♂♀(n=866)	Adults (70y.o.)	Plasma (HRGC/HRMS)	FM (DXA)	Per 1-unit (ln ng/g lipid)	β= -3.18 (-3.9; -2.45)	Sex
Waist Circumference									
Lee, DH et al. (2012)	SWE	CS	PIVUS, 2001-2004; ♂(n=490)	Adults (70y.o.)	Plasma (HRGC/HRMS)	WC (measured)	173-676 vs. 4.0-	OR=0.2 (0.1; 0.5)	Calories, exercise,


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	WP16: Obesity and childhood diabetes - link with endocrine disruptors	Security: PU	
	Author(s): V Mendes; I Delgado; B Peleteiro; J Araújo; H Barros; E Ramos; D Sarigiannis; N Baiz; I Annesi-Maesano	Version: 1	122/221

Table 10.8.1. Description of papers included in the systematic review assessing the association between PCB 194 and adiposity

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
[50]					HRMS)	>102 cm	80.6 (pg/mL)		smoking, TG, TC alcohol
Lee, DH et al. (2012) [50]	SWE	CS	PIVUS, 2001-2004; ♀(n= 480)	Adults (70y.o.)	Plasma (HRGC/HRMS)	WC (measured) >88 cm	173-676 vs. 4.0-80.6 (pg/mL)	OR=0.0 (0.0;0.1)	Calories, exercise, smoking, TG, TC alcohol
Lee, DH et al. (2012) [50]	SWE	PC	PIVUS, 2001-2009; ♂(n=306)	Adults (≥75)	Plasma (HRGC/HRMS)	WC (measured) >102 cm	173-676 vs. 4.0-80.6 (pg/mL)	OR=0.5 (0.2;1.9)	Calories, exercise, smoking, TG, TC alcohol
Lee, DH et al. (2012) [50]	SWE	PC	PIVUS, 2001-2009; ♀(n= 206)	Adults (≥75)	Plasma (HRGC/HRMS)	WC (measured) >88 cm	173-676 vs. 4.0-80.6 (pg/mL)	OR=0.2 (0.0; 0.5)	Calories, exercise, smoking, TG, TC alcohol
Visceral Adipose Tissue and Subcutaneous Adipose Tissue									
Roos, V et al. (2013) [51]	SWE	CS	PIVUS; ♂♀(n=287)	Adults (70y.o.)	Plasma (HRGC/HRMS)	VAT (MRI)	Per 1-unit (ln ng/g lipid)	β= -60.0 (-79.0; -40.0)	Sex, education, exercise, smoking
Roos, V et al. (2013) [51]	SWE	CS	PIVUS; ♂♀(n=287)	Adults (70y.o.)	Plasma (HRGC/HRMS)	SAT (MRI)	Per 1-unit (ln ng/g lipid)	β= -122.0 (-154.0; -90.0)	Sex, education, exercise, smoking

CS: Cross-sectional; PC: Prospective Cohort; PIVUS: Prospective Investigation of the Vasculature in Uppsala Seniors; GC: Gas Chromatography; HRGC: High Resolution Gas Chromatography; HRMS: High Resolution Mass Spectrometry; BMI: Body Mass Index; W: Weight; H: Height; FM: Fat Mass; DXA: Dual-energy X-ray Absorptiometry; WC: Waist Circumference; VAT: Visceral Adipose Tissue; MRI: Magnetic Resonance Imaging; SAT: Subcutaneous Adipose Tissue; p: Spearman correlation coefficient; β: Beta coefficient; OR: Odds ratio; TG: Triglycerides; TC: Total Cholesterol.
*Mean±sd.

10.9 Polychlorinated Biphenyl 206 (PCB 206)

Regarding PCB 206, three papers were identified in the systematic review assessing the association between this non-dioxin-like PCB and adiposity, all performed among PIVUS subjects [49-51] (table 10.9.1).

As in PCB 194, all the associations reported were strong, inverse and statistical significance for fat mass [49], waist circumference [50], visceral and subcutaneous adipose tissue [51].



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	WP16: Obesity and childhood diabetes - link with endocrine disruptors		Security: PU
	Author(s): V Mendes; I Delgado; B Peleteiro; J Araújo; H Barros; E Ramos; D Sarigiannis; N Baiz; I Annesi-Maesano		Version: 1 123/221

Table 10.9.1. Description of papers included in the systematic review assessing the association between PCB 206 and adiposity

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Fat Mass									
Ronn, M et al. (2011) [49]	SWE	PC	PIVUS; ♂♀(n=866)	Adults (70y.o.)	Plasma (HRGC/HRMS)	FM (DXA)	Per 1-unit (ln ng/g lipid)	β= -5.96 (-7.22; -4.69)	Sex
Waist Circumference									
Lee, DH et al. (2012) [50]	SWE	CS	PIVUS, 2001-2004; ♂(n=490)	Adults (70y.o.)	Plasma (HRGC/HRMS)	WC (measured) >102 cm	37.3-141 vs. 2.3-19.0 (pg/mL)	OR= 0.4 (0.2; 1.8)	Calories, exercise, smoking, TG, TC alcohol
Lee, DH et al. (2012) [50]	SWE	CS	PIVUS, 2001-2004; ♀(n= 480)	Adults (70y.o.)	Plasma (HRGC/HRMS)	WC (measured) >88 cm	37.3-141 vs. 2.3-19.0 (pg/mL)	OR= 0.1 (0.0; 0.2)	Calories, exercise, smoking, TG, TC alcohol
Lee, DH et al. (2012) [50]	SWE	PC	PIVUS, 2001-2009; ♂(n=306)	Adults (≥75)	Plasma (HRGC/HRMS)	WC (measured) >102 cm	37.3-141 vs. 2.3-19.0 (pg/mL)	OR= 0.8 (0.3; 2.6)	Calories, exercise, smoking, TG, TC alcohol
Lee, DH et al. (2012) [50]	SWE	PC	PIVUS, 2001-2009; ♀(n= 206)	Adults (≥75)	Plasma (HRGC/HRMS)	WC (measured) >88 cm	37.3-141 vs. 2.3-19.0 (pg/mL)	OR= 0.3 (0.1; 0.9)	Calories, exercise, smoking, TG, TC alcohol
Visceral Adipose Tissue and Subcutaneous Adipose Tissue									
Roos, V et al. (2013) [51]	SWE	CS	PIVUS; ♂♀(n=287)	Adults (70y.o.)	Plasma (HRGC/HRMS)	VAT (MRI)	Per 1-unit (ln ng/g lipid)	β= -39.0 (-60.0; -19.0)	Sex, education, exercise, smoking
Roos, V et al. (2013) [51]	SWE	CS	PIVUS; ♂♀(n=287)	Adults (70y.o.)	Plasma (HRGC/HRMS)	SAT (MRI)	Per 1-unit (ln ng/g lipid)	β= -77.0 (-111.0; -43.0)	Sex, education, exercise, smoking

PC: Prospective Cohort; CS: Cross-sectional; PIVUS: Prospective Investigation of the Vasculature in Uppsala Seniors; HRGC: High Resolution Gas Chromatography; HRMS: High Resolution Mass Spectrometry; FM: Fat Mass; DXA: Dual-energy X-ray Absorptiometry; WC: Waist Circumference; VAT: Visceral Adipose Tissue; MRI: Magnetic Resonance Imaging; SAT: Subcutaneous Adipose Tissue; β: Beta coefficient; OR: Odds ratio; TG: Triglycerides; TC: Total Cholesterol. *Mean±sd.

10.10 Polychlorinated Biphenyl 209 (PCB 209)

	D16.1 - Report on overview of cohorts/studies relating adverse health outcomes related to adiposity as an intermediate phenotypes of overweight, obesity, diabetes and metabolic disorders to environmental exposures of endocrine disruptors		
	WP16: Obesity and childhood diabetes - link with endocrine disruptors	Security: PU	
	Author(s): V Mendes; I Delgado; B Peleteiro; J Araújo; H Barros; E Ramos; D Sarigiannis; N Baiz; I Annesi-Maesano	Version: 1	124/221


Ronn, M et al. (2011), Lee, DH et al. (2012) and Roos, V et al. (2013) were the only papers identified in the systematic review assessing the association between PCB 209 and adiposity, using data from PIVUS study [49-51] (table 10.10.1).

As in PCB 194 and PCB 206, all the reported associations for PCB 209 were strong, inverse and statistical significance regardless of the adiposity measure used [49-51].

Table 10.10.1. Description of papers included in the systematic review assessing the association between PCB 209 and adiposity

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Fat Mass									
Ronn, M et al. (2011) [49]	SWE	PC	PIVUS; ♂♀(n=866)	Adults (70y.o.)	Plasma (HRGC/HRMS)	FM (DXA)	Per 1-unit (ln ng/g lipid)	β= -6.01 (-7.12; -4.9)	Sex
Waist Circumference									
Lee, DH et al. (2012) [50]	SWE	CS	PIVUS, 2001-2004; ♂(n=490)	Adults (70y.o.)	Plasma (HRGC/HRMS)	WC (measured) >102 cm	37.3-161 vs. 1.8-17.8 (pg/mL)	OR= 0.2 (0.1; 0.5)	Calories, exercise, smoking, TG, TC alcohol
Lee, DH et al. (2012) [50]	SWE	CS	PIVUS, 2001-2004; ♀(n= 480)	Adults (70y.o.)	Plasma (HRGC/HRMS)	WC (measured) >88 cm	37.3-161 vs. 1.8-17.8 (pg/mL)	OR= 0.1 (0.0; 0.2)	Calories, exercise, smoking, TG, TC alcohol
Lee, DH et al. (2012) [50]	SWE	PC	PIVUS, 2001-2009; ♂(n=306)	Adults (≥75)	Plasma (HRGC/HRMS)	WC (measured) >102 cm	37.3-161 vs. 1.8-17.8 (pg/mL)	OR= 0.7 (0.1; 3.1)	Calories, exercise, smoking, TG, TC alcohol
Lee, DH et al. (2012) [50]	SWE	PC	PIVUS, 2001-2009; ♀(n= 206)	Adults (≥75)	Plasma (HRGC/HRMS)	WC (measured) >88 cm	37.3-161 vs. 1.8-17.8 (pg/mL)	OR= 0.3 (0.1; 1.0)	Calories, exercise, smoking, TG, TC alcohol
Visceral Adipose Tissue and Subcutaneous Adipose Tissue									
Roos, V et al. (2013) [51]	SWE	CS	PIVUS; ♂♀(n=287)	Adults (70y.o.)	Plasma (HRGC/HRMS)	VAT (MRI)	Per 1-unit (ln ng/g lipid)	β= -53.0 (-73.0; -34.0)	Sex, education, exercise, smoking
Roos, V et al. (2013) [51]	SWE	CS	PIVUS; ♂♀(n=287)	Adults (70y.o.)	Plasma (HRGC/HRMS)	SAT (MRI)	Per 1-unit (ln ng/g lipid)	β= -94.0 (-126.0; -63.0)	Sex, education, exercise, smoking

PC: Prospective Cohort; CS: Cross-sectional; PIVUS: Prospective Investigation of the Vasculature in Uppsala Seniors; HRGC: High Resolution Gas Chromatography; HRMS: High Resolution Mass Spectrometry; FM: Fat Mass; DXA: Dual-energy X-ray Absorptiometry; WC: Waist Circumference; VAT: Visceral Adipose Tissue; MRI: Magnetic Resonance Imaging; SAT: Subcutaneous Adipose Tissue; β: Beta coefficient; OR: Odds ratio; TG: Triglycerides; TC: Total Cholesterol. *Mean±sd.

 HEALS FP7-ENV-2013-603946	D16.1 - Report on overview of cohorts/studies relating adverse health outcomes related to adiposity as an intermediate phenotypes of overweight, obesity, diabetes and metabolic disorders to environmental exposures of endocrine disruptors		
	WP16: Obesity and childhood diabetes - link with endocrine disruptors	Security: PU	
	Author(s): V Mendes; I Delgado; B Peleteiro; J Araújo; H Barros; E Ramos; D Sarigiannis; N Baiz; I Annesi-Maesano	Version: 1	125/221

10.11 Other non-dioxin-like PCBs

Table 10.11.1 presents the description of publications evaluating PCB 28, PCB 136 and PCB 183. For each one of these non-dioxin-like PCBs only one paper provided results on adiposity. For PCB 28, Pelletier, C *et al.* (2002) [42] reported one estimate for BMI and other for fat mass. Both were positive, but the correlation with fat mass was the only reaching statistical significance ($p=0.35$, $p=0.023$). Lee, DH *et al.* (2012) [50] evaluated the association between PCB 136 and waist circumference among PIVUS participants and a positive association for men and an inverse association for women, although both had not statistical significance. The relationship between PCB 183 and BMI was assessed only by Magnusdottir, E *et al.* (2005) [43] using a sample of infertile adult men, the association observed was positive and statistically significant.

Table 10.11.1. Description of papers included in the systematic review assessing the association between other non-dioxin-like PCBs and adiposity

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
PCB 28									
BMI									
Pelletier, C <i>et al.</i> (2002) [42]	CAN	CS	Lean sedentary and obese men; ♂(n=43)	Adults (36-58)	Serum (GC)	BMI [†]	µg/Kg lipids	$p=0.28$ ($p=0.069$)	Age
Fat Mass									
Pelletier, C <i>et al.</i> (2002) [42]	CAN	CS	Lean sedentary and obese men; ♂(n=43)	Adults (36-58)	Serum (GC)	FM (Siri equation)	µg/Kg lipids	$p=0.35$ ($p=0.023$)	Age
PCB 136									
Waist Circumference									
Lee, DH <i>et al.</i> (2012) [50]	SWE	CS	PIVUS, 2001-2004; ♂(n=490)	Adults (70y.o.)	Plasma (HRGC/HRMS)	WC (measured) >102 cm	1206-2739 vs. 107-563 pg/mL	OR= 1.5 (0.7; 3.2)	Calories, exercise, smoking, TG, TC alcohol


	D16.1 - Report on overview of cohorts/studies relating adverse health outcomes related to adiposity as an intermediate phenotypes of overweight, obesity, diabetes and metabolic disorders to environmental exposures of endocrine disruptors		
	WP16: Obesity and childhood diabetes - link with endocrine disruptors		Security: PU
	Author(s): V Mendes; I Delgado; B Peleteiro; J Araújo; H Barros; E Ramos; D Sarigiannis; N Baiz; I Annesi-Maesano		Version: 1 126/221

Table 10.11.1. Description of papers included in the systematic review assessing the association between other non-dioxin-like PCBs and adiposity

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Lee, DH et al. (2012) [50]	SWE	CS	PIVUS, 2001-2004; ♀(n= 480)	Adults (70y.o.)	Plasma (HRGC/HRMS)	WC (measured) >88 cm	1206-2739 vs. 107-563 pg/mL	OR= 0.3 (0.2; 0.6)	Calories, exercise, smoking, TG, TC alcohol
Lee, DH et al. (2012) [50]	SWE	PC	PIVUS, 2001-2009; ♂(n=306)	Adults (≥75)	Plasma (HRGC/HRMS)	WC (measured) >102 cm	1206-2739 vs. 107-563 pg/mL	OR= 0.9 (0.2; 3.4)	Calories, exercise, smoking, TG, TC alcohol
Lee, DH et al. (2012) [50]	SWE	PC	PIVUS, 2001-2009; ♀(n= 206)	Adults (≥75)	Plasma (HRGC/HRMS)	WC (measured) >88 cm	1206-2739 vs. 107-563 pg/mL	OR= 0.6 (0.2; 1.8)	Calories, exercise, smoking, TG, TC alcohol

PCB 183

BMI

Magnusdottir E et al. (2005) [43]	ISL	CS	Infertile men; ♂(n=72)	Adults (37±5.4)	Serum (GC)	BMI (self-reported W&H)	ng/g lipids	p= 0.32 (p= 0.006)	-
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CS: Cross-sectional; PC: Prospective Cohort; PIVUS: Prospective Investigation of the Vasculature in Uppsala Seniors; GC: Gas Chromatography; HRGC: High Resolution Gas Chromatography; HRMS: High Resolution Mass Spectrometry; BMI: Body Mass Index; FM: Fat Mass; DXA: Dual-energy X-ray Absorptiometry; WC: Waist Circumference; W: Weight; H: Height; p: Spearman correlation coefficient; OR: Odds ratio; TG: Triglycerides; TC: Total Cholesterol. *Mean±sd;

10.12 Sum of non-dioxin-like PCBs

Five papers have evaluated different sums of non-dioxin-like PCBs as the exposure compound [46, 56, 62, 76, 83] (table 10.8). Regardless of the outcome measure, all results shown a negative association between the sum of non-dioxin-like PCBs and adiposity, with the exception of Persky, V *et al.* (2011) [83] who found a positive correlation between non-dioxin-like PCBs and BMI among American male workers of a manufacturing plant ($p= 0.2$, $p= 0.8591$) and Dirinck, E *et al.* (2014) [62] that also found a positive correlation with waist circumference in Belgium patients from a weight management clinic ($r= 0.08$, $p= 0.249$), although none of these results had statistical significance.

Table 10.12.1. Description of papers included in the systematic review assessing the sum of non-dioxin-like PCBs[†]

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
BMI									
Ha, MH et al.	USA	CS	NHANES,	Adults	Serum	BMI [†]	ng/g lipids	p= -0.14	Age




	D16.1 - Report on overview of cohorts/studies relating adverse health outcomes related to adiposity as an intermediate phenotypes of overweight, obesity, diabetes and metabolic disorders to environmental exposures of endocrine disruptors		
	WP16: Obesity and childhood diabetes - link with endocrine disruptors		Security: PU
	Author(s): V Mendes; I Delgado; B Peleteiro; J Araújo; H Barros; E Ramos; D Sarigiannis; N Baiz; I Annesi-Maesano		Version: 1 127/221

Table 10.12.1. Description of papers included in the systematic review assessing the sum of non-dioxin-like PCBs[†]

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
(2007)			1999-2002; ♀(n= 466)	(40-85)	(HRGC/HRMS)			(p<0.01)	
Dirinck, E et al. (2011)	BEL	CS	Obese patients and controls; ♂(n=73), ♀(n=71)	Adults (21-60)	Serum (GC/MS)	BMI (measured W&H)	ng/g lipids	p= -0.25 (p<0.001)	-
Persky, V et al. (2011)	USA	CS	Workers in a manufacturing plant; ♂(n=93)	Adults (35-83)	Serum (GC)	BMI [†]	ng/g	p= 0.2 (p= 0.8591)	-
Persky, V et al. (2011)	USA	CS	Workers in a manufacturing plant; ♀(n=118)	Adults (35-88)	Serum (GC)	BMI [†]	ng/g	p= -0.02 (p= 0.8175)	-
Dirinck, E. et al. (2014)	BEL	CS	Patients weight management clinic; ♂♀(n=195)	Adults (18-84)	Serum [†]	BMI (measured W&H)	ng/g lipids	r= -0.311 (p= 0.0004)	-
Weight									
Dirinck, E. et al. (2014)	BEL	CS	Patients from a weight management clinic; ♂♀(n=195)	Adults (18-84)	Serum [†]	Weight (measured)	ng/g lipids	r= -0.23 (p= 0.0003)	-
Fat Mass									
Dirinck, E et al. (2011)	BEL	CS	Obese patients and controls; ♂(n=73), ♀(n=71)	Adults (21-60)	Serum (GC/MS)	FM (BIA)	ng/g lipids	p= -0.229 (p<0.001)	-
Dirinck, E. et al. (2014)	BEL	CS	Patients from a weight management clinic; ♂♀(n=195)	Adults (18-84)	Serum [†]	FM (BIA)	ng/g lipids	r= -0.36 (p= 0.0002)	-
Waist Circumference									
Lee, DH et al. (2007)	USA	CS	NHANES Non-diabetic; 1999-2002; ♂♀(n=721)	Adults (≥20)	Whole blood (HRGC/HRMS)	WC (measured) ♂>102; ♀>88 cm	>75 th vs. <25 th	OR= 0.6 (0.3; 1.1)	Age, sex, race, PIR, smoking, cotinine, alcohol, exercise
Dirinck, E et al. (2011)	BEL	CS	Obese patients and controls; ♂(n=73), ♀(n=71)	Adults (21-60)	Serum (GC/MS)	WC (measured)	ng/g lipids	p= -0.228 (p<0.01)	-
Dirinck, E. et al. (2014)	BEL	CS	Patients weight management clinic; ♂♀(n=195)	Adults (18-84)	Serum [†]	WC (measured)	ng/g lipids	r= 0.08 (p= 0.249)	-
Waist to Hip Ratio									
Dirinck, E et al. (2011)	BEL	CS	Obese patients and controls; ♂(n=73), ♀(n=71)	Adults (21-60)	Serum (GC/MS)	WtHR (measured)	ng/g lipids	p= -0.111 (p>0.05)	-
Dirinck, E. et al. (2014)	BEL	CS	Patients weight management clinic; ♂♀(n=195)	Adults (18-84)	Serum [†]	WtHR (measured)	ng/g lipids	r= -0.14 (p= 0.057)	-

[†]Sums do not necessarily represent the combination of substances. CS: Cross-sectional; NHANES: National Health and Nutrition Examination Survey; HRGC: High Resolution Gas Chromatography; HRMS: High Resolution Mass Spectrometry; GC: Gas Chromatography; MS: Mass Spectrometry; BMI: Body Mass Index; WC: Waist Circumference; W: Weight; H: Height; FM: Fat Mass; BIA: Bioelectrical Impedance Analysis; DXA: Dual-energy X-ray Absorptiometry; WtHR: Waist to Hip ratio; p: Spearman correlation coefficient; OR: Odds ratio; r: Pearson correlation coefficient; PIR: Poverty Income Ratio. [†]No further information.

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	WP16: Obesity and childhood diabetes - link with endocrine disruptors	Security: PU	
	Author(s): V Mendes; I Delgado; B Peleteiro; J Araújo; H Barros; E Ramos; D Sarigiannis; N Baiz; I Annesi-Maesano	Version: 1	128/221

	D16.1 - Report on overview of cohorts/studies relating adverse health outcomes related to adiposity as an intermediate phenotypes of overweight, obesity, diabetes and metabolic disorders to environmental exposures of endocrine disruptors		
	WP16: Obesity and childhood diabetes - link with endocrine disruptors	Security: PU	
	Author(s): V Mendes; I Delgado; B Peleteiro; J Araújo; H Barros; E Ramos; D Sarigiannis; N Baiz; I Annesi-Maesano	Version: 1	129/221

11. Sum of PCBs (combination of dioxin-like and non-dioxin-like PCBs)

In the systematic review twenty studies assessing the association between the sum of PCBs (combining dioxin-like and non-dioxin-like PCBs) with adiposity were identified [11, 43, 48, 52, 54, 57, 60, 65-68, 70, 79, 82, 83, 85-89]. Due to the variety of PCBs sums found, it was not possible to perform a meta-analysis, since the combination of these different sums may lead to misguided conclusions. All the results were presented in table 11.1.1. For ease of understanding, the dioxin-like PCBs are underlined

11.1 Sums of PCBs (specified compounds)

In general, most studies found negative associations between sums of PCBs and adiposity measures (table 11.1.1). However, positive associations were found in six publications, but only Stellman, SD *et al.* (2000) [54] and Muscat, JE *et al.* (2003) [86] found statistical significance. Regarding children, both Dhooge, W *et al.* (2010) [79] and Mazhitova, Z *et al.* (1998) [70] found negative and statistical significant associations with BMI.

Table 11.1.1. Description of papers included in the systematic review assessing the sum of PCBs (combination of specified dioxin-like and non-dioxin-like PCBs)

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Sum of PCB <u>118</u>, 138, 153 and 180									
Adults									
Wolff, MS <i>et al.</i> (2000b)[66]	USA	CS	Gen. Population; ♀(n=213)	Adults (34-65)	Serum (GC)	BMI [†]	ng/g lipid	ρ= -0.01 (p>0.05)	Age
Wolff, MS <i>et al.</i> (2005)[66]	USA	CS	Gen. Population; ♀(n=1007)	Adults (≥20)	Serum [†]	BMI [†]	ng/g lipid	ρ= -0.11 (p<0.001)	Age
Dhooge, W <i>et al.</i> (2010) [79]	BEL	CS	Gen. Population ♂(n=775)	Adults (50-65)	Serum (GC-ECD)	BMI (self-reported W&H)	Per 1-unit (ln ng/g fat)	β= -3.20 (-2.61; -3.79)	Age, alcohol, education, vegetables & meat intake
Dhooge, W <i>et al.</i>	BEL	CS	Gen. Population	Adults	Serum	BMI (self-	Per 1-unit	β= -6.18	Age, alcohol,


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	Author(s): V Mendes; I Delgado; B Peleteiro; J Araújo; H Barros; E Ramos; D Sarigiannis; N Baiz; I Annesi-Maesano		Version: 1 130/221

Table 11.1.1. Description of papers included in the systematic review assessing the sum of PCBs (combination of specified dioxin-like and non-dioxin-like PCBs)

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
al. (2010) [79]			♀(n=808)	(50-65)	(GC-ECD)	reported W&H)	(ln ng/g fat)	(-5.48; -6.87)	education, vegetables meat intake
Children									
Dhooge, W et al. (2010) [79]	BEL	CS	Gen. Population ♂(n=767)	Children (14-15)	Serum (GC-ECD)	BMI (self-reported W&H)	Per 1-unit (ln ng/g fat)	β= -2.45 (-2.07; -2.82)	Parental height, age, education, smoking, alcohol
Dhooge, W et al. (2010) [79]	BEL	CS	Gen. Population ♀(n=636)	Children (14-15)	Serum (GC-ECD)	BMI (self-reported W&H)	Per 1-unit (ln ng/g fat)	β= -2.0 (-1.62; -2.41)	height, age, parental education, smoking, alcohol
Sum of PCB 118, 138, 153, 156, 170 and 180									
Bergkvist, C et al. (2012) [85]	SWE	CS	Gen. Population; ♀(n=201)	Adults (58-78)	Serum (GC-HRMS)	FM (DXA)	ng/g lipid weight	ρ= -0.17 (p<0.001)	-
Bergkvist, C et al. (2012) [85]	SWE	CS	Gen. Population; ♀(n=201)	Adults (58-78)	Serum (GC-HRMS)	Weight (Measured)	ng/g lipid weight	ρ= -0.23 (p<0.001)	-
Sum of PCB 28, 52, 56/60, 66, 74, 99, 101, 105, 110, 118, 130, 137, 138, 146, 149, 153, 156, 157, 167, 170, 171, 172, 177, 178, 180, 183, 187, 189, 191, 193, 194, 195, 201, 203, 205, 206, 208 and 209									
Persky, V et al. (2011) [83]	USA	CS	Employees in a manufacturing plant and general population; ♀(n=118)	Adults (35-88)	Serum (GC)	BMI [†]	ng/g	ρ= 0.04 (0.6621)	-
Sum of PCB 8, 18, 28, 29, 44, 52, 87, 101, 105, 110, 118, 128, 138, 153, 170, 180, 187, 194, 195, 200, 205 and 206									
Moon, HB et al. (2012) [52]	KOR	CS	Myoma patients; ♀(n=53)	Adults (40-68)	Adipose Tissue (GC/MS)	BMI [†]	ng/g lipid	ρ= -0.052 (p>0.05)	-
Sum of PCB 74, 99, 118, 138, 146, 153, 156, 167, 170, 172, 178, 180, 183 and 187									
Stellman, SD et al. (2000) [54]	USA	CS	Breast cancer patients and patients w/ benign breast disease; ♀(n=555)	Adults	Adipose Tissue (GC-ECD)	BMI [†]	ng/g lipid	ρ= 0.105 (p<0.01)	-
Muscat, JE et al (2003) [86]	USA	CS	Gen. Population; ♀(n=224)	Adults (≤82)	Adipose Tissue (GC-ECD)	BMI [†]	ng/g lipid	ρ= 0.14 (p= 0.04)	-
Sum of PCB 28, 52, 101, 105, 114, 118, 123/149, 138/163, 153, 156/171, 157, 167, 170, 180 and 189									
Langer, P. et al. (2012) [60]	SVK	CS	People from polluted areas; ♂(n=429)	Adults (41-55)	Serum (HRGC-ECD)	BMI [†]	ng/g	ρ= -0.11 (p<0.05)	-
Sum of PCB 74, 99, 118, 138, 153, 156, 167, 170, 180, 183, 187 and 194									
Magnusdottir, E et al. (2005) [43]	ISL	CS	Infertile men; ♂(n=72)	Adults (37±5.4)	Serum (GC)	BMI (self-reported W&H)	ng/g lipids	ρ= 0.19 (p= 0.11)	-


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	WP16: Obesity and childhood diabetes - link with endocrine disruptors		Security: PU
	Author(s): V Mendes; I Delgado; B Peleteiro; J Araújo; H Barros; E Ramos; D Sarigiannis; N Baiz; I Annesi-Maesano		Version: 1 131/221

Table 11.1.1. Description of papers included in the systematic review assessing the sum of PCBs (combination of specified dioxin-like and non-dioxin-like PCBs)

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Sum of PCB 74, 87, 90/101, 99, <u>105</u>, 110, <u>118</u>, 146, 163/164/138, 153, <u>156</u>, 170, 177, 180, 183, 187 and 199									
Goncharov, A. et al. (2008) [11]	CAN	CS	Mohawk population; ♂(n=94), ♀(n=183)	Adults (18-83)	Serum (GC-ECD)	BMI [†]	pbb	r= 0.058 (p>0.05)	-
Sum of PCB 74, 99, <u>105</u>, <u>118</u>, 138, 153, <u>156</u>, 164, <u>167</u>, 172, 177, 178, 180, 183 and 187									
Lee, DH et al. (2014) [89]	KOR	NCC	Ulsjin cohort, 2006-2010; ♂(n= 81), ♀(n= 165)	Adults (>40)	Serum (GC-IDHRMS)	WC (measured) ♂≥90cm; ♀≥80cm	Q4 vs. Q1	OR=1.8 (0.5; 5.7)	Age, sex, smoking, drinking, exercise, TG, TC, BMI
Sum of PCB 101, <u>105</u>, <u>118</u>, 135, 153, <u>156</u> and 180									
Mazhitova, Z. et al. (1998) [70]	SWE	CS	Hospitalized children; ♂(n=6), ♀(n=6)	Children (7-15)	Plasma (GC)	BMI [†] -SDS (French standards)	ng/g	ρ= -0.86 (p<0.01)	-

Dioxin-like PCBs are underlined.

CS: Cross-sectional; NCC: Nested Case-control; GC: Gas Chromatography; ECD: Electron Capture Detection; HRMS: High Resolution Mass Spectrometry; MS: Mass Spectrometry; HRGC: High Resolution Gas Chromatography; IDHRMS: Isotope Dilution High Resolution Mass Spectrometry; BMI: Body Mass Index; W: Weight; H: Height; FM: Fat Mass; DXA: Dual-energy X-ray Absorptiometry; WC: Waist Circumference; SDS: Standard Deviation Score; ρ: Spearman correlation coefficient; β: Beta coefficient; r: Pearson correlation coefficient; OR: Odds ratio; TG: Triglycerides; TC: Total cholesterol. *Mean±sd; †No further information; ‡ Sums may not necessarily represent the same combination of substances.

11.2 Sums of PCBs (not specified)

Regarding the sums for which authors did not specify compounds being combined, mixed results were found (table 11.2.1). The two papers performed among children found negative and statistical significant associations [82, 88].

Table 11.2.1. Description of papers included in the systematic review assessing the sum of PCBs (not specified)

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Sum of PCBs (not specified)[‡]									
Adults									
Hanrahan, L. et al. (1999) [65]	USA	CS	Great Lakes' consumers and controls; ♂(n=309), ♀(n= 229)	Adults	Serum (GC-ECD)	BMI (self-reported W&H)	pbb	r=0.201 (p<0.001)	-
Moysich, KB et al. (2002) [67]	USA	CS	Postmenopausal women; ♀(n=192)	Adults (45-85)	Whole Blood (HRGC)	BMI (self-reported W&H)	log ng/g of serum	r= 0.05 (p>0.05)	-
Anderson, HA et al. (2008)	USA	CS	Consumers of Great Lakes'	Adults (59)	Serum (HRGC-ECD)	BMI [†]	ng/g lipids	ρ=0.01 (p>0.05)	-


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Table 11.2.1. Description of papers included in the systematic review assessing the sum of PCBs (not specified)


Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
[87] Qin, YY et al. (2011) [57]	HKG	CS	fish; ♂♀ (n=508) Blood donors; ♂n=60, ♀n=51	Adults	Serum (GC-MS)	BMI (self-reported W&H)	ng/g lipid	r= 0.56 (p<0.05)	-
Children									
Jackson, LW et al. (2010) [82]	USA	CS	CDS, 1998-2002; ♂(n=21), ♀(n= 23)	Children (2-2)	Serum (HRGC/HRMS)	Weight z-score (measured)	>0.88 vs. ≤0.88	β= -0.23 (-1.23; 0.77)	Maternal preconception weight
Jackson, LW et al. (2010) [82]	USA	CS	CDS, 1998-2002; ♂(n=21), ♀(n= 23)	Children (2-2)	Serum (HRGC/HRMS)	WfL z-score (measured)	>0.88 vs. ≤0.88	β= -0.23 (-1.01; 0.55)	Maternal preconception BMI
Lower chlorinated PCBs (not specified)[‡]									
Wolff, MS et al. (2000a) [48]	USA	CS	Breast disease patients and controls; ♀(n=337)	Adults	Serum (GC)	BMI [†]	ng/mL	ρ= -0.07 (p>0.05)	Age
Moysich, KB et al. (2002) [67]	USA	CS	Postmenopausal women; ♀(n=192)	Adults (45-85)	Whole Blood (HRGC)	BMI (self-reported W&H)	log ng/g of serum	r=0.13 (p>0.05)	-
Moderately chlorinated PCBs (not specified)									
Moysich, KB et al. (2002) [67]	USA	CS	Postmenopausal women; ♀(n=192)	Adults (45-85)	Whole Blood (HRGC)	BMI (self-reported W&H)	log ng/g of serum	r=0.05 (p>0.05)	-
Higher chlorinated PCBs (not specified)									
Wolff, MS et al. (2000a) [48]	USA	CS	Breast disease patients and controls; ♀(n=337)	Adults	Serum (GC)	BMI [†]	ng/mL	ρ= -0.15 (p<0.05)	Age
Moysich, KB et al. (2002) [67]	USA	CS	Postmenopausal women; ♀(n=192)	Adults (45-85)	Whole Blood (HRGC)	BMI (self-reported W&H)	log ng/g of serum	r= -0.15 (p>0.05)	-
Sum of mono-ortho PCBs and nondioxin-like PCBs (not specified)									
Burns, JS et al. (2011) [88]	RUS	PC	Gen. Population; ♂(n=468)	Children (8-9)	Serum (HRGC/HRMS)	BMI z-score (measured W&H)	435-4248 vs. 62-151 (ng/g lipid)	β= -1.04 (-1.37; -0.71)	Age, BW, gestational age, income, calories, blood lead levels.

CS: Cross-sectional; PC: Prospective Cohort; GC: Gas Chromatography; ECD: Electron Capture Detection; HRGC: High Resolution Gas Chromatography; MS: Mass Spectrometry; HRMS: High Resolution Mass Spectrometry; BMI: Body Mass Index; W: Weight; H: Height; WfL: Weight for Length; r: Pearson correlation coefficient; ρ: Spearman correlation coefficient; β: Beta coefficient; BW: Birthweight.

*Mean; †No further information; ‡ Sums may not necessarily represent the same combination of substances.

12. Organobromines

Seven publications assessed the relationship between organobromines and adiposity [49-52, 87, 90, 91] reporting data for seven compounds on this group of EDCs (table 12.1). However, it was not possible to perform a meta-analysis because

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three of the seven papers were performed in the same sample (PIVUS) [49-51]. Anderson, HA *et al.* (2008) [87] and Moon, HB *et al.* (2012) [52], only presented data for the sum of polybrominated diphenyl ethers (PBDE), which was not reported in any other study. As we have not identified more than two papers evaluating at least one of the organobromine substances, meta-analysis was not performed.

The association between brominated diphenyl ether (BDE) 47 and adiposity was assessed in five papers [49-51, 90, 91]. Ronn, M *et al.* (2011) [49], Lee, DH *et al.* (2012) [50] and Roos, V *et al.* (2013) [51] investigated individuals from PIVUS and found cross-sectional and longitudinal positive associations between BDE 47 and adiposity measures (fat mass, waist circumference and visceral and subcutaneous adipose tissue), but without statistical significance. The only negative association found among adults was observed by Lim, JS *et al.* (2008) [90] in NHANES 2003-2004 individuals using BMI as the adiposity measure, but also with no statistical significance. In children, Bradman, A *et al.* (2012) [91] found similar results for BMI z-score ($r = -0.05$, $p > 0.05$).

Lim, JS *et al.* (2008) [90] has evaluated other organobromine compounds (BDE 153, 28, 99, 100 and PBB 153) using NHANES 2003-2004 dataset. For all five analyzed compounds, the authors found no statistically significant associations. Negative correlations between BDE 99, 100, 153 and PBB 153 and BMI were observed, while the correlation between BDE 28 and BMI was positive ($\rho = 0.03$, $p > 0.01$). Regarding associations between BDE 153 and PBB 153 and waist circumference, Lim, JS *et al.* (2008) [90] has also found positive associations [OR = 2.6 (95% CI 0.7; 10.8) and OR = 2.1 (95% CI 0.6; 7.2), respectively], but also with no statistical significance.

Anderson, HA *et al.* (2008) [87] and Moon, HB *et al.* (2012) [52] presented data only for a mixture of organobromine compounds. Both found positive, but not statistical significant correlations between the sum of PBDEs and BMI in adult individuals. On the other hand, Bradman, A *et al.* (2012) [91] observed a negative association with BMI z-score in CHAMACOS children ($r = -0.12$, $p < 0.05$).


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Table 12.1. Description of papers included in the systematic review assessing the association between organobromines and adiposity measures

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Brominated diphenyl ether (BDE) 47									
BMI									
Lim, JS et al. (2008)[90]	USA	CS	NHANES, 2003-2004; ♂(n=647), ♀(n=720)	Adults (49.7±19.3)	Whole blood (HRGC/IDHRMS)	BMI (measured W&H)	ng/g lipids	ρ= -0.002 (p>0.01)	-
Bradman, A et al. (2012)[91]	USA	CS	CHAMACOS, 2006-2007; ♂♀(n=271)	Children (7-7)	Serum (GC-IDHRMS)	BMI z-score (measured W&H)	ng/g lipids	r= -0.05 (p>0.05)	-
Fat Mass									
Ronn, M et al. (2011)[49]	SWE	PC	PIVUS; ♂♀(n=866)	Adults (70y.o.)	Plasma (HRGC/HRMS)	FM (DXA)	Per 1-unit (ln ng/g lipid)	β= 0.077 (-0.8; 0.95)	Sex
Waist Circumference									
Lee, DH et al. (2012)[50]	SWE	CS	PIVUS, 2001-2004; ♂(n=490)	Adults (70y.o.)	Plasma (HRGC/HRMS)	WC (measured) >102 cm	Qu5 (22.1-294) vs. Qu1 (BDL) (pg/mL)	OR= 1.1 (0.6; 2.1)	Calorie intake, exercise, smoking, alcohol, TG, TC
Lee, DH et al. (2012)[50]	SWE	CS	PIVUS, 2001-2004; ♀(n=480)	Adults (70y.o.)	Plasma (HRGC/HRMS)	WC (measured) >88 cm	Qu5 (22.1-294) vs. Qu1 (BDL) (pg/mL)	OR=1.3 (0.7; 2.3)	Calorie intake, exercise, smoking, alcohol, TG, TC
Lee, DH et al. (2012)[50]	SWE	PC	PIVUS, 2001-2009; ♂(n=306)	Adults (≥75)	Plasma (HRGC/HRMS)	WC (measured) >102 cm	Qu5 (22.1-294) vs. Qu1 (BDL) (pg/mL)	OR=1.3 (0.5; 3.5)	Calorie intake, exercise, smoking, alcohol, TG, TC
Lee, DH et al. (2012)[50]	SWE	PC	PIVUS, 2001-2009; ♀(n=206)	Adults (≥75)	Plasma (HRGC/HRMS)	WC (measured) >88 cm	Qu5 (22.1-294) vs. Qu1 (BDL) (pg/mL)	OR=0.7 (0.3; 1.7)	Calorie intake, exercise, smoking, alcohol, TG, TC
Visceral Adipose Tissue and Subcutaneous Adipose Tissue									
Roos, V et al. (2013)[51]	SWE	CS	PIVUS; ♂♀(n=287)	Adults (70y.o.)	Plasma (HRGC/HRMS)	VAT (MRI)	Per 1-unit (ln ng/g lipid)	β= 5.1 (-6.3; 17.0)	Sex, education level, exercise, smoking
Roos, V et al. (2013)[51]	SWE	CS	PIVUS; ♂♀(n=287)	Adults (70y.o.)	Plasma (HRGC/HRMS)	SAT (MRI)	Per 1-unit (ln ng/g lipid)	β= 16.0 (-3.6; 35.0)	Sex, education level, exercise, smoking
Brominated diphenyl ether (BDE) 153									


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Table 12.1. Description of papers included in the systematic review assessing the association between organobromines and adiposity measures

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
BMI									
Lim, JS et al. (2008)[90]	USA	CS	NHANES, 2003-2004; ♂(n=647), ♀(n=720)	Adults (49.7±19.3)	Whole blood (HRGC/IDHRMS)	BMI (measured W&H)	ng/g lipids	ρ= -0.002 (p>0.01)	-
Bradman, A et al. (2012)[91]	USA	CS	CHAMACOS, 2006-2007; ♂♀(n=271)	Children (7-7)	Serum (GC-IDHRMS)	BMI z-score (measured W&H)	ng/g lipids	r= -0.37 (p<0.01)	-
Waist Circumference									
Lim, JS et al. (2008)[90]	USA	CS	NHANES, 2003-2004; ♂(n=647), ♀(n=720)	Adults (49.7±19.3)	Whole blood (HRGC/IDHRMS)	WC (measured) ♂>102; ♀>88	>75 th vs. BDL	OR= 2.8 (0.7; 10.8)	Age, sex, race, PIR, BMI, and other
Brominated diphenyl ether (BDE) 28									
BMI									
Lim, JS et al. (2008)[90]	USA	CS	NHANES, 2003-2004; ♂(n=647), ♀(n=720)	Adults (49.7±19.3)	Whole blood (HRGC/IDHRMS)	BMI (measured W&H)	ng/g lipids	ρ= 0.03 (p>0.01)	-
Brominated diphenyl ether (BDE) 99									
BMI									
Lim, JS et al. (2008)[90]	USA	CS	NHANES, 2003-2004; ♂(n=647), ♀(n=720)	Adults (49.7±19.3)	Whole blood (HRGC/IDHRMS)	BMI (measured W&H)	ng/g lipids	ρ= -0.03 (p>0.01)	-
Brominated diphenyl ether (BDE) 100									
BMI									
Lim, JS et al. (2008)[90]	USA	CS	NHANES, 2003-2004; ♂(n=647), ♀(n=720)	Adults (49.7±19.3)	Whole blood (HRGC/IDHRMS)	BMI (measured W&H)	ng/g lipids	ρ= -0.02 (p>0.01)	-
Polybrominated biphenyl (PBB) 153									
BMI									
Lim, JS et al. (2008)[90]	USA	CS	NHANES, 2003-2004; ♂(n=647), ♀(n=720)	Adults (49.7±19.3)	Whole blood (HRGC/IDHRMS)	BMI (measured W&H)	ng/g lipids	ρ= -0.14 (p<0.01)	-
Waist Circumference									
Lim, JS et al. (2008)[90]	USA	CS	NHANES, 2003-2004; ♂(n=647), ♀(n=720)	Adults (49.7±19.3)	Whole blood (HRGC/IDHRMS)	WC (measured) ♂>102; ♀>88	>75 th vs. BDL	OR= 2.1 (0.6; 7.2)	Age, sex, race, PIR, BMI, smoking, alcohol, exercise


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Table 12.1. Description of papers included in the systematic review assessing the association between organobromines and adiposity measures

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Sum of Polybrominated Diphenyl Ethers (PBDEs)[‡]									
BMI									
Anderson, HA et al. (2008)[87]	USA	CS	Consumers of Great Lakes fish; ♂♀ (n=508)	Adults (59) [*]	Serum (HRGC-ECD)	BMI [†]	ng/g lipids	ρ= 0.03 (p>0.05)	-
Moon, HB et al. (2012)[52]	KOR	CS	Myoma patients; ♀(n=53)	Adults (40-68)	Adipose Tissue (GC/MS)	BMI [†]	ng/g lipids	ρ= 0.132 (p>0.05)	-
Bradman, A et al. (2012)[91]	USA	CS	CHAMACOS, 2006-2007; ♂♀(n=271)	Children (7-7)	Serum (GC-IDHRMS)	BMI z-score (measured W&H)	ng/g lipids	r= -0.12 (p<0.05)	-

[‡] Sums do not necessarily represent the same combination of substances.

CS: Cross-sectional; PC: Prospective cohort; NHANES: National Health and Nutrition Examination Survey; CHAMACOS: Center for the Health Assessment of Mothers and Children of Salinas; PIVUS: Prospective Investigation of the Vasculature in Uppsala Seniors; HRGC: High Resolution Gas Chromatography; IDHRMS: Isotope Dilution High Resolution Mass Spectrometry; GC: Gas Chromatography; ECD: Electron Capture Detection; MS: Mass Spectrometry; BMI: Body Mass Index; W: Weight; H: Height; FM: Fat Mass; DXA: Dual-energy X-ray Absorptiometry; WC: Waist Circumference; VAT: Visceral Adipose Tissue; MRI: Magnetic Resonance Imaging; SAT: Subcutaneous Adipose Tissue; BDL: Below Detected Levels; ρ: Spearman correlation coefficient; r: Pearson correlation coefficient; β: Beta coefficient; OR: Odds ratio; TG: Triglycerides; TC: Total Cholesterol; PIR: Poverty Income Ratio.

*Median; †No further information.

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13. Phthalates

In the systematic review we have found fifteen publications addressing the association between sixteen phthalate compounds and adiposity [46, 50, 69, 92-103]. Of the sixteen identified substances, meta-analysis was performed for four compounds: mono-butyl phthalate (mBP), mono-(2-ethylhexyl) phthalate (MEHP), mono-ethyl phthalate (MEP), and mono-benzyl phthalate (MBzP).

13.1 Mono-butyl Phthalate (mBP)

Seven papers were identified evaluating the association between mBP and adiposity [69, 92-97]. Stahlhut, RW *et al.* (2007) [93] and Svensson, K *et al.* (2011) [95] were excluded from meta-analysis for presenting regression coefficients for log transformed variables. Teitelbaum, SL *et al.* (2012) [96] and Wang, H *et al.* (2013) [97] were excluded from meta-analysis for being performed among children. Hatch, EE *et al.* (2008) [94] provided estimates for both adults and children, but only those considering adult individuals were included in the analysis. Huang, PC *et al.* (2007) [92] presented stratified results according to the mBP exposure level (higher and lower) and both estimates were included in the meta-analysis plot. Although Huang, PC *et al.* (2007) [92] was performed among pregnant women, results were based in pre-pregnancy BMI values.

The three included papers reported seven different estimates that were considered in the meta-analysis [69, 92, 94]. Hatch, EE *et al.* (2008) [94] included men and women and presented age- and sex-stratified results, while Huang, PC *et al.* (2007) [92], and Brucker-Davis, F *et al.* (2010) [69] presented estimates only for women. The overall beta coefficient was 0.13 (95% CI 0.02; 0.25) ($I^2 = 79.2\%$) indicating a positive association between mBP and BMI (figure 13.1).

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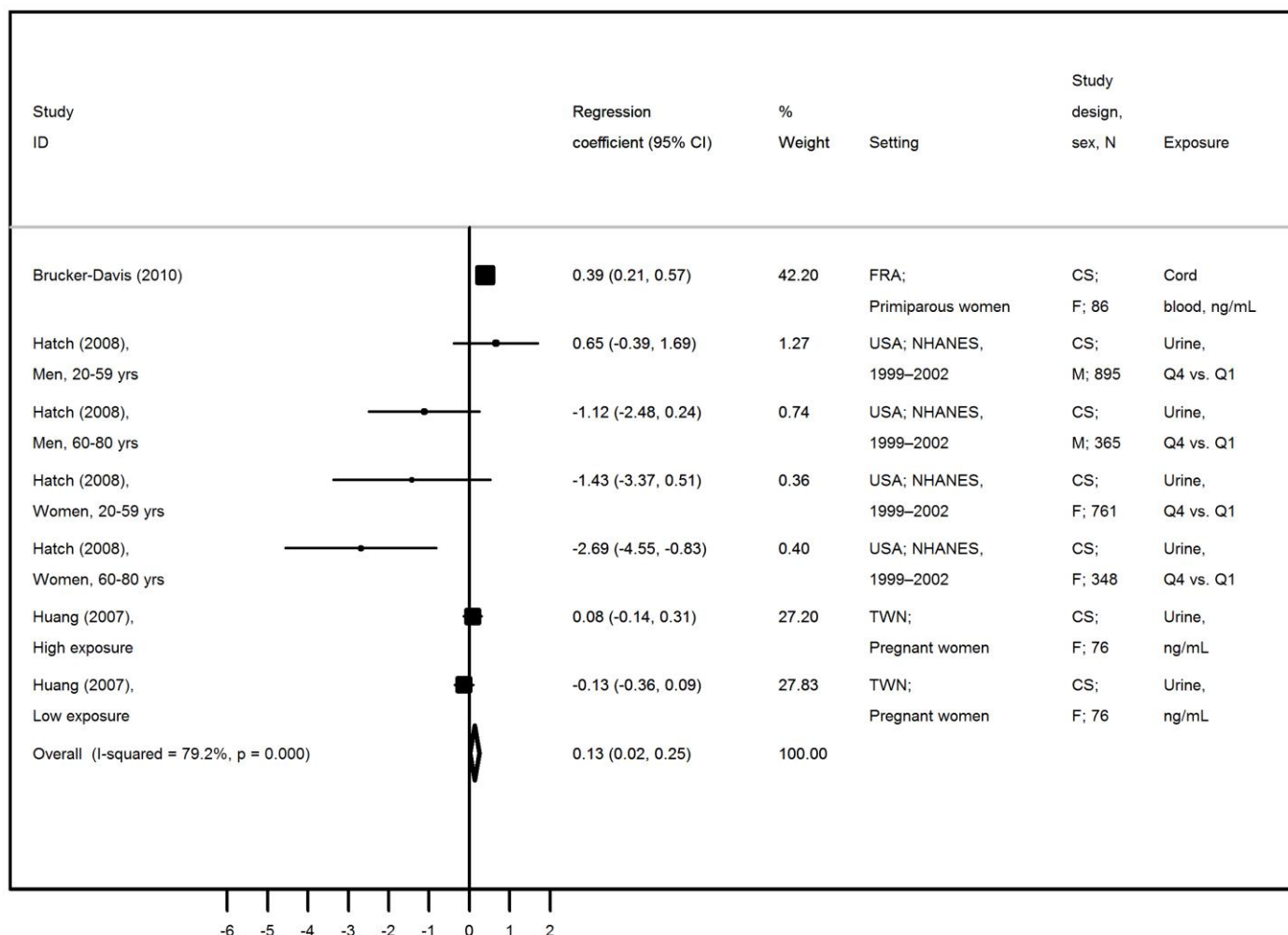



Figure 13.1. Meta-analysis of publications evaluating the association of mBP with BMI in adults. Beta coefficients and corresponding 95% CI (horizontal lines). The size of the black square indicates the study's weight in the analysis (weights are from fixed-effects analysis). The centre of the open diamond indicates the summary estimate and its width represents the 95% CI.

Table 13.1.1 presents the description of publications evaluating the association between mBP and adiposity measures in adults: Svensson, K *et al.* (2011) [95] was the only paper evaluating BMI that was not included in the meta-analysis. A positive but not statistically significant correlation was observed ($p = 0.0249$, $p > 0.05$). Lines in shading represent results for populations already included in the forest plot shown in figure

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13.1. Three papers assessed waist circumference [93-95] and provided six different estimates, while one evaluated waist to hip ratio [95]. Mixed results were found and only Hatch, EE *et al.* (2008) [94] observed statistically significant associations ($\beta = 2.91$, 95% CI 0.22; 5.6). Svensson, K *et al.* (2011) [95] was the only paper evaluating waist to hip ratio and found a negative but not significant correlation with mBP among Mexican women ($p = -0.002$, $p > 0.05$).

Table 13.1.1. Description of papers assessing the association between mBP and adiposity measures in adults

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
BMI									
Svensson, K <i>et al.</i> (2011)[95]	MEX	CS	Healthy women; ♀(n=182)	Adults (54*)	Urine (SPE/HPLC-ID-TMS)	BMI (Measured W&H)	log µg/g creatinine	$p = 0.0249$ ($p > 0.05$)	-
Waist Circumference									
Stahlhut, RW <i>et al.</i> (2007)[93]	USA	CS	NHANES 1999-2002; ♂(n=651)	Adults (>18)	Urine (HPLC/ID-TMS)	WC (Measured)	Per 1-unit (ln µg/g creatinine)	$\beta = 0.98$ ($p = 0.059$)	Age, race, total fat, calories, PA, smoking, creatinine
Hatch, EE <i>et al.</i> (2008) [94]	USA	CS	NHANES, 1999-2002; ♀(n=761)	Adults (20-59)	Urine (ID-HPLC/MS)	WC (Measured)	51.7-4693.3 vs. 0.6-11.6)	$\beta = -2.6$ (-6.15; 0.95)	Age, height, race, SES, calories and others
Hatch, EE <i>et al.</i> (2008) [94]	USA	CS	NHANES, 1999-2002; ♀(n=348)	Adults (60-80)	Urine (ID-HPLC/MS)	WC (Measured)	42.0-639.1 vs. 0.6-9.3	$\beta = -5.67$ (-9.31; -2.03)	Age, height, race, SES, calories and others
Hatch, EE <i>et al.</i> (2008) [94]	USA	CS	NHANES, 1999-2002; ♂(n=895)	Adults (20-59)	Urine (ID-HPLC/MS)	WC (Measured)	41.6 - 397.1 vs. 0.6-11.3	$\beta = 2.91$ (0.22;5.6)	Age, height, race, SES, calories and others
Hatch, EE <i>et al.</i> (2008) [94]	USA	CS	NHANES, 1999-2002; ♂(n=365)	Adults (60-80)	Urine (ID-HPLC/MS)	WC (Measured)	38.4-4363.4 vs. 0.6-10	$\beta = -2.6$ (-6.05; 0.85)	Age, height, race, SES, calories and others
Svensson, K <i>et al.</i> (2011)[95]	MEX	CS	Healthy women; ♀(n=182)	Adults (54*)	Urine (SPE/HPLC-ID-TMS)	WC (Measured)	log µg/g creatinine	$p = -0.0478$ ($p > 0.05$)	-
Waist to Hip Ratio									
Svensson, K <i>et al.</i> (2011)[95]	MEX	CS	Healthy women; ♀(n=182)	Adults (54*)	Urine (SPE/HPLC-ID-TMS)	WtHR (Measured)	log µg/g creatinine	$p = -0.002$ ($p > 0.05$)	-

Shading represents studies for which the same samples were already described in the meta-analysis plot.

CS: Cross-sectional; NHANES: National Health and Nutrition Examination Survey; SPE: Solid Phase Extraction; HPLC: High Performance Liquid


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Table 13.1.1. Description of papers assessing the association between mBP and adiposity measures in adults

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Chromatography; ID: Isotope Dilution; TMS: Tandem Mass Spectrometry; MS: Mass Spectrometry; BMI: Body Mass Index; W: Weight; H: Height; WC: Waist Circumference; WtHR: Waist to Hip Ratio; ρ : Spearman correlation coefficient; β : Beta coefficient; PA: Physical Activity; SES: Socioeconomic Status. *Mean.									

Table 13.1.2 shows the description of publications evaluating the association between mBP and adiposity measures in children. Three papers assessed the association of mBP with BMI and waist circumference [94, 96, 97] and provided six different estimates for each adiposity measure. Mixed results with no statistical significance for most estimates were observed.

Table 13.1.2. Description of papers assessing the association between mBP and adiposity measures in children

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
BMI									
Hatch, EE et al. (2008) [94]	USA	CS	NHANES, 1999–2002; ♀(n=327)	Children (6-11)	Urine (ID-HPLC/MS)	BMI (Measured W&H)	Q4(92.2-2595.3) vs. Q1(0.6-24.5)	β = 0.07 (-1.12; 1.27)	Age, height, race, SES, calories and others
Hatch, EE et al. (2008) [94]	USA	CS	NHANES, 1999–2002; ♀(n=682)	Children (12-19)	Urine (ID-HPLC/MS)	BMI (Measured W&H)	84.1-1192.9 vs.0.6-22.1	β = -0.17 (-2.24;1.7)	Age, height, race, SES, calories and others
Hatch, EE et al. (2008) [94]	USA	CS	NHANES, 1999–2002; ♂(n=329)	Children (6-11)	Urine (ID-HPLC/MS)	BMI (Measured W&H)	71.4-638.5 vs.1.5-18.4	β = 0.8 (-0.42; 2.03)	Age, height, race, SES, calories and others
Hatch, EE et al. (2008) [94]	USA	CS	NHANES, 1999–2002; ♂(n=662)	Children (12-19)	Urine (ID-HPLC/MS)	BMI (Measured W&H)	698.4-39938 vs. 0.6-80.4	β = -0.87 (-2.54; 0.79)	Age, height, race, SES, calories and others
Teitelbaum, SL et al. (2012)[96]	USA	PC	Gen. Population; ♂♀(n=361)	Children	Urine (SPE/HPLC)	BMI (Measured W&H)	Per 1-unit (ln μ g/gC)	β = 0.19 (-0.31; 0.69)	Age, sex, sedentary hours, METs, ethnicity, calories and others
Wang, H et al.	CHN	CS	Obese, OW and NW; ♂♀ (n=259)	Children (8-15)	Urine (RP-UPLC/EI-	BMI (Measured	Per 1-unit (log ng/mL)	β = 0.028 (0.001;	Age, sex


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Table 13.1.2. Description of papers assessing the association between mBP and adiposity measures in children

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
(2013)[97]					TMS)	W&H)		0.055)	
Waist Circumference									
Hatch, EE et al. (2008) [94]	USA	CS	NHANES, 1999–2002; ♀(n=327)	Children (6-11)	Urine (ID-HPLC/MS)	WC (Measured)	92.2-2595.3 vs. 0.6-24.5	$\beta=0.37$ (-2.67; 3.40)	Age, height, race, SES, calories and others
Hatch, EE et al. (2008) [94]	USA	CS	NHANES, 1999–2002; ♀(n=682)	Children (12-19)	Urine (ID-HPLC/MS)	WC (Measured)	84.1-1192.9 vs. 0.6-22.1	$\beta= -0.47$ (-4.71; 3.77)	Age, height, race, SES, calories and others
Hatch, EE et al. (2008) [94]	USA	CS	NHANES, 1999–2002; ♂(n=329)	Children (6-11)	Urine (ID-HPLC/MS)	WC (Measured)	71.4-638.5 vs. 1.5-18.4	$\beta= 1.25$ (-1.91; 4.4)	Age, height, race, SES, calories and others
Hatch, EE et al. (2008) [94]	USA	CS	NHANES, 1999–2002; ♂(n=662)	Children (12-19)	Urine (ID-HPLC/MS)	WC (Measured)	698.4-39938 vs. 0.6-80.4	$\beta= -1.47$ (-5.41; 2.48)	Age, height, race, SES, calories and others
Teitelbaum, SL et al. (2012)[96]	USA	PC	Gen. Population; ♂♀(n=361)	Children (7.34±0.89)*	Urine (SPE/HPLC)	WC (Measured)	Per 1-unit (ln µg/gC)	$\beta= 0.54$ (-0.8; 1.89)	Age, sex, sedentary hours, METs, ethnicity, calories, and others
Wang, H et al. (2013) [97]	CHN	CS	Obese, OW and NW; ♂♀(n=259)	Children (8-15)	Urine (RP-UPLC/EI-TMS)	WC (Measured)	Per 1-unit (log ng/mL)	$\beta= 0.015$ (-0.007; 0.037)	Age, sex

CS: Cross-sectional; PC: Prospective cohort; NHANES: National Health and Nutrition Examination Survey; OW: Overweight; NW: Normal weight; ID: Isotope Dilution; HPLC: High Performance Liquid Chromatography; MS: Mass Spectrometry; SPE: Solid Phase Extraction; RP- UPLC: Reversed-phase Ultra Performance Liquid Chromatography; EI: Electron Ionization; TMS: Tandem Mass Spectrometry; BMI: Body Mass Index; W. Weight; H: Height; WC: Waist Circumference; β : Beta coefficient; SES: Socioeconomic Status. *Mean±sd.

Table 13.1.3 summarizes the available data regarding the association of mBP with each adiposity measure in adults.

The overall estimate for waist circumference was negative but it did not reach statistical significance. On the contrary, the one obtained for BMI was positive and statistically significant. However, it should be taken into account that estimates included for waist circumference were provided by a single paper (Hatch, EE *et al.* (2008) [94]) and that both summary estimates presented a very high heterogeneity.


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Table 13.1.3. Summary estimates on the association between mBP with each adiposity-related measure in adults


	mBP			
	Number of included estimates	Summary Estimate*	I ²	95% CI
Adults				
Body Mass Index	7 ^a	0.13	79.2	0.02; 0.25
Waist Circumference	4 ^b	-1.19	81.2	-2.82; 0.43
Waist to Hip Ratio	1 ^c	-0.002 [†]	-	>0.05 [‡]

I² available only when meta-analysis was performed.

*Beta coefficient if not otherwise specified; [†]spearman correlation coefficient; [‡]p value.

Included papers are: ^aHuang, PC, et al. (2007) [92]; Hatch, EE et al. (2008) [94] and Brucker-Davis, F *et al.* (2010) [69];

^bHatch, EE et al. (2008) [94]; ^cSvensson, K *et al.* (2011)[95].


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13.2 Mono-(2-ethylhexyl) Phthalate (MEHP)

Twelve publications evaluated the association between MEHP and adiposity [46, 50, 92-101]. However, only two papers were eligible for meta-analysis.

Three papers provided association estimates using NHANES 1999-2002 dataset [46, 93, 94], but only Hatch, EE *et al.* (2008) [94] presented beta/correlation coefficients for BMI and was thus included in the meta-analysis. Three publications were performed among PIVUS subjects [50, 98, 99], but none presented compatible estimate measures and therefore all were excluded from meta-analysis. Buser, M *et al.* (2014a) [101] was also excluded for presenting ORs, while Svensson, K *et al.* (2013) [95] and Dirtu, AC *et al.* (2013) [100] were excluded for providing coefficients for log transformed variables. Finally, Teitelbaum, SL *et al.* (2013) [96] and Wang, H *et al.* (2013) [97] were excluded from the analysis for being performed among children.

Two publications providing six estimates were included in the meta-analysis [92, 94]. Hatch, EE *et al.* (2008) [94] provided estimates for both adults and children, but only those considering adult individuals were included in the analysis. Huang, PC *et al.* (2007) [92] presented stratified results for the exposure level (higher and lower) and both estimates were included in the meta-analysis plot. Both papers presented a cross-sectional design and evaluated BMI as the adiposity measure. The overall beta coefficient was -0.11 (95% CI -0.27; 0.04), with a percentage of variance of $I^2 = 65.1\%$ (figure 13.2).

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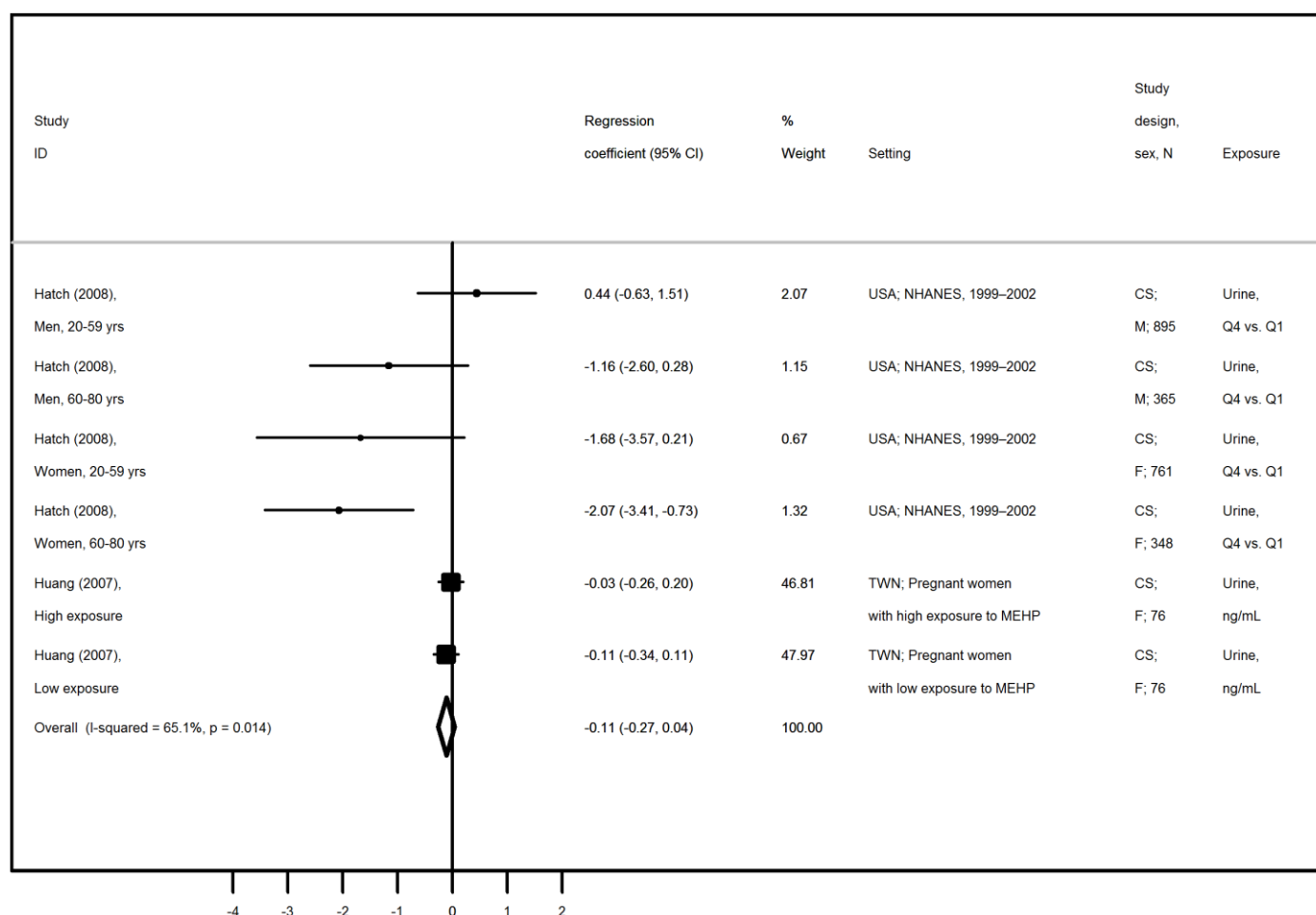


Figure 13.2. Meta-analysis of publications evaluating the association of MEHP with adiposity in adults. Beta coefficients and corresponding 95% CI (horizontal lines). The size of the black square indicates the study's weight in the analysis (weights are from fixed-effects analysis). The centre of the open diamond indicates the summary estimate and its width represents the 95% CI.



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Table 13.2.1 shows the description of papers that evaluated the association between MEHP and BMI in adults but were excluded from meta-analysis (presented in figure 13.2). In general, all estimates were negative but did not reach statistical significance.

Table 13.2.1. Description of papers assessing the association between MEHP and BMI not eligible for meta-analysis

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Svensson, K et al. (2011) [95]	MEX	CS	Gen. Population; ♀(n=182)	Adults (54*)	Urine (SPE/HPLC-IDTMS)	BMI (Measured W&H)	log µg/g creatinine	p= -0.0668 (p>0.05)	-
Lind, PM et al. (2012) [99]	SWE	CS	PIVUS 2001-2003; ♀(n=479)	Adults (70y.o.)	Serum (LC-TMS)	BMI†	Per 1-unit (log ng/mL)	β= 0.1 (-0.2; 0.41)	Education, exercise, TC, TG, smoking
Lind, PM et al. (2012) [99]	SWE	CS	PIVUS 2001-2003; ♂(n=482)	Adults (70y.o.)	Serum (LC-TMS)	BMI†	Per 1-unit (log ng/mL)	β= -0.034 (-0.26; 0.19)	Education, exercise, TC, TG, smoking
Olsen, L et al. (2012)	SWE	CS	PIVUS; ♂♀(n=1016)	Adults (70-70)	Serum (LC/TM)	BMI†	log ng/mL	β= 0.001 (-0.18; 0.18)	Gender, TC, TG, HT, smoking, DM
Buser, M et al. (2014a) [101]	USA	CS	NHANES 2007-2010; ♂♀(n=757)	Adults (43.9*)	Urine (SPE-HPLC-TMS)	BMI (measured W&H)	>27.91 vs. ≤2.03	OR= 0.84 (0.55; 1.29)	Age, sex, race, calories, and others

CS: Cross-sectional; PIVUS: Prospective Investigation of the Vasculature in Uppsala Seniors; NHANES: National Health and Nutrition Examination Survey; OW: Overweight; NW: Normal Weight; LC: Liquid Chromatography; TMS: Tandem Mass Spectrometry; SPE: Solid Phase Extraction; HPLC: High Performance Liquid Chromatography; BMI: Body Mass Index; W: Weight; H: Height; β: Beta coefficient; OR: Odds ratio; TG: Triglycerides; TC: Total Cholesterol; SES: Socioeconomic Status; MET: Metabolic Equivalent; *Mean; †No further information.

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	Author(s): V Mendes; I Delgado; B Peleteiro; J Araújo; H Barros; E Ramos; D Sarigiannis; N Baiz; I Annesi-Maesano	Version: 1	146/221

The description of papers addressing the association between MEHP and other adiposity measures in adults is presented in table 13.2.2. Most provided estimates evaluated the association with waist circumference. Lind, PM *et al.* (2012) [99] was the only paper providing estimates for fat mass and found positive associations but with no statistical significance. Regarding waist circumference, we have identified fourteen estimates [46, 50, 93-95, 99, 101], but only four reached statistical significance and all of them presented a negative association. On the other hand, results on waist to hip ratio and visceral/subcutaneous adipose tissue were all positive, but with no statistical significance [95, 99].


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Table 13.2.2. Description of papers assessing the association between MEHP and other adiposity measures in adults

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment ^t	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Fat Mass									
Lind, PM et al. (2012)[99]	SWE	CS	PIVUS 2001-2003; ♀(n=431)	Adults (70y.o.)	Serum (LC-TMS)	FM (DXA)	Per 1-unit (log ng/mL)	β= 468 (-159; 1096)	Education, TC, TG, exercise, smoking
Lind, PM et al. (2012) [99]	SWE	CS	PIVUS 2001-2003; ♂(n=410)	Adults (70y.o.)	Serum (LC-TMS)	FM (DXA)	Per 1-unit (log ng/mL)	β= 12 (-527;552)	Education, TC, TG, exercise, smoking
Waist Circumference									
Lee, DH et al. (2007) [46]	USA	CS	NHANES, 1999–2002; ♀♂(n=721)	Adults (≥20)	Serum (HRGC/IDHRMS)	WC (measured) ♂>102; ♀>88 cm	>75th vs. BDL	OR= 0.3 (0.1;0.5)	Age, sex, race, PIR, smoking, alcohol, exercise
Stahlhut, RW et al. (2007) [93]	USA	CS	NHANES, 1999-2002; ♂(n=651)	Adults (≥19)	Urine (HPLC/ID-MS)	WC (measured)	log µg/g creatinine	β= 0.62 (p=0.17)	Age, race, fat, PA, calories, smoking, creatinine
Hatch, EE et al. (2008) [94]	USA	CS	NHANES, 1999–2002; ♀(n=761)	Adults (20-59)	Urine (ID-HPLC/MS)	WC (Measured)	8.4-392.5 vs.0.7-1.4	β= -2.17 (-5.99; 1.65)	Age, height, race, SES, calories and others
Hatch, EE et al. (2008) [94]	USA	CS	NHANES, 1999–2002; ♀(n=348)	Adults (60-80)	Urine (ID-HPLC/MS)	WC (Measured)	4.4-145.6 vs.0.7-0.8	β= -4.15 (-7.48; -0.81)	Age, height, race, SES, calories and others
Hatch, EE et al. (2008) [94]	USA	CS	NHANES, 1999–2002; ♂(n=895)	Adults (20-59)	Urine (ID-HPLC/MS)	WC (Measured)	10.0-615.6 vs. 0.7-1.8	β= 0.91 (-1.43; 3.24)	Age, height, race, SES, calories and others
Hatch, EE et al. (2008) [94]	USA	CS	NHANES, 1999–2002; ♂(n=365)	Adults (60-80)	Urine (ID-HPLC/MS)	WC (Measured)	5.9-204.2 vs. 0.7-0.8	β= 0.68 (-7.42; 8.78)	Age, height, race, SES, calories and others
Svensson, K et al. (2011) [95]	MEX	CS	Gen. Population; ♀(n=182)	Adults (54*)	Urine (SPE/HPLC-IDTMS)	WC (Measured)	log µg/g creatinine	ρ= -0.0236 (p>0.05)	-
Lee, DH et al. (2012) [50]	SWE	CS	PIVUS, 2001-2004; ♂(n=490)	Adults (≥70)	Whole blood; (HRGC/HRMS)	WC (Measured) ♂> 102cm	236.3-636.4 vs.5.0-120.2 (pg/ml)	OR= 0.5 (0.2; 1.0)	Calories, exercise, smoking, TG, TC, alcohol
Lee, DH et al. (2012) [50]	SWE	CS	PIVUS, 2001-2004; ♀(n=480)	Adults (≥70)	Whole blood; (HRGC/HRMS)	WC (measured) ♀>88cm	236.3-636.4 vs.5.0-120.2 (pg/ml)	OR= 0.2 (0.1;0.4)	Calories, exercise, smoking, TG, TC, alcohol
Lee, DH et al. (2012) [50]	SWE	PC	PIVUS, 2001-2009; ♂(n=306)	Adults (≥75)	Whole blood; (HRGC/HRMS)	WC (Measured) ♂> 102cm	236.3-636.4 vs.5.0-120.2 (pg/ml)	OR= 0.3 (0.1;0.9)	Calories, exercise, smoking, TG, TC, alcohol
Lee, DH et al. (2012) [50]	SWE	PC	PIVUS, 2001-2009; ♀(n=2005)	Adults (≥75)	Whole blood; (HRGC/HRMS)	WC (Measured) ♀>88cm	236.3-636.4 vs.5.0-120.2 (pg/ml)	OR= 0.4 (0.1; 1.1)	Calories, exercise, smoking, TG, TC, alcohol
Lind, PM et al. (2012) [50]	SWE	CS	PIVUS 2001-2003; ♀(n=479)	Adults (70y.o.)	Serum (LC-TMS)	WC	Per 1-unit (log ng/mL)	β= 0.34 (-0.39; 1.1)	Education, TC, TG, exercise, smoking
Lind, PM et al. (2012) [50]	SWE	CS	PIVUS 2001-2003; ♂(n=482)	Adults (70y.o.)	Serum (LC-TMS)	WC	Per 1-unit (log ng/mL)	β= -0.27 (-0.91; 0.37)	Education, TC, TG, exercise, smoking


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Table 13.2.2. Description of papers assessing the association between MEHP and other adiposity measures in adults

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Dirtu;AC et al. (2013) [100]	BEL	CS	Obese individuals; ♂♀(n=152)	Adults (18-84)	Urine (LC)	WC (measured)	ln ng/mL	β= -0.05 (p=0.567)	Age, sex
Dirtu;AC et al. (2013) [100]	BEL	CS	Normal-weight controls ♂♀n=43	Adults (19-59)	Urine (LC)	WC (measured)	ln ng/mL	β= -0.1 (p=0.529)	Age, sex
Buser, M et al. (2014a) [101]	USA	CS	NHANES 2007-2010; ♂♀(n=757)	Adults (43.9*)	Urine (SPE-HPLC-TMS)	WC† (measured)	>27.91 vs. ≤2.03	OR=1.02 (0.78; 1.34)	Age, sex, race, calories and others

Waist to Hip Ratio

Svensson, K et al. (2011) [95]	MEX	CS	Gen. Population; ♀(n=182)	Adults (54*)	Urine (SPE/HPLC-IDTMS)	WtHR (Measure)	log µg/g creatinine	ρ= 0.0336 (p>0.05)	-
Lind, PM et al. (2012) [99]	SWE	CS	PIVUS 2001-2003; ♀(n=479)	Adults (70y.o.)	Serum (LC-TMS)	WtHR†	Per 1-unit (log ng/mL)	β= 0.002 (-0.002; 0.006)	Education, TC, TG, exercise, smoking
Lind, PM et al. (2012) [99]	SWE	CS	PIVUS 2001-2003; ♂(n=482)	Adults (70y.o.)	Serum (LC-TMS)	WtHR†	Per 1-unit (log ng/mL)	β= 0.004 (0.000; 0.009)	Education, exercise, TC, TG, smoking

Visceral Adipose Tissue and Subcutaneous Adipose Tissue

Lind, PM et al. (2012) [99]	SWE	CS	PIVUS 2001-2003; ♀(n=135)	Adults (70y.o.)	Serum (LC-TMS)	VAT (MRI)	Per 1-unit (log ng/mL)	β= 4.1 (-2.2; 10)	Education, exercise, TC, TG, smoking
Lind, PM et al. (2012) [99]	SWE	CS	PIVUS 2001-2003; ♂(n=144)	Adults (70y.o.)	Serum (LC-TMS)	VAT (MRI)	Per 1-unit (log ng/mL)	β= 3.3 (-4.9; 11)	Education, exercise, TC, TG, smoking
Lind, PM et al. (2012) [99]	SWE	CS	PIVUS 2001-2003; ♀(n=135)	Adults (70y.o.)	Serum (LC-TMS)	SAT (MRI)	Per 1-unit (log ng/mL)	β= 4.8 (-10; 20)	Education, exercise, TC, TG, smoking
Lind, PM et al. (2012) [99]	SWE	CS	PIVUS 2001-2003; ♂(n=144)	Adults (70y.o.)	Serum (LC-TMS)	SAT (MRI)	Per 1-unit (log ng/mL)	β= 0.44 (-9.6; 10)	Education, exercise, TC, TG, smoking

Shading represents papers for which the same samples were already described in the meta-analysis plot. CS: Cross-sectional; PC: Prospective Cohort; PIVUS: Prospective Investigation of the Vasculature in Uppsala Seniors; NHANES: National Health and Nutrition Examination Survey; LC: Liquid Chromatography; TMS: Tandem Mass Spectrometry; HRGC: High Resolution Gas Chromatography; ID-HRMS: Isotope Dilution High Resolution Mass Spectrometry; HPLC: High Performance Liquid Chromatography; MS: Mass Spectrometry; SPE: Solid Phase Extraction; FM: Fat Mass; DXA: Dual-energy X-ray Absorptiometry; WC: Waist Circumference; WtHR: Waist to Hip Ratio; SAT: Subcutaneous Adipose Tissue; MRI: Magnetic Resonance Imaging; VAT: Visceral Adipose Tissue; BDL: Below detected levels; β: Beta coefficient; OR: Odds ratio; TG: Triglycerides; TC: Total Cholesterol; PIR: Poverty Index Ratio; PA: Physical Activity; SES: Socioeconomic Status. *Mean±sd. †No further information;


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Table 13.2.3 presented the description of publications assessing the association between MEHP and adiposity measures in children. Seven estimates were identified assessing the association of MEHP with BMI and waist circumference [94, 96, 97, 101]. Wang, H *et al.* (2013) [97] was the only paper presenting statistically significant associations ($\beta = 0.058$, 95% CI 0.024; 0.092 and $\beta = 0.043$, 95% CI 0.016; 0.07 for BMI and waist circumference, respectively).

Table 13.2.3. Description of papers assessing the association between MEHP and other adiposity measures in children

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
BMI									
Hatch, EE et al. (2008) [94]	USA	CS	NHANES, 1999–2002; ♀(n=327)	Children (6-11)	Urine (ID-HPLC/MS)	BMI (Measured W&H)	11.1-314.3 vs. 0.7-2.4	$\beta = -0.9$ (-2.51; 0.71)	Age, height, race, SES, calories and others
Hatch, EE et al. (2008) [94]	USA	CS	NHANES, 1999–2002; ♀(n=682)	Children (12-19)	Urine (ID-HPLC/MS)	BMI (Measured W&H)	11.2-549.2 vs. 0.7-2.2	$\beta = -1.51$ (-2.81; -0.21)	Age, height, race, SES, calories and others
Hatch, EE et al. (2008) [94]	USA	CS	NHANES, 1999–2002; ♂(n=329)	Children (6-11)	Urine (ID-HPLC/MS)	BMI (Measured W&H)	11.7-196.3 vs. 0.7-2.1	$\beta = -0.22$ (-1.32; 0.89)	Age, height, race, SES, calories and others
Hatch, EE et al. (2008) [94]	USA	CS	NHANES, 1999–2002; ♂(n=662)	Children (12-19)	Urine (ID-HPLC/MS)	BMI (Measured W&H)	8.6-273.4 vs. 0.7-1.7	$\beta = -0.5$ (-1.95; 0.94)	Age, height, race, SES, calories and others
Teitelbaum, SL et al. (2012)[96]	USA	PC	Gen. Population; ♂♀(n=361)	Children	Urine (SPE/HPLC)	BMI (Measured W&H)	Per 1-unit (ln µg/gC)	$\beta = -0.03$ (-0.38; 0.31)	Age, sex, education, METs, ethnicity, calories, and others
Wang, H et al. (2013)[97]	CHN	CS	Obese, OW and NW; ♂♀(n=259)	Children (8-15)	Urine (RP-UPLC/EI-TMS)	BMI (Measured W&H)	Per 1-unit (log ng/mL)	$\beta = 0.058$ (0.024; 0.092)	Age, sex
Buser, M et al. (2014a) [101]	USA	CS	NHANES 2007-2010; ♂♀(n=548)	Children (11.9*)	Urine (SPE-HPLC-TMS)	BMI z-score (measured W&H)	>27.91 vs. ≤2.03	OR= 0.84 (0.39; 1.8)	Age, sex, race, calories, and others



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Table 13.2.3. Description of papers assessing the association between MEHP and other adiposity measures in children

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Waist Circumference									
Hatch, EE et al. (2008) [94]	USA	CS	NHANES, 1999–2002; ♀(n=327)	Children (6-11)	Urine (ID-HPLC/MS)	WC (Measured)	11.1-314.3 vs. 0.7-2.4	$\beta = -2.51$ (-6.52; 1.49)	Age, height, race, SES, calories and others
Hatch, EE et al. (2008) [94]	USA	CS	NHANES, 1999–2002; ♀(n=682)	Children (12-19)	Urine (ID-HPLC/MS)	WC (Measured)	11.2-549.2 vs. 0.7-2.2	$\beta = -2.18$ (-4.99; 0.63)	Age, height, race, SES, calories and others
Hatch, EE et al. (2008) [94]	USA	CS	NHANES, 1999–2002; ♂(n=329)	Children (6-11)	Urine (ID-HPLC/MS)	WC (Measured)	11.7-196.3 vs. 0.7-2.1	$\beta = -0.2$ (-2.98; 2.57)	Age, height, race, SES, calories and others
Hatch, EE et al. (2008) [94]	USA	CS	NHANES, 1999–2002; ♂(n=662)	Children (12-19)	Urine (ID-HPLC/MS)	WC (Measured)	8.6-273.4 vs. 0.7-1.7	$\beta = -1.39$ (-5.15; 2.37)	Age, height, race, SES, calories and others
Teitelbaum, SL et al. (2012)[96]	USA	PC	Gen. Population; ♂♀(n=361)	Children (7.34±0.89*)	Urine (SPE/HPLC)	WC (Measured)	Per 1-unit (ln µg/gC)	$\beta = 0.06$ (-0.85; 0.98)	Age, sex, education, METs, ethnicity, calories, and others
Wang, H et al. (2013)[97]	CHN	CS	Obese, OW and NW; ♂♀(n=259)	Children (8-15)	Urine (RP-UPLC/ EI-TMS)	WC (Measured)	Per 1-unit (log ng/mL)	$\beta = 0.043$ (0.016; 0.07)	Age, sex
Buser, M et al. (2014a) [101]	USA	CS	NHANES 2007-2010; ♂♀(n=548)	Children (11.9*)	Urine (SPE-HPLC-TMS)	WC (measured)	>27.91 vs. ≤2.03	OR= 0.84 (0.41; 1.72)	Age, sex, race, calories and others

CS: Cross-sectional; PC: Prospective cohort; NHANES: National Health and Nutrition Examination Survey; OW: Overweight; NW: Normal Weight; ID-HPLC: Isotope Dilution High Performance Liquid Chromatography; MS: Mass Spectrometry; SPE: Solid Phase Extraction; RP-UPLC: Reversed-phase Ultra Performance Liquid Chromatography; EI: Electrospray Ionization; TMS: Tandem Mass Spectrometry; BMI: Body Mass Index; W: Weight; H: Height; WC: Waist Circumference; β : Beta coefficient; OR: Odds ratio; SES: Socioeconomic Status; METs: Metabolic Equivalents. *Mean±sd.

Table 13.2.4 presents data for the association of MEHP with each adiposity measure in adults. Results indicate no association between MEHP and adiposity. Summary estimates for waist circumference and waist to hip ratio were similar to the one found for BMI – a weak negative association, with no statistical significance. On the other hand, estimates for fat mass, visceral and subcutaneous adipose tissue were all positive; however, they derive from a single publication [99]. It also should be noted that summary estimates presented for adiposity measures other than BMI were

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obtained only from coefficients derived from log transformed variables and therefore their

Table 13.2.4. Summary estimates for the association between MEHP with each adiposity measure in adults

	MEHP			
	Number of included estimates	Summary Estimate*	I ² (%)	95% CI
Body Mass Index	6 ^a	-0.11	65.1	-0.27; 0.04
Fat Mass	2 ^b	205.81	14.3	-203.27; 614.89
Waist Circumference	5 ^c	-0.04	0.0	-0.14; 0.06
Waist to Hip Ratio	2 ^b	-0.00	55.9	-0.00; 0.00
Visceral Adipose Tissue	2 ^b	3.80	0.0	-1.04; 8.64
Subcutaneous Adipose Tissue	2 ^b	1.74	0.0	-6.46; 9.95

I² available only when meta-analysis was performed. *Beta coefficient if not otherwise specified.

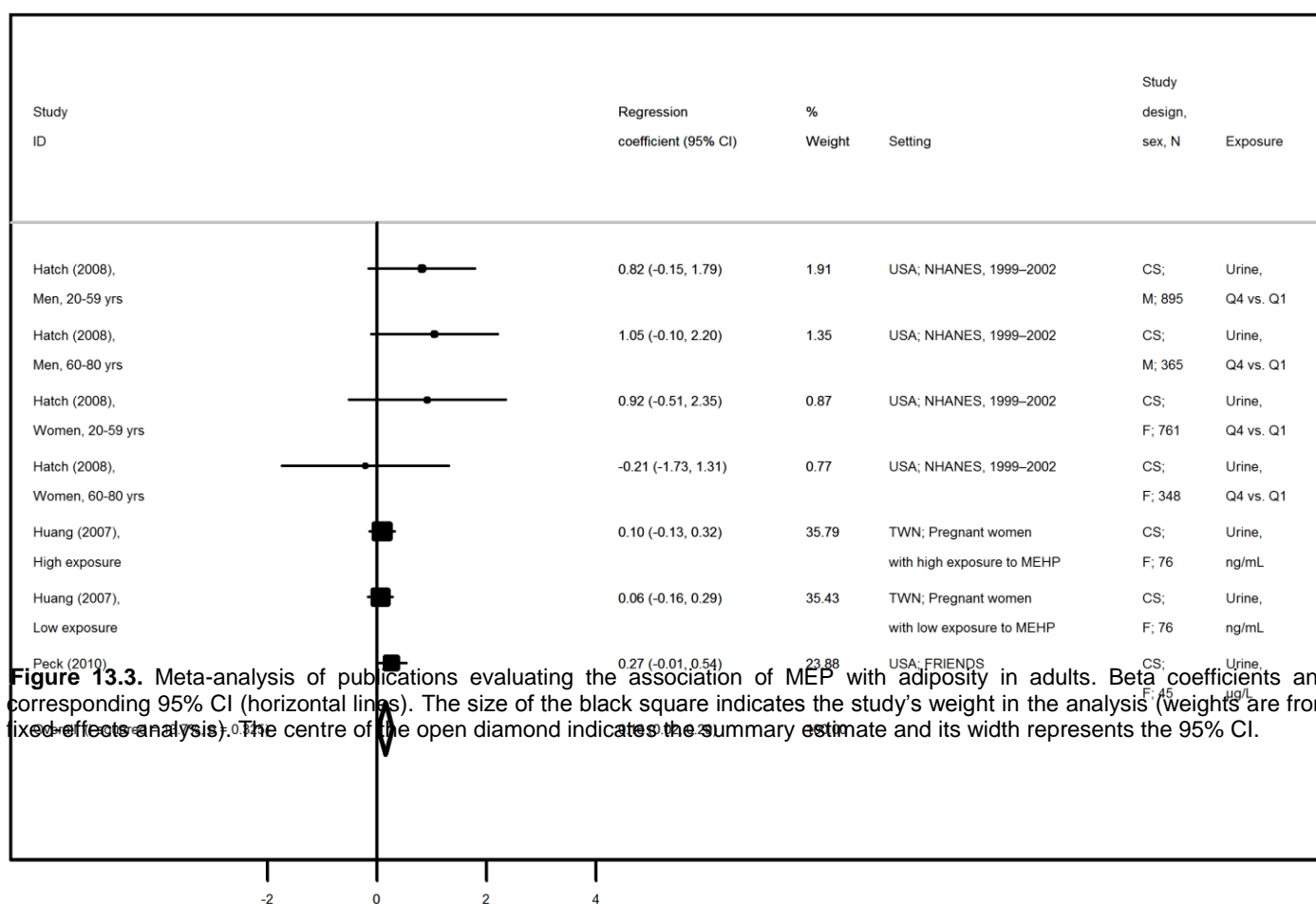
Included studies are: ^aHuang, PC et al. (2007)[92], Hatch, EE et al. (2008)[94]; ^bLind, PM et al. (2012)[99]; ^cHatch, EE et al. (2008)[94], Svensson, K et al. (2011)[95], Lind, PM et al. (2012)[99] and Dirtu, AC et al. (2013)[100];


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13.3 Mono-ethyl Phthalate (MEP)

Nine publications addressing the association between MEP and adiposity were identified in the systematic review [92-96, 98-100, 102]. Two publications were excluded from meta-analysis [93, 99]. Stahlhut, RW *et al.* (2007) [93] and Hatch, EE *et al.* (2008) [94] were performed among NHANES 1999-2002 participants and Hatch, EE *et al.* (2008) [94] was included in the meta-analysis for presenting beta/correlation coefficients for BMI. Olsen, L *et al.* (2012) [98] and Lind, PM *et al.* (2012) [99] both included PIVUS subjects, but none of the two was included in the analysis since both presented estimates for log transformed variables. Svensson, K *et al.* (2011) [95] and Dirtu, AC *et al.* (2013) [100] were excluded for the same reason. Teitelbaum, SL *et al.* (2012) [96] was excluded from meta-analysis for being performed among children.

Three papers were then included in the meta-analysis, from which seven estimates were extracted. All publications presented estimates for BMI and had a cross-sectional approach. The overall regression coefficient was $\beta = 0.16$ (95% CI 0.02;



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0.29) and the percentage of variance was relatively low ($I^2 = 13.7\%$) (figure 13.3).


Table 13.3.1 shows the description of papers that evaluated BMI but were excluded from meta-analysis (presented in figure 13.3). In general, all estimates were positive but with no statistical significance. The only exception was observed in Svensson, K *et al.* (2011) [95] ($p = -0.0473$, $p > 0.05$).

Table 13.3.1. Description of papers assessing the association between MEP and BMI not eligible for meta-analysis

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Svensson, K <i>et al.</i> (2011) [95]	MEX	CS	Gen. Population; ♀(n=182)	Adults (54*)	Urine (SPE/HPLC-IDTMS)	BMI (Measured W&H)	log µg/g creatinine	$\rho = -0.0473$ ($p > 0.05$)	-
Lind, PM <i>et al.</i> (2012) [99]	SWE	CS	PIVUS 2001-2003; ♀(n=479)	Adults (70y.o.)	Serum (LC-TMS)	BMI†	Per 1-unit (log ng/mL)	$\beta = 0.008$ (-0.67; 0.69)	Education, exercise, TC, TG, smoking
Lind, PM <i>et al.</i> (2012) [99]	SWE	CS	PIVUS 2001-2003; ♂(n=482)	Adults (70y.o.)	Serum (LC-TMS)	BMI†	Per 1-unit (log ng/mL)	$\beta = 0.31$ (-0.097; 0.72)	Education, exercise, TC, TG, smoking
Olsen, L <i>et al.</i> (2012) [98]	SWE	CS	PIVUS; ♂♀(n=1016)	Adults (70-70)	Serum (LC/TM)	BMI†	log ng/mL	$\beta = 0.197$ (-0.17; 0.56)	Gender, TC, TG, HT, smoking, DM

CS: Cross-sectional; PC: Prospective Cohort; PIVUS: Prospective Investigation of the Vasculature in Uppsala Seniors; NHANES: National Health and Nutrition Examination Survey; LC: Liquid Chromatography; TMS: Tandem Mass Spectrometry; HPLC: High Performance Liquid Chromatography; MS: Mass Spectrometry; SPE: Solid Phase Extraction; BMI: Body Mass Index; W: Weight; H: Height; β : Beta coefficient; TC: Total Cholesterol; TG: Triglycerides; SES: Socioeconomic Status. †No further information.

Table 13.3.2 shows the description of papers assessing the association between MEP and other adiposity measures in adults. Shading represents results obtained from populations already included in the above-presented forest plot. Results have in general observed a similar pattern to that found with BMI, suggesting no

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association between MEP and adiposity. The only statistically significant association was found in Lind, PM *et al.* (2012) [99] for visceral and subcutaneous adipose tissue in PIVUS participants.


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Table 13.3.2. Description of papers assessing the associations between MEP and adiposity measures in adults

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Fat Mass									
Lind, PM et al. (2012) [99]	SWE	CS	PIVUS 2001-2003; ♀(n=431)	Adults (70y.o.)	Serum (LC-TMS)	FM (DXA)	Per 1-unit (log ng/mL)	β= -469 (-1877; 938)	Education, exercise, TC, TG, smoking
Lind, PM et al. (2012) [99]	SWE	CS	PIVUS 2001-2003; ♂(n=410)	Adults (70y.o.)	Serum (LC-TMS)	FM (DXA)	Per 1-unit (log ng/mL)	β= 269 (-776; 1315)	Education, exercise, TC, TG, smoking
Waist Circumference									
Stahlhut, RW et al. (2007)[93]	USA	CS	NHANES, 1999-2002; ♂(n=651)	Adults (≥19)	Urine (HPLC/ID-MS)	WC (measured)	log µg/g creatinine	β= 0.77 (p=0.013)	Age, race, fat, calories, PA, smoking, creatinine
Hatch, EE et al. (2008) [94]	USA	CS	NHANES, 1999-2002; ♀(n=761)	Adults (20-59)	Urine (ID-HPLC/MS)	WC (Measured)	512.9-21932.2 vs. 1.7-90.5	β= 2.07 (-0.72; 4.85)	Age, height, race, SES, calories and others
Hatch, EE et al. (2008) [94]	USA	CS	NHANES, 1999-2002; ♀(n=348)	Adults (60-80)	Urine (ID-HPLC/MS)	WC (Measured)	424.0-14346.1 vs. 3.4-55.6	β= -0.22 (-3.49; 3.04)	Age, height, race, SES, calories and others
Hatch, EE et al. (2008) [94]	USA	CS	NHANES, 1999-2002; ♂(n=895)	Adults (20-59)	Urine (ID-HPLC/MS)	WC (Measured)	698.4-39938 vs. 0.6-80.4	β= 2.19 (-0.51; 4.9)	Age, height, race, SES, calories and others
Hatch, EE et al. (2008) [94]	USA	CS	NHANES, 1999-2002; ♂(n=365)	Adults (60-80)	Urine (ID-HPLC/MS)	WC (Measured)	799.5-16995.2 vs. 0.6-51.5	β= 1.68 (-1.75; 5.1)	Age, height, race, SES, calories and others
Svensson, K et al. (2011)[95]	MEX	CS	Gen. Population; ♀(n=182)	Adults (54*)	Urine (SPE/HPLC-IDTMS)	WC (Measured)	log µg/g creatinine	ρ= -0.0361 (p>0.05)	-
Lind, PM et al. (2012) [99]	SWE	CS	PIVUS 2001-2003; ♀(n=474)	Adults (70y.o.)	Serum (LC-TMS)	WC	Per 1-unit (log ng/mL)	β= -0.8 (-2.4; 0.81)	
Lind, PM et al. (2012) [99]	SWE	CS	PIVUS 2001-2003; ♂(n=478)	Adults (70y.o.)	Serum (LC-TMS)	WC	Per 1-unit (log ng/mL)	β= 0.73 (-0.45; 1.9)	Education, exercise, TC, TG smoking
Dirtu;AC et al. (2013) [100]	BEL	CS	Obese individuals; ♂♀(n=152)	Adults (18-84)	Urine (LC)	WC (measured)	ln ng/mL	β= -0.04 (p=0.673)	Age, sex
Dirtu;AC et al. (2013) [100]	BEL	CS	Normal-weight controls ♂♀(n=43)	Adults (19-59)	Urine (LC)	WC (measured)	ln ng/mL	β= -0.22 (p=0.157)	Age, sex
Waist to Hip Ratio									
Svensson, K et al. (2011)[95]	MEX	CS	Gen. Population; ♀(n=182)	Adults (54*)	Urine (SPE/HPLC-IDTMS)	WtHR (Measured WC & HC)	log µg/g creatinine	ρ= -0.0414 (p>0.05)	-
Lind, PM et al.	SWE	CS	PIVUS 2001-	Adults	Serum	WtHR†	Per 1-unit	β= -0.008	Education,



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Table 13.3.2. Description of papers assessing the associations between MEP and adiposity measures in adults

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
al. (2012) [99]	SWE	CS	2003; ♀(n=474)	(70y.o.)	(LC-TMS)		(log ng/mL)	(-0.016; 0.001)	exercise, TC, TG, smoking
Lind, PM et al. (2012) [99]			PIVUS 2001-2003; ♂(n=478)	Adults (70y.o.)	Serum (LC-TMS)	WtHR†	Per 1-unit (log ng/mL)	β= 0.005 (-0.003; 0.012)	Education, exercise, TC, TG, smoking
Visceral Adipose Tissue and Subcutaneous Adipose Tissue									
Lind, PM et al. (2012) [99]	SWE	CS	PIVUS 2001-2003; ♀(n=135)	Adults (70y.o.)	Serum (LC-TMS)	VAT (MRI)	Per 1-unit (log ng/mL)	β= 3.6 (-11; 19)	Education, exercise, TC, TG, smoking
Lind, PM et al. (2012) [99]	SWE	CS	PIVUS 2001-2003; ♂(n=144)	Adults (70y.o.)	Serum (LC-TMS)	VAT (MRI)	Per 1-unit (log ng/mL)	β= 16 (0.49; 32)	Education, exercise, TC, TG, smoking
Lind, PM et al. (2012) [99]	SWE	CS	PIVUS 2001-2003; ♀(n=135)	Adults (70y.o.)	Serum (LC-TMS)	SAT (MRI)	Per 1-unit (log ng/mL)	β= 12 (-24; 48)	Education, exercise, TC, TG, smoking
Lind, PM et al. (2012) [99]	SWE	CS	PIVUS 2001-2003; ♂(n=144)	Adults (70y.o.)	Serum (LC-TMS)	SAT (MRI)	Per 1-unit (log ng/mL)	β= 9.2 (-10; 29)	Education, exercise, TC, TG, smoking

Shading represents papers for which the same samples were already described in the meta-analysis plot. CS: Cross-sectional; PIVUS: Prospective Investigation of the Vasculature in Uppsala Seniors; NHANES: National Health and Nutrition Examination Survey; LC: Liquid Chromatography; TMS: Tandem Mass Spectrometry; HPLC: High Performance Liquid Chromatography; ID-MS: Isotope Dilution Mass Spectrometry; SPE: Solid Phase Extraction; FM: Fat Mass; DXA: Dual-energy X-ray Absorptiometry; WC: Waist Circumference; WtHR: Waist to Hip Ratio; VAT: Visceral Adipose Tissue; MRI: Magnetic Resonance Imaging; SAT: Subcutaneous Adipose Tissue; β: Beta coefficient; TC: Total Cholesterol; TG: Triglycerides; PA: Physical Activity; SES: Socioeconomic Status. *Mean±sd; †No further information.

The description of publications assessing the association between MEP and adiposity measures in children is shown in table 13.3.3. Hatch, EE *et al.* (2008) [94],

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that provided sex-stratified results, found negative, but not statistically significant associations among boys and positive associations for girls, but with statistical significance only in the 12-19 years old age group. Teitelbaum, SL *et al.* (2012) [96] have also found a positive but not significant association between MEP and waist circumference among children from both sexes ($\beta = 0.51$, 95% CI -0.45; 1.46).

Table 13.3.3. Description of papers assessing the associations between MEP and adiposity measures in children

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
BMI									
Hatch, EE et al. (2008) [94]	USA	CS	NHANES, 1999–2002; ♀(n=327)	Children (6-11)	Urine (ID-HPLC/MS)	BMI (Measured W&H)	1836.9-30710 vs. 0.6-54.4	$\beta = 0.3$ (-1.22; 1.81)	Age, height, race, SES, calories and others
Hatch, EE et al. (2008) [94]	USA	CS	NHANES, 1999–2002; ♀(n=682)	Children (12-19)	Urine (ID-HPLC/MS)	BMI (Measured W&H)	694.5-39631.7 vs. 5.9-110.6	$\beta = 1.74$ (-0.02; 3.49)	Age, height, race, SES, calories and others
Hatch, EE et al. (2008) [94]	USA	CS	NHANES, 1999–2002; ♂(n=329)	Children (6-11)	Urine (ID-HPLC/MS)	BMI (Measured W&H)	194.4-9043.6 vs. 4.7-39.0	$\beta = -0.02$ (-1.49; 1.46)	Age, height, race, SES, calories and others
Hatch, EE et al. (2008) [94]	USA	CS	NHANES, 1999–2002; ♂(n=662)	Children (12-19)	Urine (ID-HPLC/MS)	BMI (Measured W&H)	525.9-12359 vs. 0.6-72.7	$\beta = -0.13$ (-1.63; 1.37)	Age, height, race, SES, calories and others
Teitelbaum, SL et al. (2012)[96]	USA	PC	Gen. Population; ♂♀(n=361)	Children	Urine (SPE/HPLC)	BMI (Measured W&H)	Per 1-unit (ln µg/gC)	$\beta = 0.19$ (-0.17; 0.55)	Age, sex, education, METs, ethnicity, calories, and others
Waist Circumference									
Hatch, EE et al. (2008)	USA	CS	NHANES, 1999–2002; ♀(n=327)	Children (6-11)	Urine (ID-HPLC/MS)	WC (Measured)	30710-1836. vs. 0.6-54.4	$\beta = 1.05$ (-3.3; 5.4)	Age, height, race, SES,


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Table 13.3.3. Description of papers assessing the associations between MEP and adiposity measures in children

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
[94]									calories and others
Hatch, EE et al. (2008) [94]	USA	CS	NHANES, 1999–2002; ♀(n=682)	Children (12-19)	Urine (ID-HPLC/MS)	WC (Measured)	694.5-39631.7 vs. 5.9-110.6	$\beta = 4.11$ (0.37; 78.86)	Age, height, race, SES, calories and others
Hatch, EE et al. (2008) [94]	USA	CS	NHANES, 1999–2002; ♂(n=329)	Children (6-11)	Urine (ID-HPLC/MS)	WC (Measured)	11.7-196.3 vs. 0.6-51.5	$\beta = -0.67$ (-4.42; 3.09)	Age, height, race, SES, calories and others
Hatch, EE et al. (2008) [94]	USA	CS	NHANES, 1999–2002; ♂(n=662)	Children (12-19)	Urine (ID-HPLC/MS)	WC (Measured)	525.9-12359 vs. 0.6-72.7	$\beta = -1.2$ (-5.14; 2.74)	Age, height, race, SES, calories and others
Teitelbaum, SL et al. (2012)[96]	USA	PC	Gen. Population; ♂♀(n=361)	Children (7.34±0.89*)	Urine (SPE/HPLC)	WC (Measured)	Per 1-unit (ln µg/gC)	$\beta = 0.51$ (-0.45; 1.46)	Age, sex, education, METs, ethnicity, calories and others

CS: Cross-sectional; PC: Prospective cohort; NHANES: National Health and Nutrition Examination Survey; HPLC: High Performance Liquid Chromatography; MS: Mass Spectrometry; SPE: Solid Phase Extraction; BMI: Body Mass Index; W: Weight; H: Height; WC: Waist Circumference; β : Beta coefficient; SES: Socioeconomic Status; METs: Metabolic Equivalents. *Mean±sd.

Summary estimates for the association of MEP with each adiposity measure in adults are presented in table 13.3.4. Estimates presented in this table for other adiposity measures are not directly comparable to the one calculated for BMI, since they include only coefficients from log transformed variables.

Overall estimates for waist circumference and waist to hip ratio were weak and did not reach statistical significance, indicating no association between MEP and these adiposity measures. Estimates for fat mass, visceral and subcutaneous adipose tissue were positive, but also not statistically significant and they were derived from a single

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paper (Lind, PM *et al.* (2012) [99]) that has in general provided unusually strong associations, compared to results observed in other publications.

Table 13.3.4. Summary estimates for the association between MEP and each adiposity measure in adults

	MEP			
	Number of included estimates	Summary Estimate*	I ² (%)	95% CI
Adults				
Body Mass Index	7 ^a	0.16	13.7	0.02; 0.29
Fat Mass	2 ^b	6.59	0.0	-832.69; 845.86
Waist Circumference	5 ^c	-0.06	0.0	-0.16; 0.04
Waist to Hip Ratio	3 ^d	-0.00	62.6	-0.01; 0.00
Visceral Adipose Tissue	2 ^b	9.50	19.9	-1.37; 20.36
Subcutaneous Adipose Tissue	2 ^b	9.84	0.0	-7.31; 26.98

I² available only when meta-analysis was performed. *Beta coefficient if not otherwise specified.

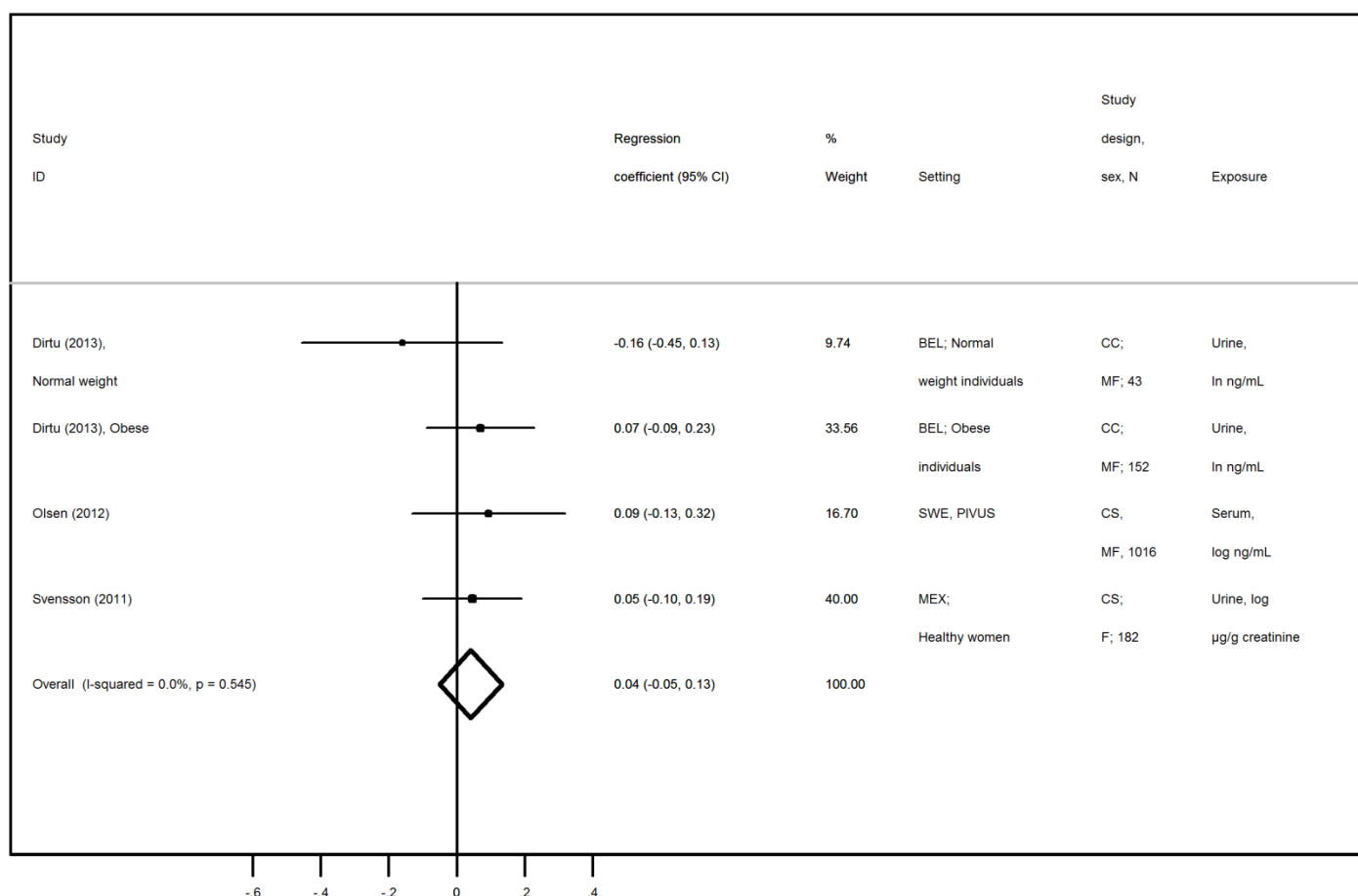
Included studies are: ^aHuang, PC *et al.* (2007)[92], Hatch, EE *et al.* (2008)[94], Peck *et al.* (2010) [102]; ^bLind, PM *et al.* (2012)[99]; ^cSvensson, K *et al.* (2011)[95], Lind, PM *et al.* (2012)[99] and Dirtu, AC *et al.* (2013)[100]; ^dSvensson, K *et al.* (2011)[95] and Lind, PM *et al.* (2012)[99].

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13.4 Mono-iso-butyl Phthalate (MiBP)

MiBP was assessed as the exposure compound in seven papers [95-101]. Both Olsen *et al.* (2012) [98] and Lind, PM *et al.* (2012) [99] were performed among PIVUS participants. Olsen, L *et al.* (2012) [98] was included for having a larger sample size. Buser, M *et al.* (2014a) [101] was excluded for providing estimates as ORs. Wang, H *et al.* (2013) [97] and Teitelbaum, SL *et al.* (2012) [96] were also excluded for being performed among children.

Three papers were then included in the meta-analysis [95, 98, 100], presented in figure 13.4. All the estimates provided by included publications presented regression coefficients for log transformed variables. The overall beta coefficient was 0.04 (95% CI -0.05; 0.13) and the heterogeneity was 0.0%. Dirtu, AC *et al.* (2013) [100] was the only paper assessing waist circumference, while Olsen, L *et al.* (2012) [98] and Svensson, K *et al.* (2011) [95] measured BMI.




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Figure 13.4. Meta-analysis of publications evaluating the association of MiBP with adiposity in adults. Beta coefficients and corresponding 95% CI (horizontal lines). The size of the black square indicates the study's weight in the analysis (weights are from fixed-effects analysis). The centre of the open diamond indicates the summary estimate and its width represents the 95% CI.

Table 13.4.1 presents the description of papers providing estimates for the association between MiBP and adiposity in adults, not included in the meta-analysis presented in figure 13.4. Lind, PM *et al.* (2012) [99], who provided sex-stratified results, observed a negative association in men from PIVUS ($\beta = -0.083$, 95% CI -0.35; 0.19) and a positive association among women ($\beta = 0.39$, 95% CI 0.002; 0.79). Buser, M *et al.* (2014a) [101] also found a positive association among NHANES 2007-2010 individuals (OR= 1.4; 95% CI 0.9; 2.16). Fat mass was measured only in Lind, PM *et al.* (2012) [99] who described results similar to those reported for BMI in the same sample. Svensson, K *et al.* (2011) [95], Lind, PM *et al.* (2012) [99] and Buser, M *et al.* (2014a) [101] evaluated the association between MiBP and waist circumference. The two estimates provided including only women were positive [95, 99], while the only estimate including exclusively men was negative, but with no statistical significance [99]. Buser, M *et al.* (2014a) [101] included adults from both sexes and found a positive association but with no statistical significance (OR= 1.18, 95% CI 0.79; 1.78). These results suggest a positive effect on women but a negative effect in men, however they should be read with caution since various estimates are from the same study and therefore it is expected that they present the same pattern of association even with different adiposity measures.


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Table 13.4.1. Description of papers assessing the association between MiBP and adiposity measures in adults

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
BMI									
Lind, PM et al. (2012) [99]	SWE	CS	PIVUS 2001-2003; ♀(n=479)	Adults (70y.o.)	Serum (LC-TMS)	BMI†	Per 1-unit (log ng/mL)	β= 0.39 (0.002; 0.79)	Education, exercise, TC, TG, smoking
Lind, PM et al. (2012) [99]	SWE	CS	PIVUS 2001-2003; ♂(n=482)	Adults (70y.o.)	Serum (LC-TMS)	BMI†	Per 1-unit (log ng/mL)	β= -0.083 (-0.35; 0.19)	Education, exercise, TC, TG, smoking
Buser, M et al. (2014a) [101]	USA	CS	NHANES 2007-2010; ♂♀(n=757)	Adults (43.9*)	Urine (SPE-HPLC-TMS)	BMI z-score (measured W&H)	>218.73 vs. ≤27.74	OR= 1.4 (0.9; 2.16)	Age, race, calorie s, cotinine, creatinine, income
Fat Mass									
Lind, PM et al. (2012) [99]	SWE	CS	PIVUS 2001-2003; ♀(n=431)	Adults (70y.o.)	Serum (LC-TMS)	FM (DXA)	Per 1-unit (log ng/mL)	β= 1079 (283; 1875)	Education, exercise, TC, TG, smoking
Lind, PM et al. (2012) [99]	SWE	CS	PIVUS 2001-2003; ♂(n=410)	Adults (70y.o.)	Serum (LC-TMS)	FM (DXA)	Per 1-unit (log ng/mL)	β= -73 (-754; 608)	Education, exercise, TC, TG, smoking
Waist Circumference									
Svensson, K et al. (2011)[95]	MEX	CS	Gen. Population; ♀(n=182)	Adults (54*)	Urine (SPE/HPLC-IDTMS)	WC (Measured)	log µg/g creatinine	ρ= 0.0151 (p>0.05)	-
Lind, PM et al. (2012) [99]	SWE	CS	PIVUS 2001-2003; ♀(n=474)	Adults (70y.o.)	Serum (LC-TMS)	WC	Per 1-unit (log ng/mL)	β= 1.3 (0.425; 2.3)	Education, exercise, TC, TG, smoking
Lind, PM et al. (2012) [99]	SWE	CS	PIVUS 2001-2003; ♂(n=478)	Adults (70y.o.)	Serum (LC-TMS)	WC	Per 1-unit (log ng/mL)	β= -0.025 (-0.8; 0.75)	Education, exercise, TC, TG, smoking
Buser, M et al. (2014a) [104]	USA	CS	NHANES 2007-2010; ♂♀(n=757)	Adults (43.9*)	Urine (SPE-HPLC-TMS)	WC (Measured)	>218.73 vs. ≤27.74	OR= 1.18 (0.79; 1.78)	Age, sex, race, calories, education, smoking, alcohol, DM
Waist to Hip Ratio									
Svensson, K et al. (2011)[95]	MEX	CS	Gen. Population; ♀(n=182)	Adults (54*)	Urine (SPE/HPLC-IDTMS)	WtHR (Measured WC&HC)	log µg/g creatinine	ρ= -0.0156 (p>0.05)	-
Lind, PM et al. (2012) [99]	SWE	CS	PIVUS 2001-2003; ♀(n=474)	Adults (70y.o.)	Serum (LC-TMS)	WtHR†	Per 1-unit (log ng/mL)	β= 0.004 (0.000; 0.009)	Education, exercise, TC, TG, smoking
Lind, PM et al. (2012) [99]	SWE	CS	PIVUS 2001-2003; ♂(n=478)	Adults (70y.o.)	Serum (LC-TMS)	WtHR†	Per 1-unit (log ng/mL)	β= 0.001 (-0.004; 0.005)	Education, exercise, TC, TG, smoking
Visceral Adipose Tissue and Subcutaneous Adipose Tissue									
Lind, PM et al. (2012) [99]	SWE	CS	PIVUS 2001-2003; ♀(n=135)	Adults (70y.o.)	Serum (LC-TMS)	VAT (MRI)	Per 1-unit (log ng/mL)	β= 14 (1.4; 26)	Education, exercise, TC, TG, smoking


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Table 13.4.1. Description of papers assessing the association between MiBP and adiposity measures in adults

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Lind, PM et al. (2012) [99]	SWE	CS	PIVUS 2001-2003; ♂(n=144)	Adults (70y.o.)	Serum (LC-TMS)	VAT (MRI)	Per 1-unit (log ng/mL)	$\beta = -5.9$ (-24; 13)	Education, exercise, TC, TG, smoking
Lind, PM et al. (2012) [99]	SWE	CS	PIVUS 2001-2003; ♀(n=135)	Adults (70y.o.)	Serum (LC-TMS)	SAT (MRI)	Per 1-unit (log ng/mL)	$\beta = 52$ (24; 81)	Education, exercise, TC, TG, smoking
Lind, PM et al. (2012) [99]	SWE	CS	PIVUS 2001-2003; ♂(n=144)	Adults (70y.o.)	Serum (LC-TMS)	SAT (MRI)	Per 1-unit (log ng/mL)	$\beta = -11$ (-24; 13)	Education, exercise, TC, TG, smoking

Shading represents studies for which the same samples were already described in the meta-analysis plot. CS: Cross-sectional; PC: Prospective cohort; PIVUS: Prospective Investigation of the Vasculature in Uppsala Seniors; NHANES: National Health and Nutrition Examination Survey; LC: Liquid Chromatography; TMS: Tandem Mass Spectrometry; SPE: Solid Phase Extraction; FM: Fat Mass; DXA: Dual-energy X-ray absorptiometry; WC: Waist Circumference; WtHR: Waist to Hip Ratio; VAT: Visceral Adipose Tissue; MRI: Magnetic Resonance Imaging; SAT: Subcutaneous Adipose Tissue; β : Beta coefficient; OR: Odds Ratio; TC: Total Cholesterol; TG: Triglycerides; DM: Diabetes Mellitus. *Mean \pm sd; †No further information.

Table 13.4.2 shows the description of papers addressing the association between MiBP and adiposity measures in children. Three studies were identified but only Wang, H *et al.* (2013) [97] observed significant associations ($\beta = 0.027$, 95% CI 0.006; 0.048 and $\beta = 0.022$, 95% CI 0.005; 0.038 for BMI and waist circumference, respectively). The other two papers found no significant associations: one showed a positive [101] while the other observed an inverse association [96]. In Teitelbaum, SL *et al.* (2012) [96], urinary MiBP was negatively associated with BMI and waist circumference.

Table 13.4.2. Description of papers assessing the association between MiBP and adiposity measures in children

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
BMI									
Teitelbaum, SL et al. (2012)[96]	USA	PC	Gen. Population; ♂♀(n=361)	Children (7.34 \pm 0.89*)	Urine (SPE/HPLC)	BMI (Measured W&H)	Per 1-unit (ln μ g/gC)	$\beta = -0.27$ (-0.73; 0.18)	Age, sex, education,, METs, ethnicity, calories, and others
Wang, H et al. (2013) [97]	CHN	CS	Obese, OW and NW; ♂♀(n=259)	Children (8-15)	Urine (RP-UPLC/ EI-TMS)	BMI (Measured W&H)	Per 1-unit (log ng/mL)	$\beta = 0.027$ (0.006; 0.048)	Age, sex
Buser, M et al. (2014a) [104]	USA	CS	NHANES 2007-2010; ♂♀(n=548)	Children (11.9*)	Urine (SPE-HPLC-TMS)	BMI z-score (measured W&H)	>218.73 vs. \leq 27.74	OR=1.82 (0.73; 4.57)	Age, race, calories, cotinine,


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Table 13.4.2. Description of papers assessing the association between MiBP and adiposity measures in children

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Waist Circumference									
Teitelbaum, SL et al. (2012)[96]	USA	PC	Gen. Population; ♂♀(n=361)	Children (7.34±0.89*)	Urine (SPE/HPLC)	WC (Measured)	Per 1-unit (ln µg/gC)	β= -0.62 (-1.84; 0.61)	Age, sex, education, METs, ethnicity, calories, and others
Wang, H et al. (2013) [97]	CHN	CS	Obese, OW and NW; ♂♀(n=259)	Children (8-15)	Urine (RP-UPLC/EI-TMS)	WC (Measured)	Per 1-unit (log ng/mL)	β= 0.022 (0.005; 0.038)	Age, sex
Buser, M et al. (2014a) [104]	USA	CS	NHANES 2007-2010; ♂♀(n=548)	Children (11.9*)	Urine (SPE-HPLC-TMS)	WC (Measured)	>218.73 vs. ≤27.74	OR= 1.85 (0.78; 4.4)	Age, race, calories, cotinine, creatinine, income


Prospective Cohort; CS: Cross-sectional OW: Overweight; NW: Normal Weight; NHANES: National Health and Nutrition Examination Survey; SPE: Solid Phase Extraction; HPLC: High Performance Liquid Chromatography; RP-UPLC: Reversed-phase Ultra Performance Liquid Chromatography, EI: Electron Ionization; TMS: Tandem Mass Spectrometry; WC: Waist Circumference; β: Beta coefficient; OR: Odds Ratio; METs: Metabolic Equivalents. *Mean±sd.

Available results on the association between MiBP and each adiposity measure in adults is summarized in table 13.4.3. Overall estimates for BMI, waist circumference and waist to hip ratio were positive but very weak and had no statistical significance. Estimates for fat mass, visceral and subcutaneous adipose tissue were strong and positive, but also not statistically significant. However, it should be taken into account that these estimates were derived from a single paper (Lind, PM *et al.* (2012) [99]).

These results suggest that MiBP levels are not associated with adiposity.

Table 13.4.3. Summary estimates for the association between MiBP and each adiposity measure in adults


MiBP

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	Number of included estimates	Summary Estimate*	I ² (%)	95% CI
Body Mass Index	2 ^a	0.06	0.0	-0.06; 0.18
Fat Mass	2 ^b	413.85	78.5	-103.61; 931.30
Waist Circumference	5 ^c	0.03	55.3	-0.07; 0.13
Waist to Hip Ratio	3 ^d	0.00	0.0	-0.00; 0.01
Visceral Adipose Tissue	2 ^b	7.90	67.6	-2.34; 18.14
Subcutaneous Adipose Tissue	2 ^b	13.85	91.2	-4.05; 31.75

I² available only when meta-analysis was performed.*Beta coefficient if not otherwise specified.

Included studies are: ^aSvensson, K et al. (2011)[95] and Olsen, L et al. (2012)[98] ; ^bLind, PM et al. (2012)[99]; ^cSvensson, K et al. (2011)[95], Lind, PM et al. (2012)[99] and Dirtu, AC et al. (2013)[100]; ^dSvensson, K et al. (2011)[95] and Lind, PM et al. (2012)[99].

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13.5 Mono-methyl Phthalate (MMP)

In the systematic review, five publications were identified evaluating the association between MMP and adiposity [92, 97-100]. However, since most results were based on PIVUS participants, those five papers did not provide a sufficient number of compatible measures in order to perform a meta-analysis.

Table 13.5.1 shows the description of papers assessing the association between MMP and adiposity among adults. In general, all results have shown positive associations, with the exception of Huang, PC *et al.* (2007) [92] that observed negative correlations although with no statistical significance.

Table 13.5.1. Description of papers assessing the association between MMP and adiposity measures in adults

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
BMI									
Huang, PC et al. (2007) [92]	TWN	CS	Pregnant women; ♀(n=76)	Adults (33.6±3.3*)	Urine (HPLC-ESI-MS/MS)	Prepregnancy BMI (self-reported)	ng/mL	ρ= -0.006 (p>0.05)	-
Huang, PC et al. (2007) [92]	TWN	CS	Pregnant women; ♀(n=76)	Adults (33.6±3.3*)	Urine (HPLC-ESI-MS/MS)	Prepregnancy BMI (self-reported)	ng/mL	ρ= -0.129 (p>0.05)	-
Lind, PM et al. (2012) [99]	SWE	CS	PIVUS 2001-2003; ♀(n=479)	Adults (70y.o.)	Serum (LC-TMS)	BMI†	Per 1-unit (log ng/mL)	β= 0.28 (-0.095; 0.66)	Education, exercise, TC, TG, smoking
Lind, PM et al. (2012) [99]	SWE	CS	PIVUS 2001-2003; ♂(n=482)	Adults (70y.o.)	Serum (LC-TMS)	BMI†	Per 1-unit (log ng/mL)	β= 0.33 (0.051; 0.61)	Education, exercise, TC, TG, smoking
Olsen, L et al. (2012) [98]	SWE	CS	PIVUS; ♂♀(n=1016)	Adults (70y.o.)	Serum (LC/TM)	BMI†	log ng/mL	β= 0.246 (0.02; 0.47)	Gender, TC, TG, HT, DM smoking
Fat Mass									
Lind, PM et al. (2012) [99]	SWE	CS	PIVUS 2001-2003; ♀(n=431)	Adults (70y.o.)	Serum (LC-TMS)	FM (DXA)	Per 1-unit (log ng/mL)	β= 705 (-179; 1484)	Education, exercise, TC, TG, smoking
Lind, PM et al. (2012) [99]	SWE	CS	PIVUS 2001-2003; ♂(n=410)	Adults (70y.o.)	Serum (LC-TMS)	FM (DXA)	Per 1-unit (log ng/mL)	β= 365 (-340; 1071)	Education, exercise, TC, TG, smoking
Waist Circumference									
Lind, PM et al. (2012) [99]	SWE	CS	PIVUS 2001-2003; ♀(n=474)	Adults (70y.o.)	Serum (LC-TMS)	WC	Per 1-unit (log ng/mL)	β= 0.98 (0.09; 1.9)	Education, exercise, TC, TG, smoking
Lind, PM et al. (2012) [99]	SWE	CS	PIVUS 2001-2003; ♂(n=478)	Adults (70y.o.)	Serum (LC-TMS)	WC	Per 1-unit (log ng/mL)	β= 0.97 (0.17; 1.78)	Education, exercise, TC, TG, smoking


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Table 13.5.1. Description of papers assessing the association between MMP and adiposity measures in adults

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Dirtu, AC et al. (2013) [100]	BEL	CS	Obese individuals; ♂♀(n=152)	Adults (18-84)	Urine (LC)	WC (Measured)	ln ng/mL	β= 0.17 (p=0.045)	Age, sex
Dirtu, AC et al. (2013) [100]	BEL	CS	Normal-weight controls; ♂♀(n=43)	Adults (19-59)	Urine (LC)	WC (Measured)	ln ng/mL	β= 0.11 (p=0.49)	Age, sex
Waist to Hip Ratio									
Lind, PM et al. (2012) [99]	SWE	CS	PIVUS 2001-2003; ♀(n=474)	Adults (70y.o.)	Serum (LC-TMS)	WtHR†	Per 1-unit (log ng/mL)	β= 0.005 (0.000; 0.009)	Education, exercise, TC, TG, smoking
Lind, PM et al. (2012) [99]	SWE	CS	PIVUS 2001-2003; ♂(n=478)	Adults (70y.o.)	Serum (LC-TMS)	WtHR†	Per 1-unit (log ng/mL)	β= 0.006 (0.001; 0.011)	Education, exercise, TC, TG, smoking
Visceral Adipose Tissue and Subcutaneous Adipose Tissue									
Lind, PM et al. (2012) [99]	SWE	CS	PIVUS 2001-2003; ♀(n=135)	Adults (70y.o.)	Serum (LC-TMS)	VAT (MRI)	Per 1-unit (log ng/mL)	β= 6.9 (-3.4; 17)	Education, exercise, TC, TG, smoking
Lind, PM et al. (2012) [99]	SWE	CS	PIVUS 2001-2003; ♂(n=144)	Adults (70y.o.)	Serum (LC-TMS)	VAT (MRI)	Per 1-unit (log ng/mL)	β= 5.2 (-5.7; 16)	Education, exercise, TC, TG, smoking
Lind, PM et al. (2012) [99]	SWE	CS	PIVUS 2001-2003; ♀(n=135)	Adults (70y.o.)	Serum (LC-TMS)	SAT (MRI)	Per 1-unit (log ng/mL)	β= 27 (3.1; 52)	Education, exercise, TC, TG, smoking
Lind, PM et al. (2012) [99]	SWE	CS	PIVUS 2001-2003; ♂(n=144)	Adults (70y.o.)	Serum (LC-TMS)	SAT (MRI)	Per 1-unit (log ng/mL)	β= 5.4 (-7.9; 19)	Education, exercise, TC, TG, smoking

CS: Cross-sectional; PIVUS: Prospective Investigation of the Vasculature in Uppsala Seniors; LC: Liquid Chromatography; TMS: Tandem Mass Spectrometry; BMI: Body Mass Index; FM: Fat Mass; DXA: Dual-energy X-ray absorptiometry; WC: Waist Circumference; WtHR: Waist to Hip Ratio; SAT: Subcutaneous Adipose Tissue; MRI: Magnetic Resonance Imaging; VAT: Visceral Adipose Tissue; β: Beta coefficient; TC: Total Cholesterol; TG: Triglycerides. †No further information.


Table 13.5.2 shows the description of the paper that has assessed the association between MMP and adiposity among children, which found no association neither with BMI nor with waist circumference.

Table 13.5.2. Description of papers assessing the association between MMP and adiposity measures in children

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Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
BMI									
Wang, H et al. (2013) [97]	CHN	CS	Obese, OW and NW; ♂♀(n=259)	Children (8-15)	Urine (RP-UPLC/EI-TMS)	BMI (Measured W&H)	Per 1-unit (log ng/mL)	$\beta = 0.01$ (-0.016; 0.036)	Age, sex
Waist Circumference									
Wang, H et al. (2013) [97]	CHN	CS	Obese, OW and NW; ♂♀(n=259)	Children (8-15)	Urine (RP-UPLC/EI-TMS)	WC (Measured)	Per 1-unit (log ng/mL)	$\beta = 0.005$ (-0.016; 0.025)	Age, sex


CS: Cross-sectional; RP-UPLC: Reversed-Phase Ultra Performance Liquid Chromatography; EI: Electron Ionization; TMS: Tandem Mass Spectrometry; BMI: Body Mass Index; W: Weight; H: Height; WC: Waist Circumference; β : Beta coefficient.

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	Author(s): V Mendes; I Delgado; B Peleteiro; J Araújo; H Barros; E Ramos; D Sarigiannis; N Baiz; I Annesi-Maesano	Version: 1	169/221

13.6 Mono-benzyl Phthalate (MBzP)

In the systematic review we have identified seven publications assessing the association between MBzP and adiposity [92-96, 100, 101]. Two papers provided association estimates using NHANES 1999-2002 dataset [93, 94], but only Hatch, EE *et al.* (2008) [94] presented beta/correlation coefficients for BMI and was thus included in the meta-analysis. Buser, M *et al.* (2014a) [101] was excluded for presenting estimates as ORs, while Svensson, K *et al.* (2011) [95] and Dirtu, AC *et al.* (2013) [100] were excluded for presenting estimates for log transformed variables. Finally, Teitelbaum, SL *et al.* (2012) [96] was excluded for being performed among children.

Two publications providing a total of six estimates were included in this meta-analysis [92, 94]. Hatch, EE *et al.* (2008) [94] provided sex- and age-stratified estimates for both adults and children, but only those considering adult individuals were included in the analysis. Although Huang, PC *et al.* (2007) [92] included pregnant women, results were based in pre-pregnancy BMI values. Stratified estimates according to the exposure level (higher and. lower) were reported and both were included in the meta-analysis. The overall beta coefficient was -0.07 (95% CI -0.22; 0.09), showing no association between MBzP and adiposity (figure 13.6.1).

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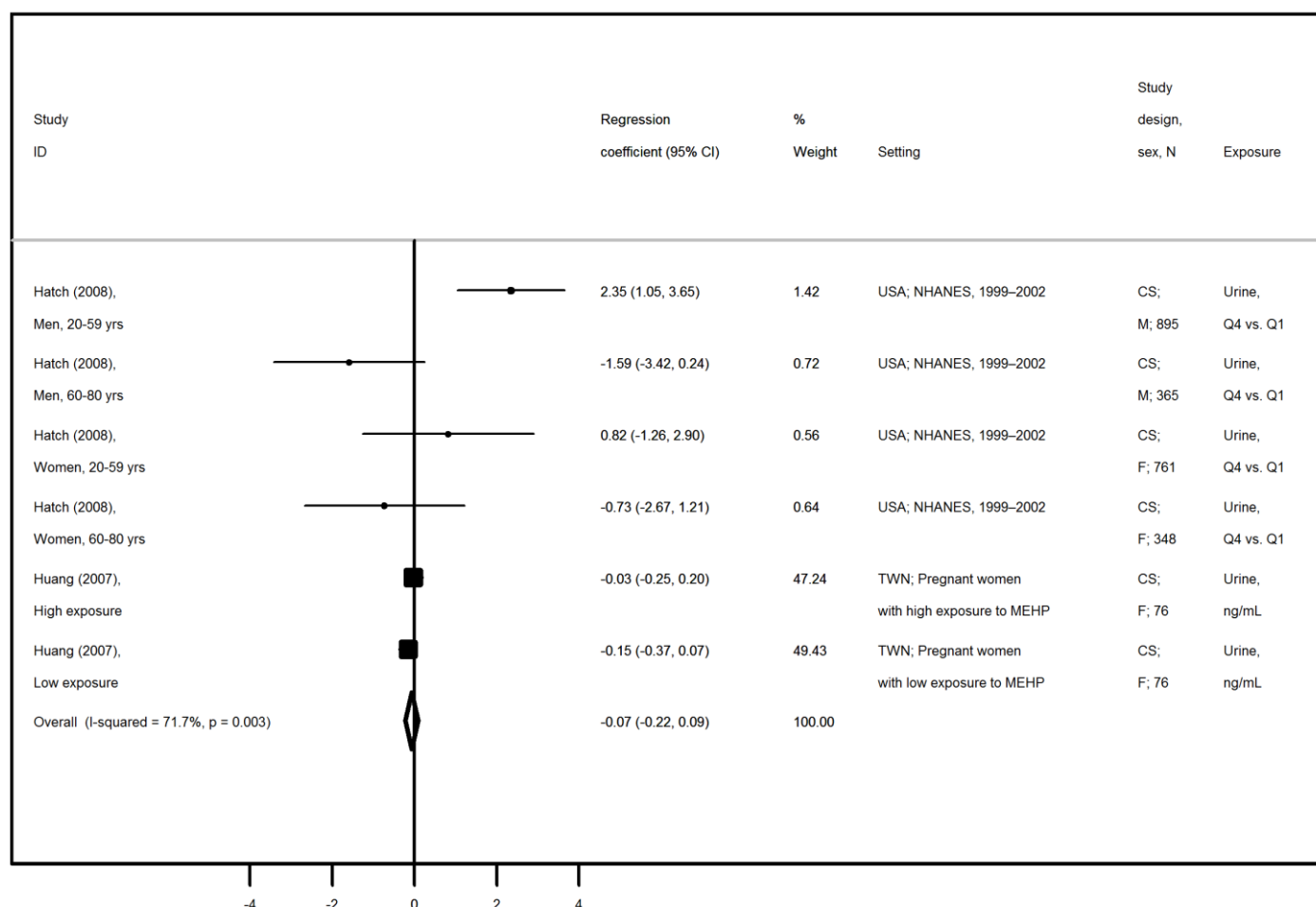


Figure 13.6.1. Meta-analysis of publications evaluating the association of MBzP with adiposity in adults. Beta coefficients and corresponding 95% CI (horizontal lines). The size of the black square indicates the study's weight in the analysis (weights are from fixed-effects analysis). The centre of the open diamond indicates the summary estimate and its width represents the 95% CI.


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Table 13.6.1 shows the description of papers evaluating the association between MBzP and adiposity measures in adults not included in the meta-analysis presented in figure 13.6.1. Lines in shading represent estimates provided for populations already represented in the forest plot. Buser, M *et al.* (2014a) [101] was the only assessing BMI that was not included in the meta-analysis. They observed a positive, but not statistically significant, association in NHANES 2007-2010 adult individuals. Regarding other adiposity measures, only two papers found statistically significant associations: Stahlhut, RW *et al.* (2007) [93] ($\beta = 1.29$, $p = 0.001$) and Hatch, EE *et al.* (2008) [94] ($\beta = 6.63$; 95% CI 3.42; 9.84), both regarding waist circumference and performed in NHANES 1999-2002 study.

Table 13.6.1. Description of papers assessing the association between MBzP and adiposity measures in adults

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
BMI									
Svensson, K <i>et al.</i> (2011)[95]	MEX	CS	Gen. Population; ♀(n=182)	Adults (54*)	Urine (SPE/HPLC-IDTMS)	BMI (Measured W&H)	log µg/g creatinine	$p = -0.0059$ ($p > 0.05$)	-
Buser, M <i>et al.</i> (2014a) [101]	USA	CS	NHANES 2007-2010; ♂♀(n=757)	Adults (43.9*)	Urine (SPE-HPLC-TMS)	BMI (measured W&H)	>143.04 vs. ≤2.66	OR= 1.09 (0.8; 1.47)	Age, sex, race, calories, education, smoking, alcohol, diabetes
Waist Circumference									
Stahlhut, RW <i>et al.</i> (2007)[93]	USA	CS	NHANES, 1999-2002; ♂(n=651)	Adults (≥19)	Urine (HPLC/ID-MS)	WC (Measured)	log µg/g creatinine	$\beta = 1.29$ ($p = 0.001$)	Age, race, fat, calories, PA, smoking, creatinine
Hatch, EE <i>et al.</i> (2008)[94]	USA	CS	NHANES, 1999-2002; ♀(n=761)	Adults (20-59)	Urine (ID-HPLC/MS)	WC (Measured)	29.8-1009.4 vs. 0.2-5.6	$\beta = 3.18$ (-0.9; 7.26)	Age, height, race, SES, calories and others
Hatch, EE <i>et al.</i> (2008) [94]	USA	CS	NHANES, 1999-2002; ♀(n=348)	Adults (60-80)	Urine (ID-HPLC/MS)	WC (Measured)	42-639.1 vs. 0.2-3.7	$\beta = -2.41$ (-6.65; 1.84)	Age, height, race, SES, calories and others
Hatch, EE <i>et al.</i> (2008) [94]	USA	CS	NHANES, 1999-2002; ♂(n=895)	Adults (20-59)	Urine (ID-HPLC/MS)	WC (Measured)	30.9-1197.6 vs. 0.2-7.3	$\beta = 6.63$ (3.42; 9.84)	Age, height, race, SES, calories and others
Hatch, EE <i>et al.</i> (2008) [94]	USA	CS	NHANES, 1999-2002; ♂(n=365)	Adults (60-80)	Urine (ID-HPLC/MS)	WC (Measured)	25.3-414.8 vs. 0.2-4.7	$\beta = -3.18$ (-7.64; 1.28)	Age, height, race, SES, calories and


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	Author(s): V Mendes; I Delgado; B Peleteiro; J Araújo; H Barros; E Ramos; D Sarigiannis; N Baiz; I Annesi-Maesano		Version: 1 172/221

Table 13.6.1. Description of papers assessing the association between MBzP and adiposity measures in adults

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Svensson, K et al. (2011)[95]	MEX	CS	Gen. Population; ♀(n=182)	Adults (54*)	Urine (SPE/HPLC-IDTMS)	WC (Measured)	log µg/g creatinine	ρ= -0.0063 (p>0.05)	-
Dirtu, AC et al. (2013) [100]	BEL	CS	Obese individuals; ♂♀(n=152)	Adults (18-84)	Urine (LC)	WC (Measured)	ln ng/mL	β= 0.12 (p=0.159)	Age, sex
Dirtu, AC et al. (2013) [100]	BEL	CS	Normal-weight controls; ♂♀(n=43)	Adults (19-59)	Urine (LC)	WC (Measured)	ln ng/mL	β= -0.11 (p=0.479)	Age, sex
Buser, M et al. (2014a) [101]	USA	CS	NHANES 2007-2010; ♂♀(n=757)	Adults (43.9*)	Urine (SPE-HPLC-TMS)	WC (Measured)	>143.04 vs. ≤2.66	OR= 0.88 (0.64; 1.21)	Age, sex, race, calories, education, smoking, alcohol, diabetes

Waist to Hip Ratio

Svensson, K et al. (2011)[95]	MEX	CS	Gen. Population; ♀(n=182)	Adults (54*)	Urine (SPE/HPLC-IDTMS)	WtHR (Measured)	log µg/g creatinine	ρ= 0.0883 (p>0.05)	-
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Shading represents papers for which the same samples were already described in the meta-analysis plot.

CS: Cross-sectional; NHANES: National Health and Nutrition Examination Survey; SPE: Solid Phase Extraction; HPLC: High Performance Liquid Chromatography; TMS: Tandem Mass Spectrometry; ID: Isotope Dilution; MS: Mass Spectrometry; BMI: Body Mass Index; W: Weight; H: Height; OR: Odds ratio; β: Beta coefficient; PA: Physical Activity; SES: Socioeconomic Status.*Mean±sd; †No further information.

The description of papers evaluating the association between MBzP and adiposity measures among children is presented in table 13.6.2. None of the estimates showed a significant effect for neither BMI nor waist circumference.

Table 13.6.2. Description of papers assessing the associations between MBzP and adiposity measures in children

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
BMI									
Hatch, EE et al. (2008)[94]	USA	CS	NHANES, 1999–2002; ♀(n=327)	Children (6-11)	Urine (ID-HPLC/MS)	BMI (Measured W&H)	68.8-1685 vs.0.6-14.4	β= 0.52 (-0.89; 1.92)	Age, height, race, SES, calories and others


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Table 13.6.2. Description of papers assessing the associations between MBzP and adiposity measures in children

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Hatch, EE et al. (2008)[94]	USA	CS	NHANES, 1999–2002; ♀(n=682)	Children (12-19)	Urine (ID-HPLC/MS)	BMI (Measured W&H)	56.9-739.7 vs. 0.2-11	$\beta = 0.84$ (-0.97; 2.65)	Age, height, race, SES, calories and others
Hatch, EE et al. (2008) [94]	USA	CS	NHANES, 1999–2002; ♂(n=329)	Children (6-11)	Urine (ID-HPLC/MS)	BMI (Measured W&H)	77.0-721.9 vs. 0.4-15	$\beta = -0.13$ (-1.53; 1.28)	Age, height, race, SES, calories and others
Hatch, EE et al. (2008) [94]	USA	CS	NHANES, 1999–2002; ♂(n=662)	Children (12-19)	Urine (ID-HPLC/MS)	BMI (Measured W&H)	54.6-969.9 vs. 0.6-16.4	$\beta = 0.84$ (-0.47; 2.15)	Age, height, race, SES, calories and others
Teitelbaum, SL et al. (2012)[96]	USA	PC	Gen. Population; ♂♀(n=361)	Children	Urine (SPE/HPLC)	BMI (Measured W&H)	Per 1-unit (ln µg/gC)	$\beta = -0.5$ (-1.51; 0.51)	Age, sex, education, METs, ethnicity, calories, and others
Buser, M et al. (2014a) [101]	USA	CS	NHANES 2007-2010; ♂♀(n=548)	Children (11.9*)	Urine (SPE-HPLC-TMS)	BMI z-score (measured W&H)	>143.04 vs. ≤5.66	OR= 2.15 (0.8; 5.57)	Age, race, calories, cotinine, creatinine, income
Waist Circumference									
Hatch, EE et al. (2008)[94]	USA	CS	NHANES, 1999–2002; ♀(n=327)	Children (6-11)	Urine (ID-HPLC/MS)	WC (Measured)	68.8-1685 vs. 0.6-14.4	$\beta = -0.5$ (-3.66; 2.66)	Age, height, race, SES, calories and others
Hatch, EE et al. (2008)[94]	USA	CS	NHANES, 1999–2002; ♀(n=682)	Children (12-19)	Urine (ID-HPLC/MS)	WC (Measured)	56.9-739.7 vs.0.2-11	$\beta = 1.46$ (-3.06; 5.98)	Age, height, race, SES, calories and others
Hatch, EE et al. (2008) [94]	USA	CS	NHANES, 1999–2002; ♂(n=329)	Children (6-11)	Urine (ID-HPLC/MS)	WC (Measured)	77-721.9 vs. 0.4-15	$\beta = 0.55$ (-3.31; 4.4)	Age, height, race, SES, calories and others
Hatch, EE et al. (2008) [94]	USA	CS	NHANES, 1999–2002; ♂(n=662)	Children (12-19)	Urine (ID-HPLC/MS)	WC (Measured)	54.6-969.9 vs.0.6-16.4	$\beta = 3.1$ (-0.67; 6.88)	Age, height, race, SES, calories and others
Teitelbaum, SL et al. (2012)[96]	USA	PC	Gen. Population; ♂♀(n=361)	Children (7.34±0.89*)	Urine (SPE/HPLC)	WC (Measured)	Per 1-unit (ln µg/gC)	$\beta = 0.12$ (-0.91; 1.14)	Age, sex, education, METs, ethnicity, calories and others
Buser, M et al. (2014a) [101]	USA	CS	NHANES 2007-2010; ♂♀(n=548)	Children (11.9*)	Urine (SPE-HPLC-TMS)	WC (Measured)	>143.04 vs. ≤5.66	OR= 1.5 (0.75;3.02)	Age, race, calories, cotinine, creatinine, income

CS: Cross-sectional; PC: Prospective cohort; NHANES: National Health and Nutrition Examination Survey; SPE: Solid Phase Extraction; HPLC: High Performance Liquid Chromatography; TMS: Tandem Mass Spectrometry; ID: Isotope Dilution; MS: Mass Spectrometry; BMI: Body Mass Index; W: Weight; H: Height; OR: Odds Ratio; β : Beta coefficient; SES: Socioeconomic Status; METs: Metabolic Equivalents.*Mean±sd;


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Table 13.6.3 summarizes available results for the association between MBzP and each adiposity measure in adults. For all adiposity measures, a positive association was found but only the summary estimate for waist circumference reached statistical significance ($\beta=2.06$, 95% CI 0.11; 4.01).


Table 13.6.3. Summary estimates for the association between MBzP and each adiposity measure in adults

	Number of included estimates	MBzP		
		Summary Estimate*	I ² (%)	95% CI
Adults				
Body Mass Index	6 ^a	-0.07	71.7	-0.22; 0.09
Waist Circumference	4 ^b	2.06	83.0	0.11; 4.01
Waist to Hip Ratio	1 ^c	0.09	-	0.06; 0.23

I² available only when meta-analysis was performed. *Beta coefficient if not otherwise specified.

Included publications are: ^aHuang, PC, et al. (2007)[92] and Hatch, EE et al. (2008)[94]; ^bHatch, EE et al. (2008)[94];

^cSvensson, K et al. (2011)[95].

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	Author(s): V Mendes; I Delgado; B Peleteiro; J Araújo; H Barros; E Ramos; D Sarigiannis; N Baiz; I Annesi-Maesano	Version: 1	175/221

13.7 Mono-(2-ethyl-5-oxohexyl) Phthalate (MEOHP)

Seven papers evaluated the association between MEOHP and adiposity [93-97, 100, 101]. As the estimates provided were not in sufficient number, meta-analysis was not performed.

Table 13.7.1 shows the description of papers evaluating the association between MEOHP and adiposity measures in adults. In general, all results regarding BMI were positive and non-statistically significant, with the exception of Svensson, K *et al.* (2011) [95] and Buser, M *et al.* (2014a) [101] that found a negative and significant. Regarding other adiposity measures, Stahlhut, RW *et al.* (2007) [93], Hatch, EE *et al.* (2008) [94], Svensson, K *et al.* (2011) [95] and Buser, M *et al.* (2014a) [101] all observed positive associations with waist circumference. Svensson, K *et al.* (2011) [95] has also evaluated waist to hip ratio and found a positive correlation but with no statistical significance ($p=0.1123$, $p>0.05$).


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Table 13.7.1. Description of papers assessing the association between MEOHP and adiposity measures in adults

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
BMI									
Hatch, EE et al. (2008)[94]	USA	CS	NHANES, 1999–2002; ♀(n=761)	Adults (20-59)	Urine (ID-HPLC/MS)	BMI (Measured W&H)	28-914.2 vs.0.8-4.8	$\beta = 0.38$ (-1.9; 2.66)	Age, height, race, SES, calories and others
Hatch, EE et al. (2008)[94]	USA	CS	NHANES, 1999–2002; ♀(n=348)	Adults (60-80)	Urine (ID-HPLC/MS)	BMI (Measured W&H)	17.9-1026.4 vs. 0.8-3.8	$\beta = 0.94$ (-2.98; 4.85)	Age, height, race, SES, calories and others
Hatch, EE et al. (2008)[94]	USA	CS	NHANES, 1999–2002; ♂(n=895)	Adults (20-59)	Urine (ID-HPLC/MS)	BMI (Measured W&H)	31.5-926.7 vs. 0.8-6.9	$\beta = 2.14$ (-0.13; 4.41)	Age, height, race, SES, calories and others
Hatch, EE et al. (2008)[94]	USA	CS	NHANES, 1999–2002; ♂(n=365)	Adults (60-80)	Urine (ID-HPLC/MS)	BMI (Measured W&H)	19.9-766.9 vs. 0.8-4.8	$\beta = 0.69$ (-2.05; 3.44)	Age, height, race, SES, calories and others
Svensson, K et al. (2011)[95]	MEX	CS	Gen. Population; ♀(n=182)	Adults (54*)	Urine (SPE/HPLC-IDTMS)	BMI (Measured W&H)	log µg/g creatinine	$\rho = -0.0111$ (p>0.05)	-
Buser, M et al. (2014a) [101]	USA	CS	NHANES 2007-2010; ♂♀(n=757)	Adults (43.9*)	Urine (SPE-HPLC-TMS)	BMI (measured W&H)	>19.5 vs. ≤4.19	OR= 1.44 (1.02; 2.05)	Age, sex, race, calories, education, smoking, alcohol, DM
Waist Circumference									
Stahlhut, RW et al. (2007)[93]	USA	CS	NHANES, 1999-2002; ♂(n=651)	Adults (≥19)	Urine (HPLC/ID-MS)	WC (measured)	log µg/g creatinine	$\beta = 1.81$ (p=0.009)	Age, race, total fat, calories, PA, smoking, creatinine
Hatch, EE et al. (2008)[94]	USA	CS	NHANES, 1999–2002; ♀(n=761)	Adults (20-59)	Urine (ID-HPLC/MS)	WC (Measured)	28-914.2 vs.0.8-4.8	$\beta = 1.52$ (-2.98; 6.06)	Age, height, race, SES, calories and others
Hatch, EE et al. (2008)[94]	USA	CS	NHANES, 1999–2002; ♀(n=348)	Adults (60-80)	Urine (ID-HPLC/MS)	WC (Measured)	17.9-1026.4 vs. 0.8-3.8	$\beta = 2.46$ (-7.41; 12.32)	Age, height, race, SES, calories and others
Hatch, EE et al. (2008)[94]	USA	CS	NHANES, 1999–2002; ♂(n=895)	Adults (20-59)	Urine (ID-HPLC/MS)	WC (Measured)	31.5-926.7 vs. 0.8-6.9	$\beta = 5.81$ (0.69; 10.94)	Age, height, race, SES, calories and others
Hatch, EE et al. (2008)[94]	USA	CS	NHANES, 1999–2002; ♂(n=365)	Adults (60-80)	Urine (ID-HPLC/MS)	WC (Measured)	19.9-766.9 vs. 0.8-4.8	$\beta = 2.31$ (-4.97; 9.59)	Age, height, race, SES, calories and others
Svensson, K et al. (2011)[95]	MEX	CS	Gen. Population; ♀(n=182)	Adults (54*)	Urine (SPE/HPLC-IDTMS)	WC (Measured)	log µg/g creatinine	$\rho = 0.0865$ (p>0.05)	-
Dirtu, AC et al. (2013)	BEL	CS	Obese individuals; ♂♀(n=152)	Adults (18-84)	Urine (LC)	WC (measured)	ln ng/mL	$\beta = 0.01$ (p=0.892)	Age, sex
Dirtu, AC et al. (2013)	BEL	CS	Normal-weight controls; ♂♀(n=43)	Adults (19-59)	Urine (LC)	WC (measured)	ln ng/mL	$\beta = -0.2$ (p=0.21)	Age, sex


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Table 13.7.1. Description of papers assessing the association between MEOHP and adiposity measures in adults

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Buser, M et al. (2014a) [101]	USA	CS	NHANES 2007-2010; ♂♀(n=757)	Adults (43.9*)	Urine (SPE-HPLC-TMS)	WC (measured)	>19.5 vs. ≤4.19	OR= 1.28 (0.98; 1.69)	Age, sex, race, calories, education, smoking, alcohol, DM

Waist to Hip Ratio

Svensson, K et al. (2011)[95]	MEX	CS	Gen. Population; ♀(n=182)	Adults (54*)	Urine (SPE/HPLC-IDTMS)	WtHR (Measured WC&HC)	log µg/g creatinine	p= 0.1123 (p>0.05)	-
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CS: Cross-sectional; NHANES: National Health and Nutrition Examination Survey; SPE: Solid Phase Extraction; HPLC: High Performance Liquid Chromatography; TMS: Tandem Mass Spectrometry; ID: Isotope Dilution; MS: Mass Spectrometry; BMI: Body Mass Index; W: Weight; H: Height; WC: Waist Circumference; WtHR: Waist to Hip Ratio; HC: Hip Circumference; OR: Odds Ratio; β: Beta coefficient; p : Spearman correlation coefficient; PA: Physical Activity; SES: Socioeconomic Status. *Mean±sd.

Table 13.7.2 shows the description of papers evaluating the association between MEOHP and adiposity measures in children. Results provided for BMI and waist circumference have in general indicated a positive association, but none of these results had statistical significance and were reported by the same papers [94, 96, 97, 101].

Table 13.7.2. Description of papers assessing the association between MEOHP and adiposity measures in children

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
BMI									
Hatch, EE et al. (2008)[94]	USA	CS	NHANES, 1999–2002; ♀(n=327)	Children (6-11)	Urine (ID-HPLC/MS)	BMI (Measured W&H)	50.5-687 vs. 0.8-11.1	β= -0.17 (-2.6; 2.26)	Age, height, race, SES, calories and others
Hatch, EE et al. (2008)[94]	USA	CS	NHANES, 1999–2002; ♀(n=682)	Children (12-19)	Urine (ID-HPLC/MS)	BMI (Measured W&H)	39.1-1380.1 vs.0.8-10.5	β= 0.89 (-1.4;3.18)	Age, height, race, SES, calories and others
Hatch, EE et al. (2008)[94]	USA	CS	NHANES, 1999–2002; ♂(n=329)	Children (6-11)	Urine (ID-HPLC/MS)	BMI (Measured W&H)	47.2-351.6 vs. 0.8-12.8	β= 0.14 (-1.21; 1.48)	Age, height, race, SES, calories and others
Hatch, EE et al. (2008)[94]	USA	CS	NHANES, 1999–2002; ♂(n=662)	Children (12-19)	Urine (ID-HPLC/MS)	BMI (Measured W&H)	36.1-607.1 vs. 0.8-8.7	β= 0.27 (-1.4; 1.94)	Age, height, race, SES, calories and others
Teitelbaum, SL et al. (2012)[96]	USA	PC	Gen. Population; ♂♀(n=361)	Children	Urine (SPE/HPLC)	BMI (Measured W&H)	Per 1-unit (ln µg/gC)	β= -0.04 (-0.43; 0.36)	Age, sex, education, METs, ethnicity, calories, and others
Wang, H et al. (2013)[97]	CHN	CS	Obese, OW and NW; ♂♀(n=259)	Children (8-15)	Urine (RP-UPLC/EI-TMS)	BMI (Measured W&H)	Per 1-unit (log ng/mL)	β= 0.025 (-0.002; 0.052)	Age, sex
Buser, M et al. (2014a)	USA	CS	NHANES 2007-2010;	Children (11.9*)	Urine (SPE-HPLC-TMS)	BMI z-score (measured)	>19.5 vs. ≤4.19	OR= 1.07 (0.45;	Age, race, calories, cotinine,


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	Author(s): V Mendes; I Delgado; B Peleteiro; J Araújo; H Barros; E Ramos; D Sarigiannis; N Baiz; I Annesi-Maesano	Version: 1	178/221

Table 13.7.2. Description of papers assessing the association between MEOHP and adiposity measures in children


Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
[101]			♂♀(n=548)			W&H)		2.58)	creatinine, income
Waist Circumference									
Hatch, EE et al. (2008)[94]	USA	CS	NHANES, 1999–2002; ♀(n=327)	Children (6–11)	Urine (ID-HPLC/MS)	WC (Measured)	50.5–687 vs. 0.8–11.1	β= 0.45 (-5.56; 6.46)	Age, height, race, SES, calories and others
Hatch, EE et al. (2008)[94]	USA	CS	NHANES, 1999–2002; ♀(n=682)	Children (12–19)	Urine (ID-HPLC/MS)	WC (Measured)	39.1–1380.1 vs. 0.8–10.5	β= 1.79 (-4.10; 7.68)	Age, height, race, SES, calories and others
Hatch, EE et al. (2008)[94]	USA	CS	NHANES, 1999–2002; ♂(n=329)	Children (6–11)	Urine (ID-HPLC/MS)	WC (Measured)	47.2–351.6 vs. 0.8–12.8	β= 0.6 (-2.68; 3.88)	Age, height, race, SES, calories and others
Hatch, EE et al. (2008)[94]	USA	CS	NHANES, 1999–2002; ♂(n=662)	Children (12–19)	Urine (ID-HPLC/MS)	WC (Measured)	36.1–607.1 vs. 0.8–8.7	β= 0.68 (-2.67; 4.02)	Age, height, race, SES, calories and others
Teitelbaum, SL et al. (2012)[96]	USA	PC	Gen. Population; ♂♀(n=361)	Children (7.34±0.89*)	Urine (SPE/HPLC)	WC (Measured)	Per 1-unit (ln µg/gC)	β= -0.01 (-1.07; 1.05)	Age, sex, education, METs, ethnicity, calories, and others
Wang, H et al. (2013)[97]	CHN	CS	Obese, OW and NW; ♂♀(n=259)	Children (8–15)	Urine (RP-UPLC/EI-TMS)	WC (Measured)	Per 1-unit (log ng/mL)	β= 0.018 (-0.004; 0.039)	Age, sex
Buser, M et al. (2014a) [101]	USA	CS	NHANES 2007–2010; ♂♀(n=548)	Children (11.9*)	Urine (SPE-HPLC-TMS)	WC (measured)	>19.5 vs. ≤4.19	OR= 1.35 (0.59; 3.08)	Age, race, calories, cotinine, creatinine, income

CS: Cross-sectional; PC: Prospective cohort; NHANES: National Health and Nutrition Examination Survey; OW: Overweight; NW: Normal Weight; SPE: Solid Phase Extraction; HPLC: High Performance Liquid Chromatography; TMS: Tandem Mass Spectrometry; ID: Isotope Dilution; MS: Mass Spectrometry; RP-UPLC: Reversed-phase Ultra Performance Liquid Chromatography; EI: Electron Ionization; BMI: Body Mass Index; W: Weight; H: Height; WC: Waist Circumference; OR: Odds Ratio; β: Beta coefficient; SES: Socioeconomic Status; METs: Metabolic Equivalents. *Mean±sd.

13.8 Mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP)

In the systematic review, seven publications assessing MEHHP were identified [93–97, 100, 101]. However, those seven papers did not provide a sufficient number of compatible measures in order to summarize the estimates.

Table 13.8.1 shows the description of papers assessing the association between MEHHP and adiposity in adults.

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Regarding BMI, Svensson, K *et al.* (2011) [95], using a sample from Mexico and Hatch, EE *et al.* (2008) [94] using NHANES 1999-2002 did not found significant associations but Buser, M *et al.* (2014a) [101] using data from NHANES 2007-2010 found a positive and significant association. Concerning other adiposity measures, all estimates provided for waist circumference were positive, with the exception of older men from NHANES 1999-2002 in Hatch, EE *et al.* (2008) [94] ($\beta = -2.82$, 95% CI -8.89; 3.25), but only two reached statistical significance. The only paper evaluating waist to hip ratio has also observed a positive and significant correlation with MEHHP among Mexican women [95].


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Table 13.8.1. Description of papers assessing the association between MEHHP and adiposity measures in adults

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
BMI									
Hatch, EE et al. (2008) [94]	USA	CS	NHANES, 1999–2002; ♀(n=761)	Adults (20-59)	Urine (ID-HPLC/MS)	BMI (Measured W&H)	28-914.2 vs. 0.8-4.8	$\beta = 1.08$ (-0.75; 2.92)	Age, height, race, SES, calories and others
Hatch, EE et al. (2008) [94]	USA	CS	NHANES, 1999–2002; ♀(n=348)	Adults (60-80)	Urine (ID-HPLC/MS)	BMI (Measured W&H)	17.9-1026.4 vs. 0.8-3.8	$\beta = -0.96$ (-4.04; 2.11)	Age, height, race, SES, calories and others
Hatch, EE et al. (2008) [94]	USA	CS	NHANES, 1999–2002; ♂(n=895)	Adults (20-59)	Urine (ID-HPLC/MS)	BMI (Measured W&H)	31.5-926.7 vs. 0.8-6.9	$\beta = 1.74$ (-0.28; 3.76)	Age, height, race, SES, calories and others
Hatch, EE et al. (2008) [94]	USA	CS	NHANES, 1999–2002; ♂(n=365)	Adults (60-80)	Urine (ID-HPLC/MS)	BMI (Measured W&H)	19.9-766.9 vs. 0.8-4.8	$\beta = 0.41$ (-2.47; 3.28)	Age, height, race, SES, calories and others
Svensson, K et al. (2011) [95]	MEX	CS	Gen. Population; ♀(n=182)	Adults (54*)	Urine (SPE/HPLC-IDTMS)	BMI (Measured W&H)	log µg/g creatinine	$\rho = -0.0666$ (p>0.05)	-
Buser, M et al. (2014a) [101]	USA	CS	NHANES 2007-2010; ♂♀(n=757)	Adults (43.9*)	Urine (SPE-HPLC-TMS)	BMI (measured W&H)	>19.5 vs. ≤4.19	OR= 1.51 (1.07; 2.14)	Age, sex, race, calories, education, smoking, alcohol, DM
Waist Circumference									
Stahlhut, RW et al. (2007)[93]	USA	CS	NHANES, 1999-2002; ♂(n=651)	Adults (≥19)	Urine (HPLC/ID-MS)	WC (measured)	log µg/g creatinine	$\beta = 1.71$ (p=0.008)	Age, race, fat, calories, PA, smoking, creatinine
Hatch, EE et al. (2008) [94]	USA	CS	NHANES, 1999–2002; ♀(n=761)	Adults (20-59)	Urine (ID-HPLC/MS)	WC (Measured)	28-914.2 vs. 0.8-4.8	$\beta = 3.13$ (-0.73; 6.99)	Age, height, race, SES, calories and others
Hatch, EE et al. (2008) [94]	USA	CS	NHANES, 1999–2002; ♀(n=348)	Adults (60-80)	Urine (ID-HPLC/MS)	WC (Measured)	17.9-1026.4 vs. 0.8-3.8	$\beta = -2.82$ (-8.89; 3.25)	Age, height, race, SES, calories and others
Hatch, EE et al. (2008) [94]	USA	CS	NHANES, 1999–2002; ♂(n=895)	Adults (20-59)	Urine (ID-HPLC/MS)	WC (Measured)	31.5-926.7 vs. 0.8-6.9	$\beta = 4.6$ (-0.3; 9.24)	Age, height, race, SES, calories and others
Hatch, EE et al. (2008) [94]	USA	CS	NHANES, 1999–2002; ♂(n=365)	Adults (60-80)	Urine (ID-HPLC/MS)	WC (Measured)	19.9-766.9 vs. 0.8-4.8	$\beta = 0.68$ (-7.42; 8.78)	Age, height, race, SES, calories and others
Svensson, K et al. (2011)[95]	MEX	CS	Gen. Population; ♀(n=182)	Adults (54*)	Urine (SPE/HPLC-IDTMS)	WC (Measured)	log µg/g creatinine	$\rho = 0.1843$ (p<0.05)	-
Dirtu, AC et al. (2013) [100]	BEL	CS	Obese individuals; ♂♀(n=152)	Adults (18-84)	Urine (LC)	WC (Measured)	ln ng/mL	$\beta = -0.04$ (p=0.598)	Age, sex
Dirtu, AC et al. (2013) [100]	BEL	CS	Normal-weight controls; ♂♀(n=43)	Adults (19-59)	Urine (LC)	WC (Measured)	ln ng/mL	$\beta = -0.29$ (p=0.063)	Age, sex


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Table 13.8.1. Description of papers assessing the association between MEHHP and adiposity measures in adults

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Buser, M et al. (2014a) [101]	USA	CS	NHANES 2007-2010; ♂♀(n=757)	Adults (43.9*)	Urine (SPE-HPLC-TMS)	WC (Measured)	>19.5 vs. ≤4.19	OR= 1.15 (0.87; 1.53)	Age, sex, race, calories, smoking, education, alcohol, DM

Waist to Hip Ratio

Svensson, K et al. (2011)[95]	MEX	CS	Gen. Population; ♀(n=182)	Adults (54*)	Urine (SPE/HPLC-IDTMS)	WtHR (Measured WC&HC)	log µg/g creatinine	ρ= 0.1982 (p<0.05)	-
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CS: Cross-sectional; NHANES: National Health and Nutrition Examination Survey; SPE: Solid Phase Extraction; HPLC: High Performance Liquid Chromatography; TMS: Tandem Mass Spectrometry; ID: Isotope Dilution; MS: Mass Spectrometry; BMI: Body Mass Index; W: Weight; H: Height; WC: Waist Circumference; WtHR: Waist to Hip Ratio; HC: Hip Circumference; OR: Odds Ratio; β: Beta coefficient; ρ : Spearman correlation coefficient; DM: Diabetes Mellitus; SES: Socioeconomic Status; PA: Physical Activity. *Mean±sd.

Table 13.8.2 shows the description of papers evaluating the association between MEHHP and adiposity measures in children. The same papers provided estimates for BMI and for waist circumference, in a total of seven estimates for BMI and seven for waist circumference. All results showed positive associations between MEHHP and adiposity, but with no statistical significance [94, 96, 97, 101].

Table 13.8.2. Description of papers assessing the association between MEHHP and adiposity measures in children

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
BMI									
Hatch, EE et al. (2008) [94]	USA	CS	NHANES, 1999–2002; ♀(n=327)	Children (6-11)	Urine (ID-HPLC/MS)	BMI (Measured W&H)	50.5-687 vs. 0.8-11.1	β= 0.54 (-1.5; 2.57)	Age, height, race, SES, calories and others
Hatch, EE et al. (2008) [94]	USA	CS	NHANES, 1999–2002; ♀(n=682)	Children (12-19)	Urine (ID-HPLC/MS)	BMI (Measured W&H)	39.1-1380.1 vs. 0.8-10.5	β= 0.74 (-1.18; 2.65)	Age, height, race, SES, calories and others
Hatch, EE et al. (2008) [94]	USA	CS	NHANES, 1999–2002; ♂(n=329)	Children (6-11)	Urine (ID-HPLC/MS)	BMI (Measured W&H)	47.2-351.6 vs. 0.8-12.8	β= 0.42 (-1.09; 1.92)	Age, height, race, SES, calories and others
Hatch, EE et al. (2008) [94]	USA	CS	NHANES, 1999–2002; ♂(n=662)	Children (12-19)	Urine (ID-HPLC/MS)	BMI (Measured W&H)	36.1-607.1 vs. 0.8-8.7	β= 1.0 (-0.69; 2.69)	Age, height, race, SES, calories and others
Teitelbaum, SL et al. (2012)[96]	USA	PC	Gen. Population; ♂♀(n=361)	Children	Urine (SPE/HPLC)	BMI (Measured W&H)	Per 1-unit (ln µg/gC)	β= 0.02 (-0.36; 0.41)	Age, sex, education, METs, ethnicity, calories, and others
Wang, H et al. (2013) [97]	CHN	CS	Obese, OW and NW; ♂♀(n=259)	Children (8-15)	Urine (RP-UPLC/EI-TMS)	BMI (Measured W&H)	Per 1-unit (log ng/mL)	β= 0.026 (-0.004; 0.055)	Age, sex
Buser, M et al. (2014a) [101]	USA	CS	NHANES 2007-2010; ♂♀(n=548)	Children (11.9*)	Urine (SPE-HPLC-TMS)	BMI z-score (measured W&H)	>19.5 vs. ≤4.19	OR= 1.08 (0.51; 2.29)	Age, race, calories, cotinine, creatinine,


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Table 13.8.2. Description of papers assessing the association between MEHHP and adiposity measures in children

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
									income
Waist Circumference									
Hatch, EE et al. (2008) [94]	USA	CS	NHANES, 1999–2002; ♀(n=327)	Children (6-11)	Urine (ID-HPLC/MS)	WC (Measured)	50.5-687 vs. 0.8-11.1	$\beta = 1.83$ (-3.48; 7.13)	Age, height, race, SES, calories and others
Hatch, EE et al. (2008) [94]	USA	CS	NHANES, 1999–2002; ♀(n=682)	Children (12-19)	Urine (ID-HPLC/MS)	WC (Measured)	39.1-1380.1 vs. 0.8-10.5	$\beta = 1.81$ (-3.19; 6.83)	Age, height, race, SES, calories and others
Hatch, EE et al. (2008) [94]	USA	CS	NHANES, 1999–2002; ♂(n=329)	Children (6-11)	Urine (ID-HPLC/MS)	WC (Measured)	47.2-351.6 vs. 0.8-12.8	$\beta = 1.27$ (-2.43; 4.96)	Age, height, race, SES, calories and others
Hatch, EE et al. (2008) [94]	USA	CS	NHANES, 1999–2002; ♂(n=662)	Children (12-19)	Urine (ID-HPLC/MS)	WC (Measured)	36.1-607.1 vs. 0.8-8.7	$\beta = 2.15$ (-1.77; 6.08)	Age, height, race, SES, calories and others
Teitelbaum, SL et al. (2012)[96]	USA	PC	Gen. Population; ♂♀(n=361)	Children (7.34±0.89*)	Urine (SPE/HPLC)	WC (Measured)	Per 1-unit (ln µg/gC)	$\beta = 0.15$ (-0.88; 1.19)	Age, sex, parental education, METs, ethnicity, calories, and others
Wang, H et al. (2013) [97]	CHN	CS	Obese, OW and NW; ♂♀(n=259)	Children (8-15)	Urine (RP-UPLC/EI-TMS)	WC (Measured)	Per 1-unit (log ng/mL)	$\beta = 0.017$ (-0.007; 0.04)	Age, sex
Buser, M et al. (2014a) [101]	USA	CS	NHANES 2007-2010; ♂♀(n=548)	Children (11.9*)	Urine (SPE-HPLC-TMS)	WC (Measured)	>19.5 vs. ≤4.19	OR= 1.11 (0.5; 2.5)	Age, race, calorie, cotinine, creatinine, income

CS: Cross-sectional; PC: Prospective cohort; NHANES: National Health and Nutrition Examination Survey; OW: Overweight; NW: Normal Weight; SPE: Solid Phase Extraction; HPLC: High Performance Liquid Chromatography; TMS: Tandem Mass Spectrometry; ID: Isotope Dilution; MS: Mass Spectrometry; RP-UPLC: Reversed-phase Ultra Performance Liquid Chromatography; EI: Electron Ionization; BMI: Body Mass Index; W: Weight; H: Height; WC: Waist Circumference; OR: Odds Ratio; β : Beta coefficient; SES: Socioeconomic Status; METs: Metabolic Equivalents. *Mean±sd.

13.9 Other Phthalates

Besides the above presented phthalates, eight other substances were also identified in the systematic review – mono-n-butyl phthalate (MnBP) [100, 101], mono-(3-carboxypropyl) phthalate (MCP) [95, 96], mono(2-ethyl-5-carboxypentyl) (MECPP) [95-97, 100, 101], mono(2-carboxymethylhexyl) phthalate (MCMHP) [97], monocyclohexyl phthalate (MCHP) [97], mono-(3-hydroxy-n-butyl) (MHBP) [97], mono(carboxynonyl) (MCNP) [101] and mono(carboxyoctyl) (MCOP) [101]. However, meta-analysis could not be performed for any of these phthalates due to the limited number of publications evaluating the association of each compound with adiposity.

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Most of the identified publications have presented positive associations between the specific phthalate and adiposity measures (table 13.9.1). Associations observed for MCMHP [97], MCHP [97], MHBP [97] and MCOP [101] were positive for both adults and children. Regarding MECPP positive associations among adults were also found [95, 100, 101], but in children results have shown a negative relationship [96, 97, 101]. On the other hand, results regarding MCPHP suggested a negative association with adiposity, both in adults and children [95, 96]. Mixed estimates were observed for MnBP [100, 101] and MCNP [101].

Table 13.9.1. Description of papers identified in the systematic review assessing the association between other phthalate compounds and adiposity

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Mono-n-butyl Phthalate (MnBP)									

BMI


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Table 13.9.1. Description of papers identified in the systematic review assessing the association between other phthalate compounds and adiposity

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Buser, M et al. (2014a) [101]	USA	CS	NHANES 2007-2010; ♂♀(n=548)	Children (11.9*)	Urine (SPE-HPLC-TMS)	BMI z-score (measured W&H)	>31.59 vs. ≤7.69	OR= 1.62 (0.54; 4.93)	Age, race, calorie intake, cotinine, creatinine, income
Buser, M et al. (2014a) [101]	USA	CS	NHANES 2007-2010; ♂♀(n=757)	Adults (43.9*)	Urine (SPE-HPLC-TMS)	BMI z-score (measured W&H)	>31.59 vs. ≤7.69	OR= 0.89 (0.65; 1.23)	Age, sex, race, calories, education, smoking, alcohol, diabetes
Waist Circumference									
Dirtu, AC et al. (2013) [100]	BEL	CS	Obese individuals; ♂♀(n=152)	Adults (18-84)	Urine (LC)	WC (Measured)	ln ng/mL	β= 0.12 (p=0.134)	Age, sex
Dirtu, AC et al. (2013) [100]	BEL	CS	Normal-weight controls; ♂♀(n=43)	Adults (19-59)	Urine (LC)	WC (Measured)	ln ng/mL	β= -0.22 (p=0.160)	Age, sex
Buser, M et al. (2014a) [101]	USA	CS	NHANES 2007-2010; ♂♀(n=548)	Children (11.9*)	Urine (SPE-HPLC-TMS)	WC (Measured)	>31.59 vs. ≤7.69	OR= 0.95 (0.51; 1.75)	Age, race, calories, cotinine, creatinine, income
Buser, M et al. (2014a) [101]	USA	CS	NHANES 2007-2010; ♂♀(n=757)	Adults (43.9*)	Urine (SPE-HPLC-TMS)	WC (measured)	>31.59 vs. ≤7.69	OR= 0.91 (0.63; 1.3)	Age, sex, race, calories, education, smoking, alcohol, diabetes
Mono-(3-carboxypropyl) Phthalate (MCPP)									
BMI									
Svensson, K et al. (2011)[95]	MEX	CS	Gen. Population; ♀(n=182)	Adults (54*)	Urine (SPE/HPLC-IDTMS)	BMI (Measured W&H)	log µg/g creatinine	ρ= -0.0686 (p>0.05)	-
Teitelbaum, SL et al. (2012)[96]	USA	PC	Gen. Population; ♂♀(n=361)	Children (7.34± 0.89*)	Urine (SPE/HPLC)	BMI (Measured W&H)	Per 1-unit (ln µg/gC)	β= -0.31 (-0.84; 0.22)	Age, sex, parental education, METs, ethnicity, calories and others
Wait Circumference									
Svensson, K et al. (2011)[95]	MEX	CS	Gen. Population; ♀(n=182)	Adults (54*)	Urine (SPE/HPLC-IDTMS)	WC (Measured)	log µg/g creatinine	ρ= -0.0475 (p>0.05)	-
Teitelbaum, SL et al. (2012)[96]	USA	PC	Gen. Population; ♂♀(n=361)	Children (7.34± 0.89*)	Urine (SPE/HPLC)	WC (Measured)	Per 1-unit (ln µg/gC)	β= -0.87 (-2.28; 0.55)	Age, sex, parental education, METs, ethnicity, calories and others


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Table 13.9.1. Description of papers identified in the systematic review assessing the association between other phthalate compounds and adiposity

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Waist to Hip Ratio									
Svensson, K et al. (2011)[95]	MEX	CS	Gen. Population; ♀(n=182)	Adults (54*)	Urine (SPE/HPLC-IDTMS)	WtHR (Measured WC&HC)	log µg/g creatinine	ρ= 0.0728 (p>0.05)	-
Mono(2-ethyl-5-carboxypentyl) phthalate (MECPP)									
BMI									
Svensson, K et al. (2011)[95]	MEX	CS	Gen. Population; ♀(n=182)	Adults (54*)	Urine (SPE/HPLC-IDTMS)	BMI (Measured W&H)	log µg/g creatinine	ρ= 0.0301 (p>0.05)	-
Teitelbaum, SL et al. (2012)[96]	USA	PC	Gen. Population; ♂♀(n=361)	Children (7.34± 0.89*)	Urine (SPE/HPLC)	BMI (Measured W&H)	Per 1-unit (ln µg/gC)	β= -0.05 (-0.49; 0.38)	Age, sex, parental education, METs, ethnicity, calories and others
Wang, H et al. (2013)[97]	CHN	CS	Obese, OW and NW; ♂♀(n=259)	Children (8-15)	Urine (RP-UPLC/EI-TMS)	BMI (Measured W&H)	Per 1-unit (log ng/mL)	β= 0.021 (-0.007; 0.049)	Age, sex
Buser, M et al. (2014a) [101]	USA	CS	NHANES 2007-2010; ♂♀(n=548)	Children (11.9*)	Urine (SPE-HPLC-TMS)	BMI z-score (measured W&H)	>49.07 vs. ≤11.03	OR= 0.96 (0.41; 2.24)	Age, race, calories, cotinine, creatinine, income
Buser, M et al. (2014a) [101]	USA	CS	NHANES 2007-2010; ♂♀(n=757)	Adults (43.9*)	Urine (SPE-HPLC-TMS)	BMI z-score (measured W&H)	>49.07 vs. ≤11.03	OR= 1.85 (1.29; 2.64)	Age, sex, race, calories, education, smoking, alcohol, diabetes
Waist Circumference									
Svensson, K et al. (2011)[95]	MEX	CS	Gen. Population; ♀(n=182)	Adults (54*)	Urine (SPE/HPLC-IDTMS)	WC (Measured)	log µg/g creatinine	ρ= 0.1302 (p>0.05)	-
Teitelbaum, SL et al. (2012)[96]	USA	PC	Gen. Population; ♂♀(n=361)	Children (7.34± 0.89*)	Urine (SPE/HPLC)	WC (Measured)	Per 1-unit (ln µg/gC)	β= -0.12 (-1.28; 1.05)	Age, sex, parental education, METs, ethnicity, calories and others
Dirtu, AC et al. (2013)[100]	BEL	CS	Obese individuals; ♂♀(n=152)	Adults (18-84)	Urine (LC)	WC (measured)	ln ng/mL	β= 0.04 (p=0.674)	Age, sex
Dirtu, AC et al. (2013)[100]	BEL	CS	Normal-weight controls; ♂♀(n=43)	Adults (19-59)	Urine (LC)	WC (measured)	ln ng/mL	β= -0.26 (p=0.095)	Age, sex
Wang, H et al.	CHN	CS	Obese, OW and NW; ♂♀(n=259)	Children (8-15)	Urine (RP-UPLC/EI-	WC (Measured)	Per 1-unit (log ng/mL)	β= 0.013 (-0.009;	Age, sex


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Table 13.9.1. Description of papers identified in the systematic review assessing the association between other phthalate compounds and adiposity

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Buser, M et al. (2014a) [101]	USA	CS	NHANES 2007-2010; ♂♀(n=548)	Children (11.9*)	TMS) Urine (SPE-HPLC-TMS)	WC (Measured)	>49.07 vs. ≤11.03	0.035) OR= 1.11 (0.54; 2.3)	Age, race, calories, cotinine, creatinine, income
Buser, M et al. (2014a) [101]	USA	CS	NHANES 2007-2010; ♂♀(n=757)	Adults (43.9*)	Urine (SPE-HPLC-TMS)	WC (Measured)	>49.07 vs. ≤11.03	OR= 1.26 (0.87; 1.84)	Age, sex, race, calories, education, smoking, alcohol, diabetes

Waist to Hip Ratio

Svensson, K et al. (2011)[95]	MEX	CS	Gen. Population; ♀(n=182)	Adults (54*)	Urine (SPE/HPLC-IDTMS)	WtHR (Measured WC&HC)	log µg/g creatinine	ρ= 0.1235 (p>0.05)	-
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Mono(2-carboxymethylhexyl) Phthalate (MCMHP)

BMI

Wang, H et al. (2013)[97]	CHN	CS	Obese, OW and NW; ♂♀(n=259)	Children (8-15)	Urine (RP-UPLC/EI-TMS)	BMI (Measured W&H)	Per 1-unit (log ng/mL)	β= 0.026 (0.002; 0.05)	Age, sex
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Waist Circumference

Wang, H et al. (2013)[97]	CHN	CS	Obese, OW and NW; ♂♀(n=259)	Children (8-15)	Urine (RP-UPLC/EI-TMS)	WC (Measured)	Per 1-unit (log ng/mL)	β= 0.017 (-0.002; 0.036)	Age, sex
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Monocyclohexyl Phthalate (MCHP)

BMI

Wang, H et al. (2013)[97]	CHN	CS	Obese, OW and NW; ♂♀(n=259)	Children (8-15)	Urine (RP-UPLC/EI-TMS)	BMI (Measured W&H)	Per 1-unit (log ng/mL)	β= 0.023 (0.002; 0.044)	Age, sex
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Waist Circumference

Wang, H et al. (2013)[97]	CHN	CS	Obese, OW and NW; ♂♀(n=259)	Children (8-15)	Urine (RP-UPLC/EI-TMS)	WC (Measured)	Per 1-unit (log ng/mL)	β= 0.019 (-0.002; 0.035)	Age, sex
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Mono(3-hydroxybutyl) Phthalate (MHBP)

BMI

Wang, H et al. (2013)[97]	CHN	CS	Obese, OW and NW; ♂♀(n=259)	Children (8-15)	Urine (RP-UPLC/EI-TMS)	BMI (Measured W&H)	Per 1-unit (log ng/mL)	β= 0.023 (0.001; 0.045)	Age, sex
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Waist Circumference

Wang, H et al.	CHN	CS	Obese, OW and NW; ♂♀(n=259)	Children (8-15)	Urine (RP-UPLC/EI-TMS)	WC (Measured)	Per 1-unit (log ng/mL)	β= 0.009 (-0.009;	Age, sex
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Table 13.9.1. Description of papers identified in the systematic review assessing the association between other phthalate compounds and adiposity

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
(2013)[97]					TMS)			0.028)	
Mono(carboxynonyl) Phthalate (MCNP)									
BMI									
Buser, M et al. (2014a) [101]	USA	CS	NHANES, 2007-2010; ♂♀†	Children (11.9*)	Urine (SPE-HPLC/TMS)	Obesity (BMI≥95 th)	>4.91 vs. ≤1.78	OR= 0.84 (0.39; 1.81)	Age, race, calories, cotinine, creatinine, income
Buser, M et al. (2014a) [101]	USA	CS	NHANES, 2007-2010; ♂♀†	Children (11.9*)	Urine (SPE-HPLC/TMS)	Overweight (BMI≥85 th)	>4.91 vs. ≤1.78	OR= 0.98 (0.56; 1.71)	Age, race, calories, cotinine, creatinine, income
Buser, M et al. (2014a) [101]	USA	CS	NHANES, 2007-2010; ♂♀†	Adults (43.9*)	Urine (SPE-HPLC/TMS)	Obesity (BMI≥ 30Kg/m ²)	>4.91 vs. ≤1.78	OR= 1.78 (1.08; 2.94)	Age, sex, race, calories, education, smoking, alcohol, diabetes
Buser, M et al. (2014a) [101]	USA	CS	NHANES, 2007-2010; ♂♀†	Adults (43.9*)	Urine (SPE-HPLC/TMS)	Overweight (BMI:25-29.9 kg/m ²)	>4.91 vs. ≤1.78	OR= 1.5 (0.91; 2.48)	Age, sex, race, calories, education, smoking, alcohol, diabetes
Mono(carboxyisooctyl) Phthalate (MCOP)									
BMI									
Buser, M et al. (2014a) [101]	USA	CS	NHANES, 2007-2010; ♂♀†	Children (11.9*)	Urine (SPE-HPLC/TMS)	Obesity (BMI≥95 th)	>20.59 vs. ≤5.50	OR= 1.34 (0.68; 2.66)	Age, race, calories, cotinine, creatinine, income
Buser, M et al. (2014a) [101]	USA	CS	NHANES, 2007-2010; ♂♀†	Children (11.9*)	Urine (SPE-HPLC/TMS)	Overweight (BMI≥85 th)	>20.59 vs. ≤5.50	OR= 1.19 (0.65; 2.19)	Age, race, calories, cotinine, creatinine, income
Buser, M et al. (2014a) [101]	USA	CS	NHANES, 2007-2010; ♂♀†	Adults (43.9*)	Urine (SPE-HPLC/TMS)	Obesity (BMI≥ 30Kg/m ²)	>20.59 vs. ≤5.50	OR= 1.75 (1.25; 2.47)	Age, sex, race, calories, education, smoking, alcohol, diabetes
Buser, M et al. (2014a) [101]	USA	CS	NHANES, 2007-2010; ♂♀†	Adults (43.9*)	Urine (SPE-HPLC/TMS)	Overweight (BMI:25-29.9 kg/m ²)	>20.59 vs. ≤5.50	OR= 1.46 (0.92; 2.31)	Age, sex, race, calories, education, smoking,



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Table 13.9.1. Description of papers identified in the systematic review assessing the association between other phthalate compounds and adiposity

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
									alcohol, diabetes

CS: Cross-sectional; PC: Prospective Cohort; OW: Overweight; NW: Normal Weight; NHANES: National Health and Nutrition Examination Survey; SPE: Solid Phase Extraction; HPLC: High Performance Liquid Chromatography; TMS: Tandem Mass Spectrometry; LC: Liquid Chromatography; ID: Isotope Dilution; RP-UPLC: Reversed-phase Ultra Performance Liquid Chromatography; EI: Electron Ionization; BMI: Body Mass Index; W: Weight; H: Height; WC: Waist Circumference; WtHR: Waist to Hip Ratio; HC: Hip Circumference; OR: Odds Ratio; β : Beta coefficient; ρ : Spearman correlation coefficient; METs: Metabolic Equivalents. †No further information; *Mean \pm sd.

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13.10 Sum of Phthalates


Table 13.10.1 presents the description of papers that assessed the association between different combinations of phthalates and adiposity.

Regarding the sum of Di(2-ethylhexyl) Phthalates (DEHP), only Svensson, K *et al.* (2011) [95] evaluated the effects of this combination of compounds in adiposity among adults and found positive associations for BMI, waist circumference and waist to hip ratio, but only the latter reached statistical significance ($p=0.1498$, $p<0.05$). Three publications evaluated the association between the sum of DEHP and adiposity among children and observed mixed associations [96, 97, 103].

The sum of dibutyl phthalate (DBP) metabolites was assessed only in Wang, H *et al.* (2013) [97] that evaluated the association of this substance with BMI and waist circumference and observed positive coefficients for both adiposity measures in a sample of obese, overweight and normal weight Chinese children.

Trasande, L *et al.* (2013) [103], Wang, H *et al.* (2013) [97] and Buser, M *et al.* (2014a) [101] addressed the relation of low-molecular-weight phthalates and high-molecular-weight phthalates with adiposity. Buser, M *et al.* (2014a) [101] was the only providing estimates for adults and observed positive and statistically significant associations between the sum of high-molecular-weight phthalates and obesity (OR= 1.77, 95% CI 1.26; 2.48) in NHANES 2007-2010 individuals. Regarding children, in general, estimates were positive but only Wang, H *et al.* (2013) [97] and Buser, M *et al.* (2014a) [101] observed statistically significant results.

Finally, two papers evaluated the sum of phthalates (each assessing a different combination of compounds). Dirtu, AC *et al.* (2013) [100] evaluated the association between the sum of nine phthalate compounds (MMP, MEP, MiBP, MnBP, MBzP, MECPP, MEOHHP, MEOHP and MEHP) and waist circumference among adult individuals and observed negative associations but with no statistical significance. Wang, H *et al.* (2013) [97] evaluated the combination of fourteen substances (MEHP, MEOHP, MECPP, MEHHP, mBP, MiBP, MEP, MCMHP, MHBP, MMP, MCHP, MBzP,

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MinP and MOP) and found positive associations in children for both BMI ($\beta = 0.049$, 95% CI 0.02; 0.079) and waist circumference ($\beta = 0.031$, 95% CI 0.006; 0.056).

Table 13.10.1. Description of papers identified in the systematic review assessing the association between the sum of phthalates and adiposity[†]

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Sum of Di(2-ethylhexyl) Phthalates (DEHP)									
BMI									
Teitelbaum, SL et al. (2012)[96]	USA	PC	Gen. Population; ♂♀(n=361)	Children (7.34±0.89*)	Urine (SPE/HPLC)	BMI (Measured W&H)	Per 1-unit (ln µg/gC)	$\beta = -0.03$ (-0.44; 0.39)	Age, sex, parental education, METs, ethnicity, calories, and others
Svensson, K et al. (2011)[95]	MEX	CS	Gen. Population; ♀(n=182)	Adults (54*)	Urine (SPE/HPLC-IDTMS)	BMI (Measured W&H)	log µg/g creatinine	$\rho = 0.0354$ ($p > 0.05$)	-
Wang, H et al. (2013)[97]	CHN	CS	Obese, OW and NW; ♂♀(n=259)	Children (8-15)	Urine (RP-UPLC/EI-TMS)	BMI (Measured W&H)	Per 1-unit (log ng/mL)	$\beta = 0.037$ (0.006; 0.067)	Age, sex
Trasande, L et al. (2013) [103]	USA	CS	NHANES, 2003-2008; ♂♀(n=2862)	Children (6-19)	Urine (HPLC-TMS)	BMI z-score (Measured W&H)	Per 1-unit (ln µM)	$\beta = -0.01$ (-0.06; 0.03)	Age, race, sex, PIR, parental education, creatinine, cotinine, calories, TV
Trasande, L et al. (2013) [103]	USA	CS	NHANES, 2003-2008; ♂♀(n=2862)	Children (6-19)	Urine (HPLC-TMS)	Overweight (BMI≥P85 th)	Per 1-unit (ln µM)	OR= 0.95 (0.85; 1.07)	Age, race, sex, PIR, parental education, creatinine, cotinine, calories, TV
Trasande, L et al. (2013) [103]	USA	CS	NHANES, 2003-2008; ♂♀(n=2862)	Children (6-19)	Urine (HPLC-TMS)	Obesity (BMI≥P95 th)	Per 1-unit (ln µM)	OR= 1.04 (0.89; 1.2)	Age, race, sex, PIR, parental education, creatinine,


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Table 13.10.1. Description of papers identified in the systematic review assessing the association between the sum of phthalates and adiposity[†]

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
									cotinine, calories, TV
Waist Circumference									
Teitelbaum, SL et al. (2012)[96]	USA	PC	Gen. Population; ♂♀(n=361)	Children (7.34±0.89*)	Urine (SPE/HPLC)	WC (Measured)	Per 1-unit (ln µg/gC)	β= 0.0 (-1.11; 1.12)	Age, sex, parental education, METs, ethnicity, calories, and others
Svensson, K et al. (2011)[95]	MEX	CS	Gen. Population; ♀(n=182)	Adults (54*)	Urine (SPE/HPLC-IDTMS)	WC (Measured)	log µg/g creatinine	ρ= 0.1427 (p>0.05)	-
Wang, H et al. (2013)[97]	CHN	CS	Obese, OW and NW; ♂♀(n=259)	Children (8-15)	Urine (RP-UPLC/EI-TMS)	WC (Measured)	Per 1-unit (log ng/mL)	β= 0.026 (0.001; 0.05)	Age, sex
Waist to Hip Ratio									
Svensson, K et al. (2011)[95]	MEX	CS	Gen. Population; ♀(n=182)	Adults (54*)	Urine (SPE/HPLC-IDTMS)	WtHR (Measured WC&HC)	log µg/g creatinine	ρ= 0.1498 (p<0.05)	-
Sum of Dibutyl Phthalate (DBP) Metabolites									
BMI									
Wang, H et al. (2013) [97]	CHN	CS	Obese, OW and NW; ♂♀(n=259)	Children (8-15)	Urine (RP-UPLC/EI-TMS)	BMI (Measured W&H)	Per 1-unit (log ng/mL)	β= 0.035 (0.008; 0.061)	Age, sex
Waist Circumference									
Wang, H et al. (2013) [97]	CHN	CS	Obese, OW and NW; ♂♀(n=259)	Children (8-15)	Urine (RP-UPLC/EI-TMS)	WC (Measured)	Per 1-unit (log ng/mL)	β= 0.023 (0.002; 0.044)	Age, sex
Low-molecular-weight Phthalates									
BMI									
Trasande, L et al. (2013) [103]	USA	CS	NHANES, 2003-2008; ♂♀(n=2862)	Children (6-19)	Urine (HPLC-TMS)	BMI z-score (Measured W&H)	Per 1-unit (ln µM)	β= 0.03 (-0.03; 0.09)	Age, race, sex, PIR, parental education, creatinine, cotinine, calories, TV
Trasande, L et al. (2013)	USA	CS	NHANES, 2003-2008;	Children (6-19)	Urine (HPLC-TMS)	Overweight (BMI≥P85 th)	Per 1-unit (ln µM)	OR= 1.01 (0.9; 1.13)	Age, race, sex, PIR,


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Table 13.10.1. Description of papers identified in the systematic review assessing the association between the sum of phthalates and adiposity[†]

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
[103]			♂♀(n=2862)						parental education, creatinine, cotinine, calories, TV
Trasande, L et al. (2013) [103]	USA	CS	NHANES, 2003-2008; ♂♀(n=2862)	Children (6-19)	Urine (HPLC-TMS)	Obesity (BMI≥P95 th)	Per 1-unit (ln μM)	OR= 1.02 (0.9; 1.17)	Age, race, sex, PIR, parental education, creatinine, cotinine, calories, TV
Wang, H et al. (2013) [97]	CHN	CS	Obese, OW and NW; ♂♀(n=259)	Children (8-15)	Urine (RP-UPLC/EI-TMS)	BMI (Measured W&H)	Per 1-unit (log ng/mL)	β= 0.041 (0.012; 0.069)	Age, sex
Buser, M et al. (2014a) [101]	USA	CS	NHANES, 2007-2010; ♂♀ [†]	Children (11.9*)	Urine (SPE-HPLC/TMS)	Obesity (BMI≥P95 th)	Q4 (>1.10) vs. Q1 (≤0.26)	OR= 2.84 (1.4; 5.78)	Age, race, calories, cotinine, creatinine, income
Buser, M et al. (2014a) [101]	USA	CS	NHANES, 2007-2010; ♂♀ [†]	Children (11.9*)	Urine (SPE-HPLC/TMS)	Overweight (BMI≥P85 th)	Q4 (>1.10) vs. Q1 (≤0.26)	OR= 1.49 (0.59; 3.77)	Age, race, calories, cotinine, creatinine, income
Buser, M et al. (2014a) [101]	USA	CS	NHANES, 2007-2010; ♂♀ [†]	Adults (43.9*)	Urine (SPE-HPLC/TMS)	Obesity (BMI≥ 30Kg/m ²)	Q4(>1.38) vs. Q1(≤0.24)	OR= 1.11 (0.77; 1.59)	Age, sex, race, calories, education, smoking, alcohol, DM
Buser, M et al. (2014a) [101]	USA	CS	NHANES, 2007-2010; ♂♀ [†]	Adults (43.9*)	Urine (SPE-HPLC/TMS)	Overweight (BMI:25-29.9 kg/m ²)	Q4(>1.38) vs. Q1(≤0.24)	OR= 0.97 (0.69; 1.37)	Age, sex, race, calories, education, smoking, alcohol, DM
Waist Circumference									
Wang, H et al. (2013)[97]	CHN	CS	Obese, OW and NW; ♂♀(n=259)	Children (8-15)	Urine (RP-UPLC/EI-TMS)	WC (Measured)	Per 1-unit (log ng/mL)	β= 0.027 (0.004; 0.049)	Age, sex
High-molecular-weight Phthalates									
BMI									
Trasande, L et al. (2013) [103]	USA	CS	NHANES, 2003-2008; ♂♀(n=2862)	Children (6-19)	Urine (HPLC-TMS)	BMI z-score (Measured W&H)	Per 1-unit (ln μM)	β= -0.01 (-0.06; 0.04)	Age, race, sex, PIR, parental education, creatinine,


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Table 13.10.1. Description of papers identified in the systematic review assessing the association between the sum of phthalates and adiposity[†]

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Trasande, L et al. (2013) [103]	USA	CS	NHANES, 2003-2008; ♂♀(n=2862)	Children (6-19)	Urine (HPLC-TMS)	Overweight (BMI≥P85 th)	Per 1-unit (ln μM)	OR= 0.96 (0.86; 1.09)	cotinine, calories, TV Age, race, sex, PIR, parental education, creatinine, cotinine, calories, TV
Trasande, L et al. (2013) [103]	USA	CS	NHANES, 2003-2008; ♂♀(n=2862)	Children (6-19)	Urine (HPLC-TMS)	Obesity (BMI≥P95 th)	Per 1-unit (ln μM)	OR= 1.04 (0.89; 1.22)	Age, race, sex, PIR, parental education, creatinine, cotinine, calories, TV
Wang, H et al. (2013)[97]	CHN	CS	Obese, OW and NW; ♂♀(n=259)	Children (8-15)	Urine (RP-UPLC/EI-TMS)	BMI (Measured W&H)	Per 1-unit (log ng/mL)	β= 0.042 (0.007; 0.077)	Age, sex
Buser, M et al. (2014a) [101]	USA	CS	NHANES, 2007-2010; ♂♀ [†]	Children (11.9*)	Urine (SPE-HPLC/TMS)	Obesity (BMI≥P95 th)	Q4(>0.73) vs. Q1(≤0.19)	OR= 1.26 (0.49; 3.26)	Age, race, calories, cotinine, creatinine, income
Buser, M et al. (2014a) [101]	USA	CS	NHANES, 2007-2010; ♂♀ [†]	Children (11.9*)	Urine (SPE-HPLC/TMS)	Overweight (BMI≥P85 th)	Q4(>0.73) vs. Q1(≤0.19)	OR= 1.38 (0.63; 3.03)	Age, race, calories, cotinine, creatinine, income
Buser, M et al. (2014a) [101]	USA	CS	NHANES, 2007-2010; ♂♀ [†]	Adults (43.9*)	Urine (SPE-HPLC/TMS)	Obesity (BMI≥ 30Kg/m ²)	Q4(>0.55) vs. Q1(≤0.13)	OR= 1.77 (1.26; 2.48)	Age, sex, race, calories, education, smoking, alcohol, diabetes
Buser, M et al. (2014a)	USA	CS	NHANES, 2007-2010; ♂♀ [†]	Adults (43.9*)	Urine (SPE-HPLC/TMS)	Overweight (BMI:25-29.9 kg/m ²)	Q4(>0.55) vs. Q1(≤0.13)	OR= 1.32 (0.9; 1.94)	Age, sex, race, calories, education, smoking, alcohol, diabetes
Waist Circumference									
Wang, H et al. (2013) [97]	CHN	CS	Obese, OW and NW; ♂♀(n=259)	Children (8-15)	Urine (RP-UPLC/EI-TMS)	WC (Measured)	Per 1-unit (log ng/mL)	β= 0.03 (0.001; 0.058)	Age, sex
Sum of Phthalates									



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Table 13.10.1. Description of papers identified in the systematic review assessing the association between the sum of phthalates and adiposity[‡]

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
BMI									
Wang, H et al. (2013) [97]	CHN	CS	Obese, OW and NW; ♂♀(n=259)	Children (8-15)	Urine (RP-UPLC/EI-TMS)	BMI (Measured W&H)	Per 1-unit (log ng/mL)	β= 0.049 (0.02; 0.079)	Age, sex
Waist Circumference									
Dirtu, AC et al. (2013) [100]	BEL	CS	Obese individuals; ♂♀(n=152)	Adults (18-84)	Urine (LC)	WC (Measured)	ln ng/mL	β= -0.02 (p=0.825)	Age, sex
Dirtu, AC et al. (2013) [100]	BEL	CS	Normal-weight controls; ♂♀(n=43)	Adults (19-59)	Urine (LC)	WC (Measured)	ln ng/mL	β= -0.24 (p=0.119)	Age, sex
Wang, H et al. (2013) [97]	CHN	CS	Obese, OW and NW; ♂♀(n=259)	Children (8-15)	Urine (RP-UPLC/EI-TMS)	WC (Measured)	Per 1-unit (log ng/mL)	β= 0.031 (0.006; 0.056)	Age, sex

[‡]Sums do not necessarily represent the same combination of substances.


PC: Prospective Cohort; CS: Cross-sectional; OW: Overweight; NW: Normal Weight; NHANES: National Health and Nutrition Examination Survey; SPE: Solid Phase Extraction; HPLC: High Performance Liquid Chromatography; ID: Isotope Dilution; TMS: Tandem Mass Spectrometry; RP-UPLC: Reversed-phase Ultra Performance Liquid Chromatography; EI: Electron Ionization; LC: Liquid Chromatography; BMI: Body Mass Index; W: Weight; H: Height; WC: Waist Circumference; WtHR: Waist to Hip Ratio; HC: Hip Circumference; β: Beta coefficient; p: Spearman correlation coefficient; OR: Odds Ratio; METs: Metabolic Equivalents; PIR: Poverty Income Ratio; TV: Television. †No further information; *Mean±sd.

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14. Bisphenol A (BPA)

We have identified fourteen publications reporting on the association between BPA and adiposity outcomes [98, 105-117]. Two papers were excluded from meta-analysis for presenting ORs as the association estimate [107, 109]. Ronn, M *et al.* (2014) [116] and Olsen, L *et al.* (2012) [98] both included PIVUS participants but were excluded for presenting only regression coefficients for log transformed variables. Five papers were also excluded for being performed among children [108, 111-113, 117]. Five publications were then included in this meta-analysis [105, 106, 110, 114, 115].

All studies presented a cross-sectional design. Sample sizes ranged from 37 to 246 adult individuals from Japan, China, Netherlands, Turkey and USA. In general, included papers used serum samples to measure BPA, but Erden, ES *et al.* (2014) [115] used whole blood and Zhao, HY *et al.* (2012) [110] used urinary concentrations of BPA. BMI was assessed in all the included publications. The overall beta coefficient was 0.32 (95% CI 0.25; 0.39), $I^2=52.9\%$. We have performed a sensitivity analysis excluding Zhao, HY *et al.* (2012) [110] and Erden, E *et al.* (2014) [115] to test the impact on the overall estimate of the biological medium used to assess the exposure. The summary estimate changed to $\beta= 0.42$ (95% CI 0.30; 0.54) and heterogeneity decreased to 43.2%, so we have chosen to exclude both papers from the final analysis (figure 14.1).

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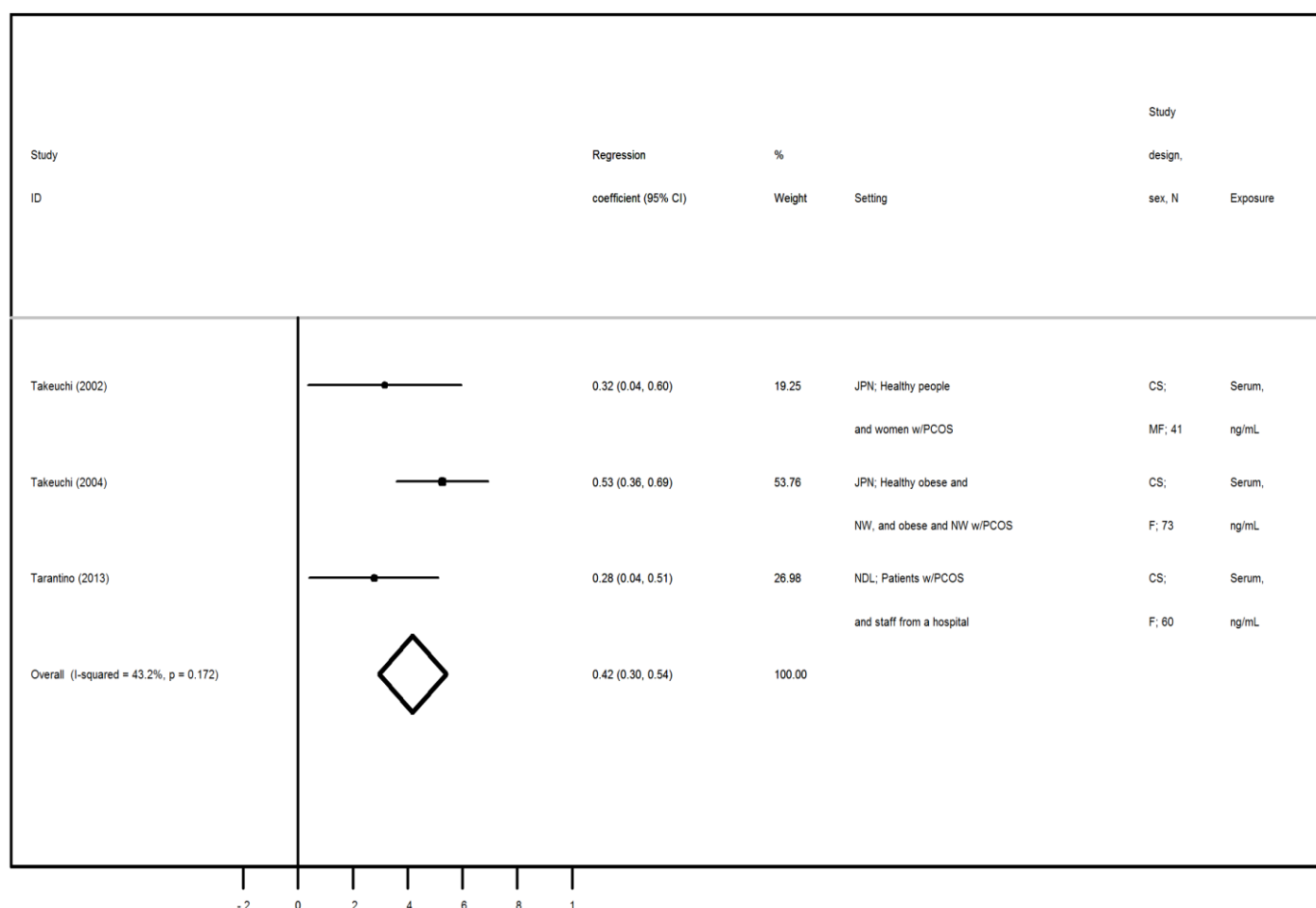



Figure 14.1. Meta-analysis of publications evaluating the association of BPA with BMI in adults. Beta coefficients and corresponding 95% CI (horizontal lines). The size of the black square indicates the study's weight in the analysis (weights are from fixed-effects analysis). The centre of the open diamond indicates the summary estimate and its width represents the 95%

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Four publications assessing the association between BPA and BMI in adults were excluded from meta-analysis [107, 109, 110, 115] (table 14.1). All results have shown positive and statistical significant associations with BMI.

Table 14.1. Description of papers assessing the association between BPA and BMI not eligible for the meta-analysis in adults

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Shankar, A et al. (2012) [107]	USA	CS	NHANES 2003-2008; ♂(n=1879)	Adults (44.3±0.5)	Urine (SPE-ID-HPLC-TMS)	BMI (measured W&H) ≥30 kg/m ²	>4.2 vs. <1.10 (ng/mL)	OR= 1.45 (1.04; 2.02)	Age, sex, ethnicity, education, alcohol, PA, DM, HT, TC
Shankar, A et al. (2012) [107]	USA	CS	NHANES 2003-2008; ♀(n=2088)	Adults (45.6±0.4)	Urine (SPE-HPLC-TMS)	BMI (measured) ≥30 kg/m ²	>4.2 vs. <1.10 (ng/mL)	OR= 1.93 (1.35; 2.74)	Age, sex, ethnicity, education, alcohol, PA, DM, HT, TC
Wang, T et al. (2012) [109]	CHN	CS	Gen. non obese population; ♂♀(n=2774)	Adults	Urine (LC-TMS)	BMI (measured W&H) 24-27 Kg/m ²	>1.43 vs. <0.47 (ng/mL)	OR= 1.29 (1.04; 1.61)	Age, sex, creatinine
Wang, T et al. (2012) [109]	CHN	CS	Gen. Population; ♂♀(n=3390)	Adults (60.8±9.9)	Urine (LC-TMS)	BMI (measured W&H) ≥28 Kg/m ²	>1.43 vs. <0.47 (ng/mL)	OR= 1.57 (1.22; 2.01)	Age, sex, creatinine
Zhao, HY et al. (2012)	CHN	CS	Premenopausal healthy women; ♀(n=246)	Adults (20-55)	Urine (LC-TMS)	BMI (measured W&H)	ng/mL	r= 0.298 (p<0.001)	-
Erden, E et al. (2014) [115]	TUR	CS	Patients w/ OSAS and controls; ♂(n=91), ♀(n=37)	Adults	Whole blood (HPLC)	BMI [†]	ng/ml	r= 0.197 (p= 0.039)	-

CS: Cross-sectional; PC: Prospective Cohort; NHANES: National Health and Nutrition Examination Survey; CHAMACOS: Center for the Health Assessment of Mothers and Children of Salinas; OSAS: Obstructive Sleep Apnea Syndrome; SPE: Solid-phase Extraction; IDHPLC: Isotope Dilution High Performance Liquid Chromatography; TMS: Tandem Mass Spectrometry; HPLC: High Performance Liquid Chromatography; UPLC: Ultra Performance Liquid Chromatography; IDTMS: Isotope Dilution Tandem Mass Spectrometry; LC: Liquid Chromatography; BMI: Body Mass Index; W: Weight; H: Height; P: Percentile; Q: Quartile; OR: Odds ratio; β: Beta coefficient; PA: Physical Activity; DM: Diabetes Mellitus; HT: Hypertension; TC: Total Cholesterol; *Mean±sd.


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Table 14.2 presents the description of publications addressing the association between BPA and other adiposity measures in adults. Shankar, A *et al.* (2012) [107] and Wang, T *et al.* (2012) [109] presented estimates as ORs and showed positive and statistical significant associations of BPA with waist circumference, both in men and women. Similar findings were presented in Zhao, HY *et al.* (2012) [110], reinforcing our results from the meta-analysis. Ronn, M *et al.* (2014) [116] was the only exception showing a negative but not significant association between BPA and fat mass among PIVUS subjects ($\beta = -130$, 95% CI -703; 442).

Table 14.2. Description of papers assessing the association between BPA and other adiposity measures in adults

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Fat Mass									
Zhao, HY <i>et al.</i> (2012)[110]	CHN	CS	Premenopausal healthy women; ♀(n=246)	Adults (20-55)	Urine (LC-TMS)	FM (DXA)	ng/mL	r= 0.195 (p<0.01)	-
Ronn, M <i>et al.</i> (2014)[116]	SWE	PC	PIVUS 2001-2004; ♂(n=427) ♀(n=453)	Adults (70y.o.)	Serum (LC-MS/TMS)	FM (DXA)	Per 1-unit (ln ng/mL)	$\beta = -130$ (-703; 442)	Sex, height, lean mass, education, energy and others
Waist Circumference									
Shankar, A <i>et al.</i> (2012)[107]	USA	CS	NHANES 2003-2008; ♂(n=1879)	Adults (44.3±0.5)*	Urine (SPE-HPLC-TMS)	WC (measured) ≥102 cm	>4.2 vs. <1.10 (ng/mL)	OR= 1.56 (1.08; 2.24)	Age, sex, ethnicity, education, alcohol, PA, DM, HT, TC
Shankar, A <i>et al.</i> (2012)[107]	USA	CS	NHANES 2003-2008; ♀(n=2088)	Adults (45.6±0.4)*	Urine (SPE-HPLC-TMS)	WC (measured) ≥88 cm	>4.2 vs. <1.10 (ng/mL)	OR= 1.64 (1.11; 2.42)	Age, sex, ethnicity, education, alcohol, PA, DM, HT, TC
Wang, T <i>et al.</i> (2012) [109]	CHN	CS	Gen. Population; ♂♀(n=3390)	Adults (60.8±9.9)*	Urine (LC-TMS)	WC (measured) ♂>90 cm; ♀>85 cm	>1.43 vs. <0.47 (ng/mL)	OR= 1.43 (1.17; 1.74)	Age, sex, creatinine
Zhao, HY <i>et al.</i> (2012)[110]	CHN	CS	Premenopausal healthy women; ♀(n=246)	Adults (20-55)	Urine (LC-TMS)	WC (measured)	ng/mL	r= 0.114 (p>0.05)	-


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Table 14.2. Description of papers assessing the association between BPA and other adiposity measures in adults

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Waist to Hip Ratio									
Zhao, HY et al. (2012)[110]	CHN	CS	Premenopausal healthy women; ♀(n=246)	Adults (20-55)	Urine (LC-TMS)	WtHR (measured)	ng/mL	r= 0.1 (p>0.05)	-

CS: Cross-sectional; PC: Prospective Cohort; ; PIVUS: Prospective Investigation of the Vasculature in Uppsala Seniors; NHANES: National Health and Nutrition Examination Survey; LC: Liquid Chromatography; TMS: Tandem Mass Spectrometry; MS: Mass Spectrometry; SPE: Solid-Phase Extraction; HPLC: High Performance Liquid Chromatography; FM: Fat Mass; DXA: Dual-energy X-ray Absorptiometry; WC: Waist Circumference; WtHR: Waist to Hip Ratio; r: Pearson correlation coefficient; β: Beta coefficient; OR: Odds ratio; PA: Physical Activity; DM: Diabetes Mellitus; HT: Hypertension; TC: Total Cholesterol.*Mean±sd.

Table 14.3 presents the description of publications addressing the association between BPA and adiposity measures in children. In general, results were similar to those found among adults, presenting mainly positive associations although in general without statistical significance.


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Table 14.3. Description of papers assessing the association between BPA and other adiposity measures in children

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
BMI									
Wang, H et al. (2012) [108]	CHN	CS	Gen. Population; ♂♀(n=259)	Children (8-15)	Urine (SPE-UPLC-IDTMS)	BMI (measured W&H)	Per 1-unit (log ng/mL)	β= 0.018 (0.004; 0.032)	Age, sex
Eng, D et al. (2013)[111]	USA	CS	NHANES 2003-2010; ♂♀(n=3370)	Children (12.1± 3.7)	Urine (ID-HPLC-TMS)	BMI (measured W&H) ≥85 th P	>4.9 vs. <1.3ng/ml	OR= 1.07 (0.8; 1.44)	Age, sex, race, creatinine, PIR, cotinine, soda
Eng, D et al. (2013)[111]	USA	CS	NHANES 2003-2010; ♂♀(n=3370)	Children (12.1± 3.7)	Urine (ID-HPLC-TMS)	BMI(measured W&H) ≥95 th P	>4.9 vs. <1.3ng/ml	OR= 2.05 (1.38; 3.04)	Age, sex, race, creatinine, PIR, cotinine, soda
Harley, K et al. (2013)[112]	USA	PC	CHAMACOS 2004-2009; ♂♀(n=274)	Children (9.4± 0.4)	Urine (SPE-IDHPLC-TMS)	BMI z-score (measured W&H)	Per 1-unit (log µg/L)	β= 0.01 (-0.08; 0.1)	Prepregnancy BMI, income, maternal education, and others
Harley, K et al. (2013)[112]	USA	CS	CHAMACOS 2008-2009; ♂♀(n=290)	Children (9.4±0.4)	Urine (SPE-IDHPLC-TMS)	BMI z-score (measured W&H)	Per 1-unit (log µg/L)	β= 0.04 (-0.07; 0.14)	Prepregnancy BMI, income, maternal education, and others
Fat Mass									
Eng, D et al. (2013)[111]	USA	CS	NHANES 2003-2010; ♂♀(n=3370)	Children (12.1± 3.7)*	Urine (IDHPLC-TMS)	FM (DXA) ≥85 th P	>4.9 vs. <1.3 (ng/ml)	OR= 2.1 (0.24; 17.8)	Age, sex, race, creatinine, PIR, cotinine, soda
Harley, K et al. (2013)[112]	USA	PC	CHAMACOS 2004-2009; ♂♀(n=274)	Children (9.4± 0.4)*	Urine (SPE-IDHPLC-TMS)	FM (BIA)	Per 1-unit (log µg/L)	β= 0.56 (-0.34; 1.46)	Prepregnancy BMI, income, maternal education, and others
Harley, K et al. (2013)[112]	USA	CS	CHAMACOS 2008-2009; ♂♀(n=290)	Children (9.4± 0.4)*	Urine (SPE-IDHPLC-TMS)	FM (BIA)	Per 1-unit (log µg/L)	β= 0.44 (-0.66; 1.55)	Prepregnancy BMI, income, maternal education, and others
Weight									
Li, DK et al. (2013)[113]	CHN	CS	Gen. Population; ♂(n=671)	Children	Urine (HPLC)	Weight (measured) >90 th P	≥2 vs. <2 (mg/L)	OR= 0.82 (0.55; 1.23)	Age, sex, school, residence, education and others
Li, DK et al. (2013)[113]	CHN	CS	Gen. Population; ♀(n=655)	Children	Urine (HPLC)	Weight (measured) >90 th P	≥2 vs. <2 (mg/L)	OR= 1.29 (0.83; 2.01)	Age, sex, school, residence, parents education and others
Waist Circumference									
Eng, D et al.	USA	CS	NHANES 2003-	Children	Urine	WC	>4.9 vs.	OR= 1.2	Age, sex, race,




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Table 14.3. Description of papers assessing the association between BPA and other adiposity measures in children

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
(2013)[111]	USA	CS	2010; ♂♀(n=3370)	(12.1±3.7)*	(IDHPLC-TMS)	(measured) ≥75 th P	<1.3 (ng/ml)	(0.86; 1.67)	creatinine, PIR, cotinine, soda
Eng, D et al. (2013)[111]			NHANES 2003-2010; ♂♀(n=3370)	Children (12.1±3.7)*	Urine (IDHPLC-TMS)	WC (measured) ≥90 th P	>4.9 vs. <1.3 (ng/ml)	OR= 1.4 (0.91; 2.15)	Age, sex, race, creatinine, PIR, cotinine, soda
Harley, K et al. (2013)[112]	USA	PC	CHAMACOS 2004-2009; ♂♀(n=274)	Children (9.4±0.4)*	Urine (SPE-IDHPLC-TMS)	WC (measured)	Per 1-unit (log µg/L)	β= -0.01 (-1.03; 1.06)	Prepregnancy BMI, income, maternal education, and others
Harley, K et al. (2013)[112]	USA	CS	CHAMACOS 2008-2009; ♂♀(n=290)	Children (9.4±0.4)*	Urine (SPE-IDHPLC-TMS)	WC (measured)	Per 1-unit (log µg/L)	β= 0.87 (-0.35; 2.09)	Prepregnancy BMI, income, maternal education, and others
Li, DK et al. (2013)[113]	CHN	CS	Gen. Population; ♀(n=655)	Children	Urine (HPLC)	WC (measured) >90 th P	≥2 vs. <2 (mg/L)	OR= 2.6 (0.98; 6.91)	Age, sex, school, residence, parents education and others
Waist to Hip Ratio									
Eng, D et al. (2013)[111]	USA	CS	NHANES 2003-2010; ♂♀(n=3370)	Children (12.1±3.7)*	Urine (IDHPLC-TMS)	WtHR (measured) ≥0.5	>4.9 vs. <1.3 (ng/ml)	OR= 1.56 (1.11; 2.17)	Age, sex, race, creatinine, PIR, cotinine, soda
Li, DK et al. (2013)[113]	CHN	CS	Gen. Population; ♀(n=655)	Children	Urine (HPLC)	WtHR (measured) >90 th P	≥2 vs. <2 (mg/L)	OR= 2.38 (0.92; 6.16)	Age, sex, school, residence, education and others
Wells, EM et al. (2014)[117]	USA	CS	NHANES 2003-2010; ♂♀(n=2836)	Children (6-18)	Urine (SPE-IDHPLC-TMS)	WtHR (measured)	≥5.1 vs. ≤1.4 (ng/mL)	β= 0.016 (0.007; 0.026)	Creatinine, age, sex, race, education, smoking, calories
Hip Circumference									
Li, DK et al. (2013)[113]	CHN	CS	Gen. Population; ♀(n=655)	Children	Urine (HPLC)	HC (measured) >90 th P	≥2 vs. <2 (mg/L)	OR= 2.88 (1.12; 7.45)	Age, sex, school, residence, education and other

CS: Cross-sectional; PC: Prospective Cohort; NHANES: National Health and Nutrition Examination Survey; CHAMACOS: Center for the Health Assessment of Mothers and Children of Salinas; IDHPLC: Isotope Dilution High Performance Liquid Chromatography; TMS: Tandem Mass Spectrometry; SPE: Solid-Phase Extraction; FM: Fat Mass; DXA: Dual-energy X-ray Absorptiometry; BIA: Bioelectrical Impedance Analysis; WC: Waist Circumference; WtHR: Waist to Hip Ratio; HC: Hip Circumference; P: Percentile; OR: Odds ratio; β: Beta coefficient; PIR: Poverty Income Ratio. *Mean±sd.

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15. Other EDCs


Seven other chemicals were identified in the systematic review (aroclor 1260 [42, 44], 2,4-Dichlorophenol (2,4-DCP) [104, 118, 119], 2,5-Dichlorophenol (2,5-DCP) [104, 118, 119], toxaphene [43], triclosan [104], mirex [42] and chrysene [57]). However, as none of these substances pertained to the same chemical groups previously defined, we have chosen to present them as an aside group. Additionally, combinations of compounds with distinct chemical properties have also been assessed [42, 52, 54, 74, 76, 86, 88, 89, 120, 121]. As we have identified a very limited number of studies assessing the association between each of these EDCs or combination of EDCs and adiposity, no meta-analysis was performed for any of the chemicals/combination of chemicals.

Pelletier, C *et al.* (2002) [42] and Hue, O *et al.* (2006) [44] both evaluated the relationship between aroclor 1260 and adiposity in obese and normal weight men, finding contradictory results – a positive correlation in Pelletier, C *et al.* (2002) [42] and a negative correlation in Hue, O *et al.* (2006) [44]. However, results reached statistical significance only in Pelletier, C *et al.* (2002) [42], that also observed a very similar association for fat mass.

Three publications evaluated 2,4-DCP and 2,5-DCP [104, 118, 119]. Positive associations were found for both chemicals, but were statistically significant only among NHANES 2007-2010 adolescents in Buser, M *et al.* (2014b) [104].

Similar results were observed regarding triclosan in both children and adolescents [104], as well as for chrysene, among adults [57]. On the other hand, results found for toxaphene and mirex provided negative and non-statistical significant estimates [42, 43].

Distinct combinations of dioxins, furans and dioxin-like PCBs were evaluated in four papers [52, 74, 88, 120]. In adults, conflicting results were observed – Moon, HB *et al.* (2012) [52] found a negative correlation among myoma patients, although with no statistical significance, while Chang, JW *et al.* (2011) [120] found a positive and

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statistically association in Individuals who reside near a PCP factory. A positive association was also observed for Japanese adolescents [74], while in children from Russia this association was negative, though both with statistical significance [88].

Six papers evaluated the association between the sum of persistent organic pollutants (POPs) with adiposity [42, 54, 76, 86, 89, 121]. Regardless of the adiposity measure used, all studies found positive associations among adults individuals. These associations reached statistical significance in 6 of the 10 provided estimates.

Table 15. Description of papers included in the systematic review assessing the association between other EDCs and adiposity measures

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Adults									
Aroclor 1260									
BMI									
Pelletier, C et al. (2002)	CAN	CS	Lean sedentary and obese men; ♂(n=43)	Adults (36-58)	Serum (GC)	BMI [†]	µg/Kg lipids	ρ= 0.35 (p= 0.023)	Age
Hue, O et al. (2006)	CAN	CS	Obese BPD-DS selected and NW; ♂(n=42)	Adults	Serum (GC-DE)	BMI (measured W&H)	µg/kg of lipids	r= -0.09 (p= 0.58)	-
Fat Mass									
Pelletier, C et al. (2002)	CAN	CS	Lean sedentary and obese men; ♂(n=43)	Adults (36-58)	Serum (GC)	FM (Siri equation)	µg/Kg lipids	ρ= 0.34 (p= 0.027)	Age
2,4-Dichlorophenol (2,4-DCP)									
Twum, C et al. (2011)	USA	CS	NHANES, 2003-2006; ♂♀(n=6770)	Children (6-19)	Urine (SPE-HPLC-TMS)	BMI z-score (measured W&H)	Q4 (≥3.7) vs. Q1 (<0.6)	OR= 1.07 (0.79; 1.45)	Age, race, gender, income, fat intake
Buser, M et al. (2014b)	USA	CS	NHANES 2007-2010; ♂♀(n=548)	Children (6-11)	Urine (SPE-HPLC-TMS)	BMI z-score (measured W&H)	Q4(>1.97) vs. Q1(≤0.38)	β=0.09 (-0.25; 0.44)	Age, sex, race, calories, TV, video game use, cotinine, income, creatinine
Buser, M et al. (2014b)	USA	CS	NHANES 2007-2010; ♂♀(n=548)	Children (6-11)	Urine (SPE-HPLC-TMS)	WC (measured)	Q4(>1.97) vs. Q1(≤0.38)	β= 1.42 (-1.37; 4.22)	Age, sex, race, calories, TV, video game use, cotinine, income, creatinine
Buser, M et al. (2014b)	USA	CS	NHANES 2007-2010; ♂♀(n=757)	Adolesc. (12-19)	Urine (SPE-HPLC-TMS)	BMI z-score (measured W&H)	Q4(>1.97) vs. Q1(≤0.38)	β= 0.36 (0.01; 0.72)	Age, sex, race, calories, TV, video game use, cotinine, income, creatinine


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Table 15. Description of papers included in the systematic review assessing the association between other EDCs and adiposity measures

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Buser, M et al. (2014b)	USA	CS	NHANES 2007-2010; ♂♀(n=757)	Adolesc. (12-19)	Urine (SPE-HPLC-TMS)	WC (measured)	Q4(>1.97) vs. Q1(≤0.38)	β= 5.14 (1.14; 9.14)	Age, sex, race, calories, TV, video game use, cotinine, income, creatinine
Wei, Y et al. (2014)	USA	CS	NHANES 2007-2008; ♂♀(n=2963)	Adults (20-85)	Urine (SPE-IDHPLC-TMS)	BMI ≥30 kg/m ²	Q4≥34.17 vs. Q1<3.26	OR= 1.03 (0.78; 1.36)	Age, gender, race, education, total fat, PA
2,5-Dichlorophenol (2,5-DCP)									
Twum, C et al. (2011)	USA	CS	NHANES, 2003-2006; ♂♀(n=6770)	Children (6-19)	Urine (SPE-HPLC-TMS)	BMI z-score (measured W&H)	Q4 (≥74.6) vs. Q1 (<5.7)	OR= 1.44 (1.06; 1.95)	Age, race, gender, income, fat intake
Buser, M et al. (2014b)	USA	CS	NHANES 2007-2010; ♂♀(n=548)	Children (6-11)	Urine (SPE-HPLC-TMS)	BMI z-score (measured W&H)	Q4(>27.91) vs. Q1≤2.03	β= 0.07 (-0.3; 0.45)	Age, sex, race, calories, TV, video game use, cotinine, income, creatinine
Buser, M et al. (2014b)	USA	CS	NHANES 2007-2010; ♂♀(n=548)	Children (6-11)	Urine (SPE-HPLC-TMS)	WC (measured)	Q4(>27.91) vs. Q1≤2.03	β= 1.37 (-2.01; 4.74)	Age, sex, race, calories, TV, video game use, cotinine, income, creatinine
Buser, M et al. (2014b)	USA	CS	NHANES 2007-2010; ♂♀(n=757)	Adolesc. (12-19)	Urine (SPE-HPLC-TMS)	BMI z-score (measured W&H)	Q4(>27.91) vs. Q1≤2.03	β= 0.46 (0.08; 0.85)	Age, sex, race, calories, TV, video game use, cotinine, income, creatinine
Buser, M et al. (2014b)	USA	CS	NHANES 2007-2010; ♂♀(n=757)	Adolesc. (12-19)	Urine (SPE-HPLC-TMS)	WC (measured)	Q4(>27.91) vs. Q1≤2.03	β= 6.83 (1.86; 11.8)	Age, sex, race, calories, TV use, cotinine, income, creatinine
Wei, Y et al. (2014)	USA	CS	NHANES 2007-2008; ♂♀(n=2963)	Adults (20-85)	Urine (SPE-IDHPLC-TMS)	BMI ≥30 kg/m ²	Q4≥34.17 vs. Q1<3.26	OR= 1.62 (1.21; 2.17)	Age, sex, race, education, total fat, PA
Toxaphene									
Magnusdottir, E et al. (2005)	ISL	CS	Infertile men; ♂(n=72)	Adults (37±5.4)	Serum (GC)	BMI (self-reported W&H)	ng/g lipids	p= 0.05 (p= 0.06)	-
Triclosan									
Buser, M et al. (2014b)	USA	CS	NHANES 2007-2010; ♂♀(n=548)	Children (6-11)	Urine (SPE-HPLC-TMS)	BMI z-score (measured W&H)	Q4(>36.53) vs. Q1(≤3.53)	β=0.02 (-0.26; 0.31)	Age, sex, race, calories, TV use, cotinine, income, creatinine
Buser, M et al. (2014)	USA	CS	NHANES 2007-2010;	Children (6-11)	Urine (SPE-HPLC-TMS)	WC (measured)	Q4(>36.53) vs.	β= -0.52 (-3.07;	Age, sex, race, calories, TV use,


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Table 15. Description of papers included in the systematic review assessing the association between other EDCs and adiposity measures

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
			♂♀(n=548)				Q1(≤3.53)	1.9)	cotinine, income, creatinine
Buser, M et al. (2014b)	USA	CS	NHANES 2007-2010; ♂♀(n=757)	Adolesc. (12-19)	Urine (SPE-HPLC-TMS)	BMI z-score (measured W&H)	Q4(>36.53) vs. Q1(≤3.53)	β= -0.14 (-0.4; 0.13)	Age, sex, race, calories, TV use, cotinine, income, creatinine
Buser, M et al. (2014b)	USA	CS	NHANES 2007-2010; ♂♀(n=757)	Adolesc. (12-19)	Urine (SPE-HPLC-TMS)	WC (measured)	Q4(>36.53) vs. Q1(≤3.53)	β= -2.11 (-4.81; 0.59)	Age, sex, race, calories, TV use, cotinine, income, creatinine
Mirex									
Pelletier, C et al. (2002)	CAN	CS	Lean sedentary and obese men; ♂(n=43)	Adults (36-58)	Serum (GC)	BMI†	µg/Kg lipids	ρ= -0.02 (p=0.924)	Age
Pelletier, C et al. (2002)	CAN	CS	Lean sedentary and obese men; ♂(n=43)	Adults (36-58)	Serum (GC)	FM (Siri equation)	µg/Kg lipids	ρ= -0.14 (p=0.28)	Age
Chrysene									
Qin, YY et al. (2011)	HKG	CS	Blood donors; ♂(n=60), ♀(n=51)	Adults	Serum (GC-MS)	BMI (self-reported W&H)	ng/g lipid	r=0.505 (p<0.05)	-
Polychlorinated dibenzo-p-dioxins/furans (PCDD/F)									
Moon, HB et al. (2012)	KOR	CS	Myoma patients; ♀(n=53)	Adults (40-68)	Adipose Tissue (GC/MS)	BMI†	ng/g lipid	ρ= -0.262	-
Chang, JW et al. (2011)	TWN	CS	Individuals who reside near a PCP factory; ♂(n=758), ♀(n=691)	Adults (≥18)	Serum (HRGC/HRMS)	WC†	pg WHO-TEQ/g lipid	r=0.249 (p<0.001)	-
Sum of PCDDs, PCDFs, coplanar PCBs									
Burns, JS et al. (2011)	RUS	PC	Gen. Population; ♂(n=468)	Children (8-9)	Serum (HRGC/HRMS)	BMI z-score (measured W&H)	Qu5(537-2963) vs. Qu1(123-264) (ng/g lipid)	β= -0.67 (-1.01; -0.33)	Age, BW, gestational age, income, calories blood lead levels
TEQ PCDDs, PCDFs, dioxin-like PCBs									
Uemura, H et al. (2009)	JPN	CS	Gen. Population; ♂♀(n=1374)	Children & Adults (15-73)	Whole blood (GC/MS)	BMI (measured W&H) ≥25 kg/m ²	≥ 31.00 vs. < 12.00 (pg TEQ/g lipid)	OR=1.9 (1.1;3.3)	Age, sex, smoking, alcohol, regional block, residential area, survey


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Table 15. Description of papers included in the systematic review assessing the association between other EDCs and adiposity measures

Authors, year of publication	Country	Type of study	Subjects characteristics	Age group	Exposure Assessment	Outcome Assessment	Exposure contrast	Estimate (95% CI)	Adjustment for confounders
Sum of POPs [‡]									
Lee, DH et al. (2014)	KOR	NCC	Uljin cohort 2006-2010; ♂(n= 81), ♀(n= 165)	Adults (>40)	Serum (GC-IDHRMS)	WC (measured) ♂≥90; ♀≥80cm	Q4 vs. Q1	OR= 1.4 (0.4; 4.7)	Age, sex, smoking, alcohol, exercise, TG, TC, BMI
Lee, DH et al. (2014)	KOR	NCC	Uljin cohort 2006-2010; ♂(n= 81), ♀(n= 165)	Adults (>40)	Serum (GC-IDHRMS)	WC (measured) ♂≥90; ♀≥80cm	Q4 vs. Q1	OR= 3.5 (1; 11.5)	Age, sex, smoking, alcohol, exercise, TG, TC, BMI
Pelletier, C et al. (2002)	CAN	CS	Lean sedentary men and obese men; ♂(n=43)	Adults (36-58)	Serum (GC)	BMI†	µg/Kg lipids	ρ= 0.41 (p= 0.007)	Age
Pelletier, C et al. (2002)	CAN	CS	Lean sedentary men and obese men; ♂(n=43)	Adults (36-58)	Serum (GC)	FM (Siri equation)	µg/Kg lipids	ρ= 0.43 (p= 0.004)	Age
Muscat, JE et al. (2003)	USA	CS	Gen. Population; ♀(n=224)	Adults (≤82)	Adipose Tissue (GC-ECD)	BMI†	ng/g lipid	ρ= 0.35 (p>0.05)	-
Pestana, D et al. (2014)	POR	CS	Individuals undergoing bariatric surgery; ♂♀(n= 189)	Adults (19-65)	Adipose Tissue (GC-ECD)	BMI (measured W&H)	ng/g of fat	ρ= 0.045 (p>0.05)	-
Pestana, D et al. (2014)	POR	CS	Individuals undergoing bariatric surgery; ♂♀(n= 158)	Adults	Adipose Tissue (GC-ECD)	WC (measured)	ng/g of fat	ρ= 0.031 (p>0.05)	-
Stellman, SD et al. (2000)	USA	CS	Breast cancer, benign breast diseases and undergoing non-breast-related surgery; ♀(n=555)	Adults	Adipose Tissue (GC-ECD)	BMI†	ng/g lipid	ρ= 0.351 (p<0.01)	-
Ha, MH et al. (2007)	USA	CS	NHANES1999-2002; ♂(n= 889)	Adults (40-85)	Serum HRGC/HRMS	BMI†	ng/g lipids	ρ= 0.2 (p<0.01)	Age
Ha, MH et al. (2007)	USA	CS	NHANES1999-2002; ♀(n= 889)	Adults (40-85)	Serum HRGC/HRMS	BMI†	ng/g lipids	ρ= 0.19 (p<0.01)	Age

CS: Cross-sectional; PC: Prospective Cohort; NCC: Nested Case-control; NHANES: National Health and Nutrition Examination Survey; BPD-DS: Biliopancreatic Diversion with Duodenal Switch; NW: Normal Weight; GC: Gas Chromatography; DE: Dual Electron; HPLC: High Performance Liquid Chromatography; SPE: Solid-Phase Extraction; TMS: Tandem Mass Spectrometry; HRGC: High Resolution Gas Chromatography; HRMS: High Resolution Mass Spectrometry; IDHRMS: Isotope Dilution High Resolution Mass Spectrometry; MS: Mass spectrometry; WC: Waist Circumference; W: Weight; BMI: Body Mass Index; H: Height; FM: Body Fat; Q: Quartile; Qu: Quintile; β: Beta coefficient; OR: Odds ratio; ρ: Spearman correlation coefficient; r: Pearson correlation coefficient; PA: Physical Activity; TG: Triglycerides; TC: Total cholesterol. *Mean±sd; †No further information; ‡Sums do not necessarily represent the same combination of substances.

Discussion

To our knowledge, this is the first comprehensive systematic review on the association between EDCs and adiposity, presenting such a broad range of compounds. Eighty one publications were identified, most of the studies were cross-sectional, but some case-control and prospective studies were also found. Most studies were developed in middle- or high-income countries.

Among adult individuals summary estimates were calculated for a total of twenty EDCs: oxychlordan, trans-nonachlor, DDT (p,p'-DDE, DDE and p,p'-DDT), β -HCH, HCB, dioxin-like PCBs (PCB 118 and 156), non-dioxin-like PCBs (PCB 99, 138, 153, 170, 180 and 187), phthalates (mBP, MEHP, MEP and MBzP) and BPA.

Since the objective of our review was to evaluate the association between EDCs and adiposity all measures of adiposity were eligible, we found results for BMI, fat mass, weight, waist circumference and derivate indexes, visceral and subcutaneous adipose tissue. The most commonly used adiposity measure across all substances was BMI and therefore, for the majority of EDCs, estimates included in the meta-analysis evaluated the association between EDCs and BMI. Nevertheless, to not lose information concerning other measures of adiposity, for each one of the analysed EDCs, results for all the available adiposity measures were presented and separate summary estimates were also calculated whenever appropriated.

As the quantification of adiposity in adults and children is very different, the same measure may have a different meaning in each of these age groups. For this reason we decided present separate results from adults and children. For all the identified substances, most papers provided estimates for adult individuals and therefore, meta-analysis was performed only for adults.

From the meta-analyses performed including adult individuals, a positive and statistically significant overall estimate was found for eight compounds: oxychlordan, p,p'-DDE, DDE (not specified), β -HCH, HCB, PCB 118, PCB 99 and BPA. Conversely, a negative and statistically significant association was observed for PCB 180. No significant associations were found for the other compounds, positive for trans-nonachlor, PCB 156, PCB 138, PCB 187, mBP, MEP, MiBP, MBzP and MMP; negative for PCB 153, PCB 170, MEHP, MEOHP, p,p'-DDT and MEHHP.

Regarding the eight compounds for which we found a positive and significant association, all the included results were based on BMI and presented a high

heterogeneity. However, these results were consistent with those observed for other adiposity measures for each of the EDC, reinforcing the association.

It is important to note that these results should be read with caution due to the methodological differences and the high heterogeneity in most of the analyses. In order to enhance the comparability of studies selected for the meta-analysis, additional exclusions were made. We decided to exclude studies performed among populations for which we expected changes in adiposity related with their specific characteristics, such as pregnant women, cancer patients or patients with any other relevant conditions. We also excluded results that included populations that were expected to have particularly high exposure levels, such as occupationally exposed individuals or individuals from geographical areas with known high exposures. As the number of studies performed among these populations was limited, it was not possible to perform a separate analysis for these specific populations.

The measures of association used to quantify the association between EDCs and adiposity imply the comparison with a reference value, which usually corresponds to the population groups with lower levels of exposure. Therefore, results provided in different studies were often difficult to compare because of differences in the exposure EDCs levels between populations. The impact of differences of exposure levels may be even more relevant if the dose–response relationship do not follow a regular dynamic. There is evidence that EDCs can exhibit adverse effects at lower concentrations than those being tested in toxicological studies, contradicting the assumption that these dose-response relationships are monotonic [122-124]. Additionally, it has been suggested that while lower levels of exposure such as those usually found in environment may promote weight gain, higher exposure doses to some EDCs may lead to weight loss and growth restriction [14, 123]. The impact of these differences on the overall estimates was difficult to evaluate since many of the studies did not provide descriptive data regarding exposure. In order to minimize the effect of large differences, we separated results obtained among populations with high levels of exposure, because among these populations the lowest exposure group will already present high levels of exposure, which may correspond to the highest levels of exposure in other populations. Nevertheless, the results from the 12 identified studies on individuals with higher exposure levels (e.g. workers in plants manufacture, veterans) [11, 60, 65, 71-73, 78, 80, 81, 83, 87, 120] have in general presented results in line with those observed among other populations included in the meta-analyses.

Although most of the meta-analyses result from studies evaluating BMI, the adiposity measure was not an exclusion criterion. In order to test if the type of adiposity measure had a relevant effect on the overall estimate, whenever estimates assessing other measures of adiposity fulfilled the inclusion criteria, they were included in the meta-analysis. A sensitivity analysis was then performed in order to decide whether or not that estimate would be included in the final analysis. In general, estimates using waist circumference as the adiposity measure did not increase heterogeneity and were thus included. Estimates using other adiposity measures that increased the heterogeneity were excluded from the meta-analyses and were presented only in descriptive tables.

On the other hand, for most of the compounds there were many estimates not included in the meta-analysis and were presented only in the descriptive table. Actually, most of those estimates were from studies that provided more than one adiposity measure for the same population, which was already included in the meta-analyses (usually BMI) and we cannot include two estimates with results not independent of each other. Nevertheless, when papers provided age- and/or sex-stratified estimates all were included in the meta-analysis. In this case, it should be noted that possible biases present in those studies may be overrepresented in the overall estimate.

Despite the measures taken in order to promote homogeneity between studies included in the meta-analyses, these results should be read with caution due to the methodological differences and the high heterogeneity in most of the analyses. When possible, we have tested possible sources of variance across studies (such as type of study, adiposity measure used and exposure assessment). In some cases, these methodological differences explained at least some of the high variance across included estimates (trans-nonachlor, DDE, PCB 118, PCB 156, PCB 99, PCB 170 and PCB 180) and heterogeneity between estimates has decreased with sensitivity analysis. Under these circumstances, we chose to consider as a final result the summary estimate from the meta-analysis with more restricted number of studies. However, for many other substances, since for most compounds the number of included papers was very limited, we were not able to test other sources of heterogeneity.

Although we could not test them, we can hypothesize some other aspects that may have an impact on variance across studies. Many of the identified papers that

were included in the final analysis have a small sample size, or were conducted among very specific population samples that may not necessarily be comparable (e.g. benign breast disease patients vs. infertile men). Other conditioning factor is the variety of assay methodologies and biological means (total blood, serum, adipose tissue, urine) used to assess exposure levels. These methodological options may result in differences on validity and precision among studies that contribute to the heterogeneity observed.

Also we need to highlight that although 81 papers were identified in the systematic review, many of them were developed within the same study (e.g. PIVUS, NHANES, etc.) that may artificially reproduce the same result, particularly for compounds that share the same source of exposure. In this situation, the same individual is exposed to various compounds, and probably the prevailing effect is from the compound with greater strength of association. Furthermore most studies were not designed to answer this specific research question and present a cross-sectional approach (only 8 presented data from longitudinal analysis [49, 50, 59, 61, 88, 96, 112, 116]) increasing the probability of reverse causality.

In spite of these limitations, in order to help us understand if there was a pattern of consistency in the observed estimates, we have also calculated summary estimates for each adiposity measure, whenever possible (i.e. whenever two or more estimates were provided as beta/correlation coefficients, if not pertaining to the same population) and, in general, we found consistency in the direction of the association, regardless of the adiposity measure used. Additionally, for these compounds, papers that were not allowed in summary estimates (e.g. providing ORs or performed among specific groups) have also showed results in accordance with those found in meta-analyses. The consistency of results gives us confidence in the results presented. However the main conclusion is the need of more studies, namely larger and long-term cohort studies that will allow the assessment of the impact of EDCs on adiposity.

References

1. Pruss-Ustun, A., et al., *Knowns and unknowns on burden of disease due to chemicals: a systematic review*. Environ Health, 2011. **10**: p. 9.
2. Bergman, Å., et al., *State of the science of endocrine disrupting chemicals 2012: an assessment of the state of the science of endocrine disruptors prepared by a group of experts for the United Nations Environment Programme and World Health Organization*. 2013: World Health Organization.
3. Groshart, C. and P. Okkerman, *Towards the establishment of a priority list of substances for further evaluation of their role in endocrine disruption-preparation of a candidate list of substances as a basis for priority setting*. Final report, 2000: p. 35.
4. Farré, M.I., et al.
5. Legler, J., et al., *Obesity, diabetes, and associated costs of exposure to endocrine-disrupting chemicals in the European Union*. J Clin Endocrinol Metab, 2015. **100**(4): p. 1278-88.
6. Trasande, L., et al., *Estimating burden and disease costs of exposure to endocrine-disrupting chemicals in the European union*. J Clin Endocrinol Metab, 2015. **100**(4): p. 1245-55.
7. Homan, G.F., M. Davies, and R. Norman, *The impact of lifestyle factors on reproductive performance in the general population and those undergoing infertility treatment: a review*. Hum Reprod Update, 2007. **13**(3): p. 209-23.
8. Hauser, R., *The environment and male fertility: recent research on emerging chemicals and semen quality*. Semin Reprod Med, 2006. **24**(3): p. 156-67.
9. Cohn, B.A., et al., *DDT and breast cancer in young women: new data on the significance of age at exposure*. Environ Health Perspect, 2007. **115**(10): p. 1406-14.
10. Chapin, R.E., et al., *NTP-CERHR expert panel report on the reproductive and developmental toxicity of bisphenol A*. Birth Defects Res B Dev Reprod Toxicol, 2008. **83**(3): p. 157-395.
11. Goncharov, A., et al., *High serum PCBs are associated with elevation of serum lipids and cardiovascular disease in a Native American population*. Environ Res, 2008. **106**(2): p. 226-39.
12. Codru, N., et al., *Diabetes in relation to serum levels of polychlorinated biphenyls and chlorinated pesticides in adult Native Americans*. Environ Health Perspect, 2007. **115**(10): p. 1442-7.
13. Vasiliu, O., et al., *Polybrominated biphenyls, polychlorinated biphenyls, body weight, and incidence of adult-onset diabetes mellitus*. Epidemiology, 2006. **17**(4): p. 352-9.
14. Grun, F. and B. Blumberg, *Endocrine disrupters as obesogens*. Mol Cell Endocrinol, 2009. **304**(1-2): p. 19-29.
15. Bergman, A., et al., *The impact of endocrine disruption: a consensus statement on the state of the science*. Environ Health Perspect, 2013. **121**(4): p. A104-6.
16. Lovejoy, J.C. and A. Sainsbury, *Sex differences in obesity and the regulation of energy homeostasis*. Obes Rev, 2009. **10**(2): p. 154-67.
17. Pan, G., et al., *Decreased serum free testosterone in workers exposed to high levels of di-n-butyl phthalate (DBP) and di-2-ethylhexyl phthalate (DEHP): a cross-sectional study in China*. Environ Health Perspect, 2006. **114**(11): p. 1643-8.
18. Swan, S.H., *Environmental phthalate exposure in relation to reproductive outcomes and other health endpoints in humans*. Environ Res, 2008. **108**(2): p. 177-84.

19. Hany, J., et al., *Developmental exposure of rats to a reconstituted PCB mixture or aroclor 1254: effects on organ weights, aromatase activity, sex hormone levels, and sweet preference behavior*. Toxicol Appl Pharmacol, 1999. **158**(3): p. 231-43.
20. Lovekamp, T.N. and B.J. Davis, *Mono-(2-ethylhexyl) phthalate suppresses aromatase transcript levels and estradiol production in cultured rat granulosa cells*. Toxicol Appl Pharmacol, 2001. **172**(3): p. 217-24.
21. Wojtowicz, A.K., T. Milewicz, and E.L. Gregoraszczuk, *DDT and its metabolite DDE alter steroid hormone secretion in human term placental explants by regulation of aromatase activity*. Toxicol Lett, 2007. **173**(1): p. 24-30.
22. Kjeldsen, L.S., M. Ghisari, and E.C. Bonefeld-Jorgensen, *Currently used pesticides and their mixtures affect the function of sex hormone receptors and aromatase enzyme activity*. Toxicol Appl Pharmacol, 2013. **272**(2): p. 453-64.
23. Zoeller, R.T., *Environmental chemicals impacting the thyroid: targets and consequences*. Thyroid, 2007. **17**(9): p. 811-7.
24. Grun, F. and B. Blumberg, *Environmental obesogens: organotins and endocrine disruption via nuclear receptor signaling*. Endocrinology, 2006. **147**(6 Suppl): p. S50-5.
25. Hurst, C.H. and D.J. Waxman, *Activation of PPARalpha and PPARgamma by environmental phthalate monoesters*. Toxicol Sci, 2003. **74**(2): p. 297-308.
26. Baillie-Hamilton, P.F., *Chemical toxins: a hypothesis to explain the global obesity epidemic*. J Altern Complement Med, 2002. **8**(2): p. 185-92.
27. Howdeshell, K.L., et al., *Exposure to bisphenol A advances puberty*. Nature, 1999. **401**(6755): p. 763-4.
28. Newbold, R.R., et al., *Developmental exposure to estrogenic compounds and obesity*. Birth Defects Res A Clin Mol Teratol, 2005. **73**(7): p. 478-80.
29. Sitarek, K. and S. Gralewicz, *Early developmental effects of separate or combined perinatal exposure to methylmercury (MeHg) and 2,2',4,4',5,5'-hexachlorobiphenyl (PCB 153) in the rat*. Int J Occup Med Environ Health, 2009. **22**(2): p. 89-105.
30. Kelishadi, R., P. Poursafa, and F. Jamshidi, *Role of environmental chemicals in obesity: a systematic review on the current evidence*. J Environ Public Health, 2013. **2013**: p. 896789.
31. de Cock, M. and M. van de Bor, *Obesogenic effects of endocrine disruptors, what do we know from animal and human studies?* Environ Int, 2014. **70**: p. 15-24.
32. Tang-Peronard, J.L., et al., *Endocrine-disrupting chemicals and obesity development in humans: a review*. Obes Rev, 2011. **12**(8): p. 622-36.
33. Goodman, M., J.S. LaKind, and D.R. Mattison, *Do phthalates act as obesogens in humans? A systematic review of the epidemiological literature*. Critical Reviews in Toxicology, 2014. **44**(2): p. 151-175.
34. Lakind, J.S., M. Goodman, and D.R. Mattison, *Bisphenol A and indicators of obesity, glucose metabolism/type 2 diabetes and cardiovascular disease: a systematic review of epidemiologic research*. Crit Rev Toxicol, 2014. **44**(2): p. 121-50.
35. Oppeneer, S.J. and K. Robien, *Bisphenol A exposure and associations with obesity among adults: a critical review*. Public Health Nutr, 2015. **18**(10): p. 1847-63.
36. Damstra, T., et al., *Global assessment of the state-of-the-science of endocrine disruptors*. Geneva: World Health Organization, 2002.
37. World Health Organization (2014) *Global Status Report on Non-Communicable Diseases*, 2014. <http://www.who.int/nmh/publications/ncd-status-report-2014/en/>.
38. Lim, S.S., et al., *A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a*

- systematic analysis for the Global Burden of Disease Study 2010. *Lancet*, 2012. **380**(9859): p. 2224-60.
39. Nieminen, P., Lehtiniemi, H., Vähäkangas, K., Huusko, A., Rautio, A., *Standardised regression coefficient as an effect size index in summarizing findings in epidemiological studies*. *Epidemiology, Biostatistics and Public Health*, 2013. **10**(4): p. 1-15.
 40. Deeks, J.J., Altman, D. G., Bradburn, M. J., *Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis*, in *Systematic Reviews in Health Care: Meta-Analysis in Context*, G.D.S. M. Egger, and D. G. Altman, Editor. 2008, BMJ: London. p. 285-312.
 41. Higgins, J.P. and S.G. Thompson, *Quantifying heterogeneity in a meta-analysis*. *Stat Med*, 2002. **21**(11): p. 1539-58.
 42. Pelletier, C., J.P. Despres, and A. Tremblay, *Plasma organochlorine concentrations in endurance athletes and obese individuals*. *Med Sci Sports Exerc*, 2002. **34**(12): p. 1971-5.
 43. Magnusdottir, E.V., et al., *Persistent organochlorines, sedentary occupation, obesity and human male subfertility*. *Hum Reprod*, 2005. **20**(1): p. 208-15.
 44. Hue, O., et al., *Increased plasma levels of toxic pollutants accompanying weight loss induced by hypocaloric diet or by bariatric surgery*. *Obes Surg*, 2006. **16**(9): p. 1145-54.
 45. Lee, D.H., et al., *A strong dose-response relation between serum concentrations of persistent organic pollutants and diabetes: results from the National Health and Examination Survey 1999-2002*. *Diabetes Care*, 2006. **29**(7): p. 1638-44.
 46. Lee, D.H., et al., *Relationship between serum concentrations of persistent organic pollutants and the prevalence of metabolic syndrome among non-diabetic adults: results from the National Health and Nutrition Examination Survey 1999-2002*. *Diabetologia*, 2007. **50**(9): p. 1841-51.
 47. Cho, M.R., et al., *Associations of fat mass and lean mass with bone mineral density differ by levels of persistent organic pollutants: National Health and Nutrition Examination Survey 1999-2004*. *Chemosphere*, 2011. **82**(9): p. 1268-76.
 48. Wolff, M.S., et al., *Organochlorine exposures and breast cancer risk in New York City women*. *Environ Res*, 2000. **84**(2): p. 151-61.
 49. Ronn, M., et al., *Circulating levels of persistent organic pollutants associate in divergent ways to fat mass measured by DXA in humans*. *Chemosphere*, 2011. **85**(3): p. 335-43.
 50. Lee, D.H., et al., *Associations of persistent organic pollutants with abdominal obesity in the elderly: The Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study*. *Environ Int*, 2012. **40**: p. 170-8.
 51. Roos, V., et al., *Circulating levels of persistent organic pollutants in relation to visceral and subcutaneous adipose tissue by abdominal MRI*. *Obesity (Silver Spring)*, 2013. **21**(2): p. 413-8.
 52. Moon, H.B., et al., *Polybrominated diphenyl ethers, polychlorinated biphenyls, and organochlorine pesticides in adipose tissues of Korean women*. *Arch Environ Contam Toxicol*, 2012. **62**(1): p. 176-84.
 53. Inmaculada Sanz-Gallardo, M., et al., *Determinants of p,p'-dichlorodiphenyldichloroethane (DDE) concentration in adipose tissue in women from five European cities*. *Arch Environ Health*, 1999. **54**(4): p. 277-83.
 54. Stellman, S.D., et al., *Breast cancer risk in relation to adipose concentrations of organochlorine pesticides and polychlorinated biphenyls in Long Island, New York*. *Cancer Epidemiol Biomarkers Prev*, 2000. **9**(11): p. 1241-9.
 55. Dorea, J.G., et al., *Perinatal metabolism of dichlorodiphenyldichloroethylene in Nicaraguan mothers*. *Environ Res*, 2001. **86**(3): p. 229-37.

56. Dirinck, E., et al., *Obesity and persistent organic pollutants: possible obesogenic effect of organochlorine pesticides and polychlorinated biphenyls*. Obesity (Silver Spring), 2011. **19**(4): p. 709-14.
57. Qin, Y.Y., et al., *Halogenated POPs and PAHs in blood plasma of Hong Kong residents*. Environ Sci Technol, 2011. **45**(4): p. 1630-7.
58. Al-Saleh, I., et al., *Levels of DDT and its metabolites in placenta, maternal and cord blood and their potential influence on neonatal anthropometric measures*. Sci Total Environ, 2012. **416**: p. 62-74.
59. Burns, J.S., et al., *Serum concentrations of organochlorine pesticides and growth among Russian boys*. Environ Health Perspect, 2012. **120**(2): p. 303-8.
60. Langer, P., et al., *Blood testosterone in middle aged males heavily exposed to endocrine disruptors is decreasing more with HCB and p,p'-DDE related to BMI and lipids, but not with Sigma15PCBs*. Endocr Regul, 2012. **46**(2): p. 51-9.
61. Wu, H., et al., *Persistent organic pollutants and type 2 diabetes: a prospective analysis in the nurses' health study and meta-analysis*. Environ Health Perspect, 2013. **121**(2): p. 153-61.
62. Dirinck, E.L., et al., *Exposure to persistent organic pollutants: relationship with abnormal glucose metabolism and visceral adiposity*. Diabetes Care, 2014. **37**(7): p. 1951-8.
63. Teeyapant, P., et al., *Serum concentrations of organochlorine pesticides p,p'-DDE in adult Thai residents with background levels of exposure*. J Toxicol Sci, 2014. **39**(1): p. 121-7.
64. Elobeid, M.A., et al., *Endocrine disruptors and obesity: an examination of selected persistent organic pollutants in the NHANES 1999-2002 data*. Int J Environ Res Public Health, 2010. **7**(7): p. 2988-3005.
65. Hanrahan, L.P., et al., *Serum PCB and DDE levels of frequent Great Lakes sport fish consumers-a first look. The Great Lakes Consortium*. Environ Res, 1999. **80**(2 Pt 2): p. S26-S37.
66. Wolff, M.S., et al., *Risk of breast cancer and organochlorine exposure*. Cancer Epidemiol Biomarkers Prev, 2000. **9**(3): p. 271-7.
67. Moysich, K.B., et al., *Exposures associated with serum organochlorine levels among postmenopausal women from western New York State*. Am J Ind Med, 2002. **41**(2): p. 102-10.
68. Wolff, M.S., et al., *Improving organochlorine biomarker models for cancer research*. Cancer Epidemiol Biomarkers Prev, 2005. **14**(9): p. 2224-36.
69. Brucker-Davis, F., et al., *Exposure to selected endocrine disruptors and neonatal outcome of 86 healthy boys from Nice area (France)*. Chemosphere, 2010. **81**(2): p. 169-76.
70. Mazhitova, Z., et al., *Chlorinated contaminants, growth and thyroid function in schoolchildren from the Aral Sea region in Kazakhstan*. Acta Paediatr, 1998. **87**(9): p. 991-5.
71. Collins, J.J., et al., *Body mass index and serum chlorinated dibenzo-p-dioxin and dibenzofuran levels*. Chemosphere, 2007. **66**(6): p. 1079-85.
72. Michalek, J.E., et al., *Investigation of TCDD half-life heterogeneity in veterans of Operation Ranch Hand*. J Toxicol Environ Health, 1992. **35**(1): p. 29-38.
73. Yi, S.W., et al., *Serum 2,3,7,8-tetrachlorodibenzo-p-dioxin levels and their association with age, body mass index, smoking, military record-based variables, and estimated exposure to Agent Orange in Korean Vietnam veterans*. J Prev Med Public Health, 2013. **46**(5): p. 226-36.
74. Uemura, H., et al., *Prevalence of metabolic syndrome associated with body burden levels of dioxin and related compounds among Japan's general population*. Environ Health Perspect, 2009. **117**(4): p. 568-73.
75. Moon, H.B., et al., *Concentrations and accumulation profiles of PCDDs, PCDFs and dioxin-like PCBs in adipose fat tissues of Korean women*. J Environ Monit, 2011. **13**(4): p. 1096-101.

76. Ha, M.H., D.H. Lee, and D.R. Jacobs, *Association between serum concentrations of persistent organic pollutants and self-reported cardiovascular disease prevalence: results from the National Health and Nutrition Examination Survey, 1999-2002*. *Environ Health Perspect*, 2007. **115**(8): p. 1204-9.
77. Nelson, J.W., E.E. Hatch, and T.F. Webster, *Exposure to polyfluoroalkyl chemicals and cholesterol, body weight, and insulin resistance in the general U.S. population*. *Environ Health Perspect*, 2010. **118**(2): p. 197-202.
78. Barry, V., et al., *Early life perfluorooctanoic acid (PFOA) exposure and overweight and obesity risk in adulthood in a community with elevated exposure*. *Environ Res*, 2014. **132**: p. 62-9.
79. Dhooze, W., et al., *Internal exposure to pollutants and body size in Flemish adolescents and adults: associations and dose-response relationships*. *Environ Int*, 2010. **36**(4): p. 330-7.
80. Blanco-Munoz, J., et al., *Exposure to organophosphate pesticides and male hormone profile in floriculturist of the state of Morelos, Mexico*. *Hum Reprod*, 2010. **25**(7): p. 1787-95.
81. Raafat, N., M.A. Abass, and H.M. Salem, *Malathion exposure and insulin resistance among a group of farmers in Al-Sharkia governorate*. *Clin Biochem*, 2012. **45**(18): p. 1591-5.
82. Jackson, L.W., et al., *Prenatal and postnatal exposure to polychlorinated biphenyls and child size at 24 months of age*. *Reprod Toxicol*, 2010. **29**(1): p. 25-31.
83. Persky, V., et al., *Associations of polychlorinated biphenyl exposure and endogenous hormones with diabetes in post-menopausal women previously employed at a capacitor manufacturing plant*. *Environ Res*, 2011. **111**(6): p. 817-24.
84. Adlard, B., et al., *Persistent organic pollutants (POPs) and metals in primiparous women: a comparison from Canada and Mexico*. *Sci Total Environ*, 2014. **500-501**: p. 302-13.
85. Bergkvist, C., et al., *Validation of questionnaire-based long-term dietary exposure to polychlorinated biphenyls using biomarkers*. *Mol Nutr Food Res*, 2012. **56**(11): p. 1748-54.
86. Muscat, J.E., et al., *Adipose concentrations of organochlorine compounds and breast cancer recurrence in Long Island, New York*. *Cancer Epidemiol Biomarkers Prev*, 2003. **12**(12): p. 1474-8.
87. Anderson, H.A., et al., *Polybrominated diphenyl ethers (PBDE) in serum: findings from a US cohort of consumers of sport-caught fish*. *Chemosphere*, 2008. **73**(2): p. 187-94.
88. Burns, J.S., et al., *Serum dioxins and polychlorinated biphenyls are associated with growth among Russian boys*. *Pediatrics*, 2011. **127**(1): p. e59-68.
89. Lee, Y.M., et al., *Prospective associations between persistent organic pollutants and metabolic syndrome: a nested case-control study*. *Sci Total Environ*, 2014. **496**: p. 219-25.
90. Lim, J.S., D.H. Lee, and D.R. Jacobs, Jr., *Association of brominated flame retardants with diabetes and metabolic syndrome in the U.S. population, 2003-2004*. *Diabetes Care*, 2008. **31**(9): p. 1802-7.
91. Bradman, A., et al., *Factors associated with serum polybrominated diphenyl ether (PBDE) levels among school-age children in the CHAMACOS cohort*. *Environ Sci Technol*, 2012. **46**(13): p. 7373-81.
92. Huang, P.C., et al., *Associations between urinary phthalate monoesters and thyroid hormones in pregnant women*. *Hum Reprod*, 2007. **22**(10): p. 2715-22.
93. Stahlhut, R.W., et al., *Concentrations of urinary phthalate metabolites are associated with increased waist circumference and insulin resistance in adult U.S. males*. *Environ Health Perspect*, 2007. **115**(6): p. 876-82.

94. Hatch, E.E., et al., *Association of urinary phthalate metabolite concentrations with body mass index and waist circumference: a cross-sectional study of NHANES data, 1999-2002*. Environ Health, 2008. **7**: p. 27.
95. Svensson, K., et al., *Phthalate exposure associated with self-reported diabetes among Mexican women*. Environ Res, 2011. **111**(6): p. 792-6.
96. Teitelbaum, S.L., et al., *Associations between phthalate metabolite urinary concentrations and body size measures in New York City children*. Environ Res, 2012. **112**: p. 186-93.
97. Wang, H., et al., *Urinary phthalate metabolites are associated with body mass index and waist circumference in Chinese school children*. PLoS One, 2013. **8**(2): p. e56800.
98. Olsen, L., L. Lind, and P.M. Lind, *Associations between circulating levels of bisphenol A and phthalate metabolites and coronary risk in the elderly*. Ecotoxicol Environ Saf, 2012. **80**: p. 179-83.
99. Lind, P.M., et al., *Serum concentrations of phthalate metabolites are related to abdominal fat distribution two years later in elderly women*. Environ Health, 2012. **11**: p. 21.
100. Dirtu, A.C., et al., *Phthalate metabolites in obese individuals undergoing weight loss: Urinary levels and estimation of the phthalates daily intake*. Environ Int, 2013. **59**: p. 344-53.
101. Buser, M.C., H.E. Murray, and F. Scinicariello, *Age and sex differences in childhood and adulthood obesity association with phthalates: analyses of NHANES 2007-2010*. Int J Hyg Environ Health, 2014. **217**(6): p. 687-94.
102. Peck, J.D., et al., *Intra- and inter-individual variability of urinary phthalate metabolite concentrations in Hmong women of reproductive age*. J Expo Sci Environ Epidemiol, 2010. **20**(1): p. 90-100.
103. Trasande, L., et al., *Race/ethnicity-specific associations of urinary phthalates with childhood body mass in a nationally representative sample*. Environ Health Perspect, 2013. **121**(4): p. 501-6.
104. Buser, M.C., H.E. Murray, and F. Scinicariello, *Association of urinary phenols with increased body weight measures and obesity in children and adolescents*. J Pediatr, 2014. **165**(4): p. 744-9.
105. Takeuchi, T. and O. Tsutsumi, *Serum bisphenol a concentrations showed gender differences, possibly linked to androgen levels*. Biochem Biophys Res Commun, 2002. **291**(1): p. 76-8.
106. Takeuchi, T., et al., *Positive relationship between androgen and the endocrine disruptor, bisphenol A, in normal women and women with ovarian dysfunction*. Endocr J, 2004. **51**(2): p. 165-9.
107. Shankar, A., S. Teppala, and C. Sabanayagam, *Urinary bisphenol a levels and measures of obesity: results from the national health and nutrition examination survey 2003-2008*. ISRN Endocrinol, 2012. **2012**: p. 965243.
108. Wang, H.X., et al., *Association between bisphenol A exposure and body mass index in Chinese school children: a cross-sectional study*. Environ Health, 2012. **11**: p. 79.
109. Wang, T., et al., *Urinary bisphenol A (BPA) concentration associates with obesity and insulin resistance*. J Clin Endocrinol Metab, 2012. **97**(2): p. E223-7.
110. Zhao, H.Y., et al., *The effects of bisphenol A (BPA) exposure on fat mass and serum leptin concentrations have no impact on bone mineral densities in non-obese premenopausal women*. Clin Biochem, 2012. **45**(18): p. 1602-6.
111. Eng, D.S., et al., *Bisphenol A and chronic disease risk factors in US children*. Pediatrics, 2013. **132**(3): p. e637-45.
112. Harley, K.G., et al., *Prenatal and postnatal bisphenol A exposure and body mass index in childhood in the CHAMACOS cohort*. Environ Health Perspect, 2013. **121**(4): p. 514-20, 520e1-6.

113. Li, D.K., et al., *Urine bisphenol-A level in relation to obesity and overweight in school-age children*. PLoS One, 2013. **8**(6): p. e65399.
114. Tarantino, G., et al., *Bisphenol A in polycystic ovary syndrome and its association with liver-spleen axis*. Clin Endocrinol (Oxf), 2013. **78**(3): p. 447-53.
115. Erden, E.S., et al., *Investigation of serum bisphenol A, vitamin D, and parathyroid hormone levels in patients with obstructive sleep apnea syndrome*. Endocrine, 2014. **45**(2): p. 311-8.
116. Ronn, M., et al., *Bisphenol A is related to circulating levels of adiponectin, leptin and ghrelin, but not to fat mass or fat distribution in humans*. Chemosphere, 2014. **112**: p. 42-8.
117. Wells, E.M., L.W. Jackson, and M.B. Koontz, *Association between bisphenol A and waist-to-height ratio among children: National Health and Nutrition Examination Survey, 2003-2010*. Ann Epidemiol, 2014. **24**(2): p. 165-7.
118. Twum, C. and Y. Wei, *The association between urinary concentrations of dichlorophenol pesticides and obesity in children*. Rev Environ Health, 2011. **26**(3): p. 215-9.
119. Wei, Y., J. Zhu, and A. Nguyen, *Urinary concentrations of dichlorophenol pesticides and obesity among adult participants in the U.S. National Health and Nutrition Examination Survey (NHANES) 2005-2008*. Int J Hyg Environ Health, 2014. **217**(2-3): p. 294-9.
120. Chang, J.W., et al., *Simultaneous exposure of non-diabetics to high levels of dioxins and mercury increases their risk of insulin resistance*. J Hazard Mater, 2011. **185**(2-3): p. 749-55.
121. Pestana, D., et al., *Persistent organic pollutant levels in human visceral and subcutaneous adipose tissue in obese individuals--depot differences and dysmetabolism implications*. Environ Res, 2014. **133**: p. 170-7.
122. Welshons, W.V., S.C. Nagel, and F.S. vom Saal, *Large effects from small exposures. III. Endocrine mechanisms mediating effects of bisphenol A at levels of human exposure*. Endocrinology, 2006. **147**(6 Suppl): p. S56-69.
123. vom Saal, F.S., et al., *Chapel Hill bisphenol A expert panel consensus statement: integration of mechanisms, effects in animals and potential to impact human health at current levels of exposure*. Reprod Toxicol, 2007. **24**(2): p. 131-8.
124. Sheehan, D.M., et al., *No threshold dose for estradiol-induced sex reversal of turtle embryos: how little is too much?* Environ Health Perspect, 1999. **107**(2): p. 155-9.

	Adults						Children					
Component	Meta-analyse B (95% CI)	Negative (<0.05) - A	Negative (>0.05) - B	Positive (>0.05) - C	Positive (<0.05) - D	Comments	Meta-analyse B (95% CI)	Negative (<0.05) - A	Negative (>0.05) - B	Positive (>0.05) - C	Positive (<0.05) - D	Comments
1. Chlordanes												
Oxychlordane	0.30 (0.01; 0.59)	0	0	0	0		-----	0	0	0	0	
Oxychlordane	0.08 (0.04; 0.12)	0	0	0	0		-----	0	0	0	0	
Trans-nonachlor	0.11 (0.00; 0.21)	0	1	0	2		-----	0	0	0	0	
Trans-nonachlor	0.04 (0.00; 0.08)	0	1	1	2		-----	0	0	0	0	
Sum	-----	0	0	1	0		-----	0	0	0	0	
2. DDT												
p,p'-DDE	0.25 (0.10; 0.40)	1	2	4	2			1	0	0	0	
p,p'-DDE	0.19 (0.16 0.21)	1	2	4	2			1	0	0	0	
DDE - not specified	0.16 (0.05; 0.26)	1	0	0	1			0	0	0	0	
DDE - not specified	0.18 (0.14; 0.22)	1	0	0	2			0	0	0	0	
p,p'-DDT	0.00 (-0.07; 0.06)	0	0	3	1			0	0	0	0	
p,p'-DDT	0.01 (-0.05; 0.06)	0	0	3	1			0	0	0	0	
o,p'-DDT	-----											
Sum of DDT	-----	0	0	1	1			1	0	0	0	A - in hospitalized children (n=12)
p,p'-DDD	-----							0	0	0	0	
3. PCDDs												
OCDD	-----	0	1	3	7			0	0	0	0	
HpCDD	-----	0	0	2	4	C - one study in occupational setting		0	0	0	0	
HxCDD	-----	0	0	1	1	D - study in occupational setting		0	0	0	0	
PeCDD	-----	0	0	0	1	D - study in occupational setting		0	0	0	0	
TCDD	-----	0	0	2	1	C and D - studies in occupational setting		0	0	0	0	
TEQ Sum of PCDDs	-----	1	0	1	0	A - in Myoma patients		0	0	0	0	
Sum of PCDDs	-----	0	0	0	2			0	0	0	0	
4. PCDFs												
	-----		5	10	1	D - study in myoma patients		0	0	0	0	
5. PFCA s												
PFNA	-----			1					1			1 B- in boys;D-in girls
PFOA	-----		3	2					1	1		
PFOS	-----			1					2			
PFHxS	-----		1						2			
6. HCH												
β-HCH	0.43 (0.26; 0.60)	0	0	1	0			0	1	0	0	
β-HCH	0.44 (0.35; 0.53)	0	0	1	0			0	1	0	0	
Sum (α-, β- and γ-HCH)	-----	1	0	0	0	A- study in myoma patients		0	0	0	0	
7. HCB												
HCB	0.82 (0.50; 1.14)		1	1				2			1	
HCB	0.44 (0.38; 0.49)		1	1				2			1	
8. Organophosphate												
DETP	-----		1			B- occupational						
Malathion	-----					1 D- occupational						
9. Dioxin-like PCBs												
PCB 118	0.57 (0.36; 0.77)	1	1	3	4	A - BMI at delivery;					2	
PCB 118	0.43 (0.33; 0.53)	1	1	3	5	A - BMI at delivery;					2	
PCB 156	0.08 (-0.08; 0.24)	2	1			mixt results - no association						
PCB 156	0.08 (-0.08; 0.24)	3	1			mixt results - no association.						
PCB 105	-----			2	1	positive all from PIVUS						
PCB 126	-----			3	1	positive most from PIVUS						
PCB 157	-----	1	2			negative all from PIVUS						
PCB 189	-----	1	2			negative all from PIVUS						
PCB 114	-----	0	0	0	0				1			only one study
PCB 167	-----	0			1	only one study in infertile men						
PCB 169	-----	1				only one study						
sun of dioxin-like PCBs	-----			1	3	positive D- one in occupattinal setting						
10. Non-dioxin-like PCBs												
PCB 99	0.27 (0.10; 0.45)	0	2	1	0	positive		0	0	0	0	
PCB 99	0.28 (0.14; 0.42)	0	2	1	1	positive		0	0	0	0	
PCB 138	0.02 (-0.12; 0.17)	1	0	1	0	no association		0	0	0	0	
PCB 138	0.03 (-0.00; 0.06)	2	0	1	0	no association falta		0	0	0	0	