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Published in:
Journal of Environmental and Occupational Science

DOI (link to publication from Publisher):
10.5455/jeos.20131018011638

Publication date:
2013

Document Version
Publisher's PDF, also known as Version of record

J Environ Occup Sci 2013; 2(3): 141-148 *ISSN: 2146-8311*

GESDAV

Journal of Environmental and Occupational Science

available at www.scopemed.org

Original Research

Polychlorinated biphenyl concentrations in adipose tissue as determinants of abdominal obesity in the elderly

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Received: October 14, 2013

Accepted: October 18, 2013

Published: October 22, 2013

DOI : 10.5455/jeos.20131018011638

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Key words: PCBs, Waist circumference, determinants, abdominal obesity, prospective sampling, adipose tissue

Abstract

Aim / Background: Obesity prevalence has more than doubled globally within the last 30 years. Obesity affects life quality and impacts the risks and prognosis for a number of serious diseases. Established causes include a high caloric diet combined with a sedentary lifestyle and possibly the widespread cessation of smoking. These do not fully explain the epidemic and evidence from animal experiments suggests PCBs predict obesity development. Knowledge on effects of these compounds as determinants of human abdominal obesity is limited.

Methods: In the current study we investigated whether low dose exposure to PCBs in adipose tissue experienced by a general Danish population predicted increased abdominal circumference. We used 214 persons, aged ≥ 50 years that had previously been used as healthy controls in a study investigating PCBs and risk of non-Hodgkins lymphoma. Adipose tissue was collected upon enrolment and PCBs were quantified using gas chromatography-mass spectroscopy.

Results: Median levels of the included PCBs were lower in women, except for PCB118. All PCBs were positively associated with increased abdominal circumference, although this association was non-significant.

Conclusion: These data indicate a positive link between PCBs and increased abdominal circumference. More work is needed to elucidate the role of compounds such as PCBs in development of the present obesity epidemic.

INTRODUCTION

Obesity prevalence, defined as a body mass index (BMI) > 30 kg/m^2), has more than doubled globally within the last 30 years [1] and this increase has been observed in both rich and poor countries and in all segments of the society[2]. In Europe 30-80 % of the adult population is overweight (BMI > 25 kg/m^2) and in Denmark the development and continued increase in obesity resembles the development in a range of other European countries [3,4].

Obesity and overweight affect quality of life as well as impact the risks and prognosis for a number of serious diseases [5,6]. The established causes of obesity include a high caloric diet combined with a sedentary lifestyle and possibly the widespread cessation of smoking, but these do not fully explain the epidemic. It has been suggested that environmental contaminants such as PCBs are related to central obesity [7–9].

PCBs were introduced in the late 1920s and manufacture was stopped in the 1970s due to evidence of environmental build-up [10]. During this period

more than 1.5 million metric tons were produced worldwide, and it is believed that at least one-third of these PCBs found their way into the natural environment [11,12] where they are ubiquitously present as a complex mixture of mother compounds and metabolites. The production and environmental release of PCBs coincides with the rising epidemic of obesity over the past 30 years in western populations. PCBs are characterised by high lipid solubility, environmental persistence and bioaccumulation, and their semi-volatile characteristics predispose them to long-range transport [13]. PCBs enter human tissue primarily through the consumption of dietary fat [14,15] and are not readily cleared from the body. There is also presently heightened awareness that indoor air in PCB contaminated buildings may confer an important exposure to PCBs with resulting health concerns [16]. Evaporation of PCBs from building materials can nowadays result in considerable indoor air concentrations of total PCBs and recent studies have quantified this source of exposure to levels of 150 to over 10,000 ng/m^3 [17–23]. It has furthermore been shown that inhalation exposure in contaminated buildings will significantly contribute to the PCB body burden of the lower-chlorinated and more volatile PCB-congeners [18, 20, 24–26]. Half-lives in humans are influenced by on-going exposure, fluctuations in body weight and intrinsic elimination and when eliminating the influence of these factors, the estimated half-lives of individual PCB congeners in humans range from 2.6 to 15.5 years [27,28].

A significant link between persistent organic pollutants such as PCBs and the metabolic syndrome, characterised by a cluster of metabolic disorders including central obesity, has been established [29,30]. The association between PCBs and obesity, particularly abdominal obesity is supported by several animal studies suggesting that exposure to these compounds alter mechanisms involved in weight homeostasis [31–34]. However, our knowledge of the effects of environmental chemicals including PCBs on weight gain in humans has not been fully elucidated. Facing the emerging challenges in controlling the obesity epidemic, the possibility that PCBs contributes to predicting obesity has huge public health impact.

In the present prospective study, we investigate the hypothesis that exposure to PCBs assessed as levels in fat tissue determines increased abdominal obesity quantified as increased waist circumference.

MATERIALS AND METHODS

Design and study participants

The study was based on the prospective Diet, Cancer and Health cohort consisting of 57,053 participants, aged 50 to 64 years, enrolled in 1993-1997 [35]. The participants had to be born in Denmark, live in the Copenhagen or Aarhus areas, and be without a cancer diagnosis registered in the Danish Cancer Registry. At baseline, laboratory technicians measured weight, height and circumference at the natural waist, or, in case of an indeterminable waist narrowing, halfway between the lower rib and the iliac crest, and this was recorded to the nearest half centimeter. An adipose tissue biopsy from the buttock of each participant was also taken at enrolment using a luer-lock system (Terumo, Terumo Co., Tokyo, Japan) yielding an average of 29 mg (range, 1-97 mg) tissue and all samples were frozen at −20°C and within 8 hours put in liquid nitrogen vapour (max, −150°C) for long-term storage, within 2 hours of collection. The baseline examination also included a self-administered, interviewer checked, questionnaire on diet, beverages, present and previous smoking habits (status, intensity and duration), as well as other items related to health, lifestyle and socio-economic status. At the 5-y follow up, self-reported values of weight and waist circumference at the level of the umbilicus were collected. The body site for measurement of waist circumference was changed to the level of the umbilicus at follow-up to simplify the measurement instructions for participants that could use the umbilicus as a body mark for measurement [36].

A case-cohort study was previously conducted to determine risk factors of non-Hodgkin's lymphoma. A total of 239 cases and 245 gender matched cancer free sub-cohort members were included in that study and the method of selection has previously been described in detail elsewhere [37]. The analyses in the present paper were based on the 245 random cancer free sub-cohort members, aged ≥ 50 years, thus eliminating the possible effect of cancer on weight which would interfere in the concentrations of the PCBs measured. Of these 245 cancer free persons we excluded thirty-one (13 men and 18 women) in the present study due to missing 5-year follow-up data on waist circumference leaving 214 persons (113 men and 101 women) of which 91 were normal weight, 96 were overweight and 27 were obese.

The agreement between self-reported waist circumference at the level of the umbilicus and technician-measured waist circumference at the natural waist has been evaluated [36]. This previous study concluded that although self-reported waist circumference was a usable proxy for technician measured waist circumference, that regression analyses using this proxy should be adjusted for baseline BMI and baseline waist circumference [36].

The study was approved by the Scientific Ethics Committee for Copenhagen and Frederiksberg and The

Danish Data Protection Agency and written informed consent was obtained from all participants prior to enrolment.

PCB analyses

Ten PCB congeners (International Union of Pure and Applied Chemistry nos. 99, 118, 138, 153, 156, 170, 180, 183, 187, and 201), all with at least five chlorine substitutions, were measured. These ten were selected as they were among the 26 congeners considered most environmentally threatening due to their prevalence, relative abundance in animal tissues, and potential toxicity [38]. Samples were analyzed at the Centre de toxicologie du Québec, Institut National de Santé Publique du Québec. The laboratory is accredited under ISO 17025 by the Standards Council of Canada and participates in many national and international quality control programs including the Northern Contaminants Program of the Ministry of the Environment of Ontario, the External Quality Assessment Scheme, QUASIMEME http://www.quasimeme.marlab.ac.uk/) as well as the German External Quality Assessment Scheme for Biological Monitoring in Occupational and Environmental Medicine.

The adipose tissue samples were aspirated from the needle into a vacutainer tube under vacuum. The tissue samples were then fortified with internal standards, mixed with dichloromethane and chemically dried using sodium sulphate. A part of the organic solvent was used to determine the percentage of total lipids in the sample. The remaining fraction was concentrated by evaporation and subsequently purified using gel permeation chromatography and cleaned-up on a florisil column. The extracts were analyzedon a gas chromatography-mass spectroscopy instrument from (Agilent Technologies (Hewlett-Packard; Palo Alto, CA) model 6890/5973) using a DB-XLB capillary column. (Agilent Technologies; 60 m long, 0.25 mm inner diameter and 0.25 μm film thickness). The measurement of ions, generated after negative chemical ionization with reagent gas of methane, was performed in selective ion mode. Peak areas were calculated relative to labeled internal standards (PCB 141-$^{13}C_{12}$, PCB 153-$^{13}C_{12,}$ PCB 180-$^{13}C_{12}$). Samples (3 μl) were injected in the pulsed split-less mode. The temperature program was as follows: 2 min at 100 °C followed by an increase to 200 °C at a rate of 20 °C min^{-1}, increase to 245 °C at a rate of 1.5 °C min^{-1} hold 10 minutes, increase to 280 °C at a rate of 20 °C min^{-1} hold 5 minutes and finally an increase to 330 °C at a rate of 30 °C min^{-1} hold 15 minutes. The total run time was 70.42 minutes.

The total lipid content was determined on the designated extract using a gravimetric method. Two hundred microliters were precisely weighed on an analytic balance and the solvent evaporated at room temperature in a dessicator. The resulting lipid weight was adjusted to the initial sample weight and the percentage of lipid content was calculated. The PCB concentrations were expressed in microgram per kilogram of lipids.

Determination of analytical uncertainties found in adipose samples is crucial for the interpretation of data. In this study, each batch consisted of 16 samples, one calibration standard, one procedural blank and one sample of internal reference material. The internal reference material was cod liver oil containing all PCBs analyzed and was provided by the National Institute of Standards & Technology (Gaithersburg, MD). The results of the analyses of the reference materials were used to validate the methods on a routine basis. When unacceptably high deviations were obtained from the certified values, the batches concerned were reanalysed. The variation obtained for all compounds during the analysis of all samples was within 15 % of the certified values. Precision was monitored by plotting the results of the internal reference material in control charts with warning and action limits (2 and 3 times the standard deviation of the target value, respectively). The inter-day precision was between 5.1 % to 7.3 % for the PCB congeners. Based on spiked levels (5 μg/kg in corn oil, $n = 3$) recovery was between 87% and 96% for the different PCB congeners.

Statistical methods

The association between the individual PCBs and development in waist circumference from baseline to 5-year follow up were analyzed by generalized linear models using the GLM procedure of SAS (version 9.4; SAS Institute, Cary, NC) with and without adjustment for baseline age (linear, years), gender, energy intake (linear, kj/day), exercise (low, medium, high and vigourous), cigarette smoking (current, former and never) and alcohol consumption (kj/day). All analyses were adjusted for baseline BMI and baseline waist circumference as recommended by Bigaard and co-workers [36].

RESULTS

The characteristics of the participants are presented in Table 1, men had slightly higher baseline waist circumferences, lower median changes in waist circumference (follow-up minus baseline measurements), higher total energy and alcohol energy intakes, whilst median baseline age was similar for both genders.

A higher proportion of men were overweight or obese (> 25 kg/m^2) at baseline, had low total physical weekly activities and tended to be current smokers. Men had

higher median lipid-adjusted concentrations of PCB's in adipose tissue with the exception of PCB118 which was similar (Table 2).

We found no clear evidence of associations between increased abdominal circumference and adipose concentrations of the PCB congeners included in this study (Table 3).

Table 1. Characteristics of the study population

	All (N=214)		Men (N=113)		Women (N=101)	
	No. (%)	**median (5^{th};95^{th} percentile)**	**No. (%)**	**median (5^{th};95^{th} percentile)**	**No. (%)**	**median (5^{th};95^{th} percentile)**
Age (years) [a]		56.3 (51.0; 64.2)		56 (51; 65)		56 (51; 64)
Total energy intake (KJ/day) [a]		9774 (6444; 14135)		10708 (7527; 15205)		8752 (6067; 13178)
Alcohol consumption (g/day) [a]		452 (20; 1861)		650 (41; 2161)		297 (17; 1007)
Activity [a,b]						
Low (less than 38 hrs/wk)	52 (24.3)		34 (30.1)		18 (17.8)	
Middle (between 38 and 54 hrs/wk)	54 (25.2)		31 (27.4)		23 (22.8)	
High (between 54 and 86 hrs/wk)	55 (25.7)		26 (23.0)		29 (28.7)	
Vigorous (more than 86 hrs/wk)	53 (24.8)		22 (19.5)		31 (30.7)	
Cigarette smoking [a]						
Current	68 (31.8)		44 (39.0)		24 (23.8)	
Former	59 (27.6)		38 (33.6)		21 (20.8)	
Never	87 (40.7)		31 (27.4)		56 (53.5)	
BMI (kg/m^2) [a]		25.6 (20.8; 32.3)		25.7 (22.0; 32.2)		25.2 (20.2; 32.3)
≤25 normal	91 (42.5)		43 (38.1)		48 (47.5)	
>25 overweight, obese	123 (57.3)		70 (61.9)		53 (52.5)	
Waist circumference baseline (cm) [a]		89 (70; 112)		94 (83; 117)		81 (67; 102)
Normal waist [c]	164 (76.6)		89 (78.8)		75 (74.3)	
Obese	50 (23.4)		24 (21.2)		26 (25.7)	
Waist circumference at 5-year follow-up (cm)		93 (76; 112)		97 (86; 117)		86 (72; 109)
Normal waist [c]	139 (65.0)		83 (73.5)		56 (55.5)	
Obese	75 (35.1)		30 (26.5)		45 (45.5)	

[a] Baseline values; [b]This score is a general indicator of how active each participant was and includes information on sport, occupation involving physical activity, gardening, walking/cycling as a means of transport and house cleaning; [c]Abdominal obesity was defined as waist circumference > 102 cm in men and > 88 cm in women according to Lee and co-workers [9]

Table 2. Concentration (µg/kg lipid) of PCBs in adipose tissue

Compound	IQR all*	Median (5^{th}; 95^{th} percentile)	
		Men (N=113)	Women (N=101)
PCB99	17	31 (15; 61)	22 (12; 46)
PCB118	25	35 (16; 73)	36 (20; 68)
PCB138	70	140 (75; 300)	130 (61; 240)
PCB153	120	310 (190; 550)	280 (140; 440)
PCB156	13	35 (22; 60)	32 (20; 51)
PCB170	44	120 (72; 180)	100 (66; 140)
PCB180	70	220 (140; 350)	190 (130; 270)
PCB183	13	26 (15; 54)	22 (9; 41)
PCB187	22	61 (39; 110)	52 (27; 84)
PCB201	9	22 (13; 34)	17 (10; 27)

*IQR=inter-quartile range (75^{th} minus 25^{th} percentile)

Table 3. Associations between 5 year follow-up waist circumference and adipose tissue concentrations of PCBs

Explanatory variable[a]	n	Model 1[b] (95% CI)	P-value	Model 2[b,c] (95% CI)	P-value
PCB 99	155	0.38 (-0.90; 1.67)	0.56	0.31 (-1.10; 1.71)	0.67
PCB 118	204	-0.05 (-1.25; 1.15)	0.93	0.45 (-0.85; 1.75)	0.50
PCB 138	213	0.31 (-0.63; 1.25)	0.51	0.37 (-0.62; 1.37)	0.46
PCB 153	214	0.45 (-0.49; 1.40)	0.34	0.55 (-0.47; 1.58)	0.29
PCB 156	206	0.56 (-0.49; 1.62)	0.29	0.51 (-0.67; 1.69)	0.40
PCB 170	213	0.84 (-0.42; 2.08)	0.19	0.83 (-0.61; 2.28)	0.26
PCB 180	214	0.69 (-0.32; 1.70)	0.18	0.72 (-0.44; 1.88)	0.23
PCB 183	198	-0.01 (-1.10; 1.07)	0.98	0.16 (-0.99; 1.32)	0.78
PCB 187	210	0.41 (-0.52; 1.33)	0.39	0.50 (-0.54; 1.54)	0.34
PCB 201	200	0.72 (-0.63; 2.08)	0.30	0.81 (-0.85; 2.47)	0.34

[a]Per IQR µg/kg

[b]Estimated change in endpoint per IQR (µg/kg) change in the predictor variable, e.g. an estimate of 0.38 for PCB99 in model 1 is interpreted as a 0.38 cm increase in waist circumference per IQR (µg/kg) increase in PCB99. Model adjusted for baseline BMI and baseline waist circumference as recommended by Bigaard and co-workers [36]

[c]As for model 1 and adjusted for baseline age (linear, years), gender, energy intake (linear, kj/day), activity (low, medium, high and vigourous), cigarette smoking (current, former and never) and alcohol consumption (kj/day).

DISCUSSION

We investigated the association between adipose PCB concentrations and abdominal circumference using a prospective cohort. We found no clear evidence of associations between increased abdominal circumference and adipose concentrations of the PCB congeners included in this study. Based on a reliable study design and exposure assessment of PCB levels in prospectively sampled adipose tissue from a general population of 214 elderly persons, we show new results adding valuable information to the limited knowledge regarding PCB exposure and obesity.

Endocrine disrupting compounds are thought to cause obesity by a variety of mechanisms such as altering homeostatic metabolic set points or disrupting appetite controls studies [31–34] but knowledge of these mechanisms in humans remains limited. One previous study has investigated these associations in the elderly [9], reporting linear relationships for low-chlorinated PCBs (4-5 chlorine atoms) and inverse relationships for highly chlorinated (≥ 7 chlorine atoms) PCBs measured

in serum. Whilst another reports a negative association between obesity and all PCB congeners in serum within a younger population of persons 21 to 60 years [39]. In the present study we find positive non-significant associations between increased abdominal obesity and PCB congeners not in line with the two previous studies. The choice of biological specimen used in exposure quantification may explain the discrepant results. Our study uses prospectively sampled adipose tissue in exposure assessment. Adipose tissue is the principal storage medium for lipophilic PCBs in the human body [40] and has been regarded by various authors [41–43] as the preferred indicator of human exposure as it represents cumulative internal exposure. Serum samples are more easily obtained and less costly, but may represent more recent exposure than levels in adipose samples collected at the same time [44] and PCBs in adipose tissue seem relevant for obesity development.

The generally lower PCB concentrations in women may be explained by elimination via lactation amongst women and this association is well established [45,46], as lactation mobilizes body stores of fat, thus reducing the body burden of lipophilic compounds.

An advantage of this study is the prospective collection of adipose so any change in weight and body composition after baseline would not interfere in the concentrations of the PCBs measured. This prospective design also limits recall bias regarding energy intake, exercise, cigarette smoking and alcohol consumption. But on the other hand changes in these habits within the 5 year period after baseline could also affect any associations. A limitation of the present study is the small sample size, which was related to the fact that we used adipose tissue already analysed for controls used in a previous study investigating PCBs and risk of non-Hodgkins lymphoma coupled with the practicalities related to cost a use on precious new samples. More work is needed in this area to confirm whether an association between PCBs and obesity does in fact exist in humans.

CONCLUSION

We show a positive non-significant association between adipose concentrations of PCB congeners and change in waist circumference. Given the current worldwide obesity epidemic, more work is needed to fully elucidate the complex role of endocrine-disrupting compounds such as PCBs on body weight.

ACKNOWLEDGEMENTS

Dr Bräuner was supported by the following Foundations: The Danish Medical Research Council, Danish Cancer Society, Aase and EjnarDanielsens, King Christian the 10th, A.P. Møller, The Hartmann Brothers, The Foundation of 1870, Snedker Jacobsen and hustru Astrid Jacobsen, Architect Holger Hjortenberg and hustru Dagmar Hjortenberg, Civil Engineer Frode V. Nyegaard and Simon Spies.

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