Endocrine-disrupting polychlorinated biphenyls in metabolically healthy and unhealthy obese subjects before and after weight loss: difference at the start but not at the finish[1,2]

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ABSTRACT

Background: A subset of obese individuals does not exhibit metabolically unfavorable features; this group is referred to as metabolically healthy obese (MHO). Serum concentrations of polychlorinated biphenyls (PCBs), which are chemicals with endocrine-disrupting properties, have been shown to be lower in MHO than in metabolically unhealthy obese (MUO).

Objective: We studied PCB serum concentrations during and after weight loss and their relation with metabolic health.

Design: We determined metabolic health features (weight, blood pressure, lipids, inflammation, and glucose metabolism) and serum PCB concentrations of 27 PCBs in a cohort of 184 overweight and obese subjects. Metabolic health was evaluated with the use of the criteria of the metabolic syndrome (MetS) [metabolic syndrome according to Adult Treatment Panel III criteria present (MetS+) or metabolic syndrome according to Adult Treatment Panel III criteria absent (MetS−)] or with extended criteria with inflammation and insulin resistance taken into account (MUO compared with MHO). Participants were treated with lifestyle counseling or bariatric surgery. A metabolic and toxicological re-evaluation was performed after 6 and 12 mo.

Results: At baseline, serum ΣPCB concentrations were significantly higher in MUO than in MHO (ΣPCBs: 138 ±105 compared with 365 ± 481 ng/g lipid weight; $P = 0.01$) but not in MetS+ compared with MetS− subjects. No difference was detected in the percentage increase in PCB serum concentrations in MetS+ compared with MetS− subjects (median: 58% compared with 43% and 31% compared with 69% at 6 and 12 mo, respectively). The comparison of persistent with resolved MetS and MUO did not reveal any difference in ΣPCB concentration increments (median: 49% compared with 58% at 12 mo for MUO; $P > 0.05$). In a regression model with age, smoking, and body mass index corrected for, PCB serum concentrations at baseline were not predictive of the persistence or resolution of a metabolically unfavorable state.

Conclusion: Our study indicates that the increment in serum concentrations of PCBs does not differ according to metabolic health and does not seem to influence the beneficial metabolic health effects of weight loss. This study was registered at clinicaltrials.gov at NCT01778868. *Am J Clin Nutr* 2016;103:989–98.

Keywords: endocrine disruptors, metabolically healthy, metabolic syndrome, obesity, polychlorinated biphenyls

INTRODUCTION

The prevalence of obesity, which is defined as BMI (kg/m^2) >30, has reached alarming proportions with 30–80% of the European adult population currently being overweight (BMI >25) and obesity affecting up to one-third of the population (1). Obesity, in particular abdominal obesity, is often accompanied by unfavorable medical conditions such as arterial hypertension, dyslipidemia, and glucose-metabolism abnormalities (2). This cluster of conditions is referred to as the metabolic syndrome (MetS)[6] and causes severely increased risk of cardiovascular morbidity and mortality (3, 4). However, a subset of obese individuals does not display these metabolic abnormalities. For example, in the 1999–2004 NHANES, ∼30% of obese US adults did not display any cardiometabolic abnormalities (5).

It remains unclear what factors trigger the development of a metabolically unhealthy phenotype in an obese individual. It has been suggested that the body fat distribution or birth weight are important determinants (6–8), but recently, some researchers have postulated that polychlorinated biphenyls (PCBs) contribute to the unhealthy phenotype too (9). PCBs are known endocrine-disrupting chemicals that have been linked to the development of obesity and type 2 diabetes mellitus (10, 11). In animal models, the exposure to PCBs has accelerated the

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[2] Supplemental Tables 1 and 2 are available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://ajcn.nutrition.org.

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[6] Abbreviations used: ATPIII, Adult Treatment Panel III; CRP, C-reactive protein; LOQ, level of quantification; lw, lipid weight; MetS, metabolic syndrome; MetS−, metabolic syndrome according to Adult Treatment Panel III criteria absent; MetS+, metabolic syndrome according to Adult Treatment Panel III criteria present; MHO, metabolically healthy obese; MUO, metabolically unhealthy obese; PCB, polychlorinated biphenyl.

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development of insulin resistance, glucose intolerance, low-grade inflammation, and visceral obesity (12, 13). PCBs were used worldwide since the 1930s for various industrial purposes. More than 100 individual PCB congeners have been identified in commercial mixtures, whose chemical and toxicologic properties are related to the number and position of the chlorine atoms. Despite the ban on their production in the United States and Europe since the 1970s, their ongoing use, chemical stability, resistance to degradation, and lipophilicity have led to a substantial bioaccumulation in most compartments of the ecosystem and human tissues (14). This bioaccumulation leads to an ongoing human exposure to PCBs through a variety of pathways, with the most important being dietary intake (15). Several studies have shown an increase in PCB serum concentrations during weight loss as a result of their release from the fat compartment (16–18). To date, weight loss remains the most-important tool to reverse obesity-associated comorbidities (19). It is unclear to what extent the increase in serum PCB concentrations can hinder the resolution of comorbidities during and after weight loss.

To determine the contribution of PCBs to the metabolically unfavorable features of obesity, this study raised the following 5 related questions: *1*) Do serum concentrations of PCBs at baseline differ between metabolically healthy and metabolically unhealthy individuals in our obese cohort? *2*) Is there a significant difference in the increment of PCB serum concentrations after 6 and 12 mo of weight loss between metabolically healthy and unhealthy obese individuals? *3*) Is there a significant difference in the increment of PCB serum concentrations between metabolically unhealthy obese (MUO) individuals who remain metabolically unhealthy after weight loss and individuals who become metabolically healthy after weight loss? *4*) Do serum concentrations of PCBs before weight loss or their rises during weight loss predict metabolic health after weight loss? *5*) Does the rise in PCB serum concentrations predict the change in the individual components of metabolic health (fasting glucose, waist circumference, triglycerides, HDL cholesterol, systolic blood pressure, diastolic blood pressure, and C-reactive protein)?

METHODS

Population

A cohort of 184 overweight and obese men (n = 53) and women (n = 131) was prospectively selected from patients who were visiting the weight-management clinic of the Antwerp University Hospital between 2010 and 2012. All participants were ≥18 y of age. Subject characteristics are described in **Table 1**. Participants were treated with a weight-loss protocol that include dietary counseling and physical activity or with bariatric surgery. According to local Belgian criteria, patients are eligible for bariatric surgery if they have BMI ≥40 or if they have BMI ≥35 and the presence of diabetes mellitus, therapy resistant arterial hypertension, or obstructive sleep apnea. In the dietary intervention group, almost all patients started consuming a hypocaloric protein-enriched 700-kcal diet, and 2 patients started consuming a hypocaloric 1500-kcal diet. For patients who consumed the 700-kcal diet, caloric intake was gradually increased after 6 wk by 200 kcal/mo. During the last 6 mo of the study, caloric intake was stabilized at 1200 kcal/d. For this study, both groups were pooled in the same analyses. After bariatric surgery, patients received nutritional advice that consisted of a balanced low-calorie diet. Patients were re-evaluated after 6 and 12 mo. This study was approved by the ethical committee of the Antwerp University Hospital (Belgian Registry; B30020097009) and registered at clinicaltrials.gov (NCT01778868). All participants provided written informed consent.

Anthropometric data

Anthropometric measures were taken in the morning with patients in a fasting state and undressed. Height was measured to the nearest 0.5 cm, and body weight was measured with a digital scale to the nearest 0.2 kg. Waist circumference was measured at the midlevel between the lower rib margin and the iliac crest. Anthropometric measures were performed at baseline and at 6 and 12 mo.

Blood sampling

Venous blood samples were obtained in a fasting state from an anticubital vein between 0800 and 1000 into sterile evacuated tubes (BD). Blood samples for the chemical analysis of PCBs were immediately centrifuged at 2500–3000 × g during 15 min. Serum was stored in glass vials at −20°C. In obese subjects without a known history of type 2 diabetes mellitus, an oral-glucose-tolerance test with 75 g glucose was performed with sampling at 0, 15, 30, 60, 90, 120, 150, and 180 min. Glycated hemoglobin, glucose, and insulin were measured at the hospital laboratory. Diabetes was classified according to the American Diabetes Association definition (20). The oral-glucose-tolerance test was repeated in all subjects after 12 mo. Total cholesterol, triglycerides, and high-sensitivity C-reactive protein (CRP) were measured at the hospital laboratory with the use of a validated method (Dimension Vista 1500 Systems; Siemens) at baseline and at 6 and 12 mo of follow-up.

Fat sampling

Of 66 individuals who were undergoing bariatric surgery, 50 subjects agreed to provide adipose tissue samples; these samples were collected during surgery from both the visceral and subcutaneous fat compartments. Samples were stored in glass vials at −20°C until analysis.

Determination of PCBs

Analyses of PCBs, in both serum and adipose tissue samples, were performed at the Toxicological Centre (University of Antwerp). The samples were analyzed for 27 PCB congeners (International Union of Pure and Applied Chemistry nos. 28, 74, 95, 99, 101, 105, 118, 149, 146, 153, 138, 187, 183, 128, 167, 174, 177, 171, 172, 156, 180, 170, 199, 196/203, 194, 206, and 209). PCB concentrations were expressed on a lipid-adjusted basis [ng/g lipid weight (lw)]. All concentrations were added to create the sum of all PCBs (ΣPCBs). Total lipids were calculated with the use of the following formula (21):

$$\text{Total lipids (g/L)} = \text{total cholesterol (g/L)} \times 2.27 + \text{triglycerides (g/L)} + 0.62 \quad (1)$$

Concentrations below the method level of quantification (LOQ) were assigned a value of DF × LOQ with DF being the

TABLE 1
Descriptive statistics of study population at baseline and follow-up[1]

	Baseline (n = 184)	Baseline with follow-up data (n = 71)	6-mo follow-up (n = 71)	12-mo follow-up (n = 50)
Sex, M:F, n	53:131	24:47	24:47	17:33
Age, y	41 ± 13[2]	44 ± 13	44 ± 13	47 ± 12
Active smoker, yes:no, n	29:155	10:61	10:61	3:47
BMI, kg/m^2	35.4 ± 8.6	40.2 ± 5.2[3]	34 ± 5	32 ± 6
Waist, cm	108 ± 21	121 ± 13[3]	107 ± 14	104 ± 15
Men	120 ± 19	127 ± 11	112 ± 14	107 ± 13
Women	103 ± 20	117 ± 13	104 ± 13	102 ± 16
Fasting glucose, mg/dL	89 ± 24	94 ± 31	87 ± 11	88 ± 11
HOMA-IR	3.1 ± 2.3	4.0 ± 2.5	2.7 ± 2	2.5 ± 1.4
Glucose-tolerance status, n				
NGT	110	28		32
IFG	3	2		0
IGT	46	22		14
IFG + IGT	6	4		2
T2DM	19	15		2
Blood pressure, mm Hg				
Systolic	124 ± 14	125 ± 13	116 ± 12	118 ± 13
Diastolic	76 ± 10	75 ± 9	72 ± 9	71 ± 9
Triglycerides, mg/dL	138 ± 81	171 ± 90[3]	123 ± 17	118 ± 58
HDL, mg/dL	53 ± 17	47 ± 15	52 ± 14	56 ± 14
Men	44 ± 13	40 ± 12	45 ± 10	49 ± 10
Women	57 ± 17	80 ± 16	56 ± 14	60 ± 14
CRP, mg/dL	0.62 ± 0.65	0.75 ± 0.64[3]	0.52 ± 0.82	0.27 ± 0.30
MetΣ ATPIII, present:absent, n (%)	75:108 (41:59)	47:23 (61:38)[4]	24:47 (34:66)	18:32 (36:64)
MUO:MHO[5]	136:48 (74:26)	61:7 (86:10)[4]	51:15 (72:21)[4]	43:5 (86:10)[4]
PCB serum concentrations,[6] ng/g lipid weight				
PCB153	45.3 (2.5, 624.0)	48.2 (2.5, 624.0)	67.4 (7.8, 276.5)	79.1 (17.3, 364.6)
PCB138	23.6 (0.3, 317.0)	26.4 (0.3, 317.0)	36.0 (4.7, 151.9)	39.8 (9.6, 162.7)
PCB180	27.9 (1.6, 432.0)	27.4 (1.6, 404.0)	40.9 (3.6, 204.6)	54.7 (9.9, 252.5)
ΣPCB	172.2 (14.3, 2189.0)	174.9 (14.3, 2189.0)	254.0 (32.4, 1249.5)	284.3 (65.8, 1572.4)

[1]Diabetes was classified according to the American Diabetes Association definition. CRP, C-reactive protein; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; MetΣ ATPIII, metabolic syndrome according to Adult Treatment Panel III criteria; MHO, metabolically healthy obese; MUO, metabolically unhealthy obese; NGT, normal glucose tolerance; PCB, polychlorinated biphenyl; T2DM, type 2 diabetes mellitus.

[2]Clinical data are presented as mean ± SD.

[3]Data were significantly ($P < 0.05$) higher in the baseline-with-follow-up group than in the baseline group.

[4]Data were missing for some subjects, which resulted in an inability to classify them as MetΣ ATPIII present or absent or as MUO or MHO.

[5]See Methods for criteria.

[6]Values presented as median (minimum, maximum) given their not-normal distribution.

proportion (%) of measurements with concentrations above the LOQ or the detection frequency. Details regarding the analytic methods and quality assurance and quality control have been published previously (22, 23).

Metabolic health status

Participants were classified as metabolically healthy or unhealthy on the basis of 3 different sets of criteria as follows: *1*) the MetS as defined by the Adult Treatment Panel III (ATPIII) criteria (24), *2*) the MetS as defined by the International Diabetes Federation (3), and *3*) the metabolically healthy phenotype, which is a combination of criteria that is based on the ATPIII criteria and extended by the HOMA-IR as a marker for insulin resistance and CRP as a marker for inflammation as proposed by Wildman et al. (5) and Karelis et al (25). An HOMA-IR >1 was defined as metabolically unhealthy in this study. Subjects with the presence or absence of the MetS are represented as metabolic syndrome according to ATPIII criteria present (MetS+) and metabolic syndrome according to ATPIII criteria absent (MetS−), respectively. Participants were considered MUO if they fulfilled ≥2 of 7 criteria or metabolically healthy obese (MHO) if they fulfilled <2 criteria.

Statistical analysis

Statistical calculations were performed with the use of IBM SPSS software (version 21.0; IBM SPSS). Concentrations less than the method LOQ were assigned a value of DF × LOQ, with DF being the proportion (%) of measurements with concentrations above the LOQ or the detection frequency. The normality of distribution was verified with the use of the Kolmogorov–Smirnov test. All PCB concentrations displayed a skewed distribution. After transformation, i.e., $y = \log(x + 1)$, some PCB concentrations were transformable to normality. To detect differences in serum PCB concentrations between individuals with MetS+ compared with MetS− and MUO compared with MHO, independent t tests or Mann-Whitney U tests were performed

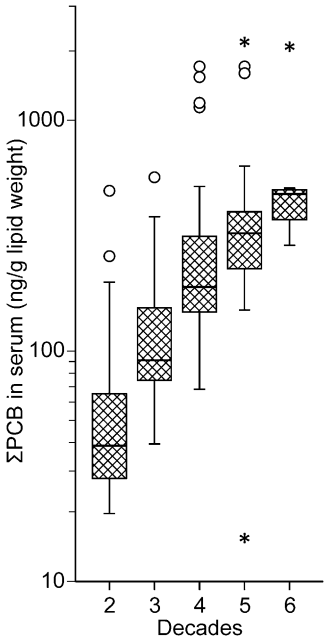

FIGURE 1 Serum PCB concentrations in the entire study population (n = 184) according to decade. ΣPCB is the sum of 27 measured PCB congeners (see Methods for details). Open circles indicate values within 3 SDs. *Value outside 3 SDs. PCB, polychlorinated biphenyl.

depending on the normality of the distribution of the variables. $P < 0.05$ was considered statistically significant. Subjects were identified who were MUO or had MetS+ at baseline and remained MUO or had MetS+ at 6 and 12 mo of follow-up (persistent MetS+ or MUO). Likewise, subjects were identified who had MetS+ or were MUO at baseline but were no longer had MetS+ or were MUO at 6 or 12 mo of follow-up (resolved MetS or MUO). A binary logistic regression was performed to assess the impact of age, smoking behavior, BMI, and PCB serum concentrations at baseline on the likelihood of having a persistent or resolved MetS or being MUO. Finally, regression analyses were performed with the use of ΔBMI and ΔPCB (PCB153, PCB138, PCB180, and ΣPCB separately) as independent variables and Δglucose, Δwaist, Δtriglycerides, ΔHDL cholesterol, Δsystolic blood pressure, Δdiastolic blood pressure, and ΔCRP as dependent variables. These regression analyses were performed with the 6-and 12-mo follow-up data.

RESULTS

Study population

A total of 184 subjects were included in the study (53 men and 131 women with a mean ± SD age of 41 ± 13 y) (Table 1; data on diet and surgery group descriptive statistics are shown in **Supplemental Tables 1** and **2**). With the use of the traditional criteria, ~40% of subjects were diagnosed with the MetS (MetS+). Because of the almost perfect match between groups defined with the use of the International Diabetes Federation or ATPIII criteria for MetS, all additional analyses presented were restricted to the APTIII criteria for convenience. With the use of the more-elaborate criteria with HOMA-IR and CRP, 74% of subjects were considered MUO.

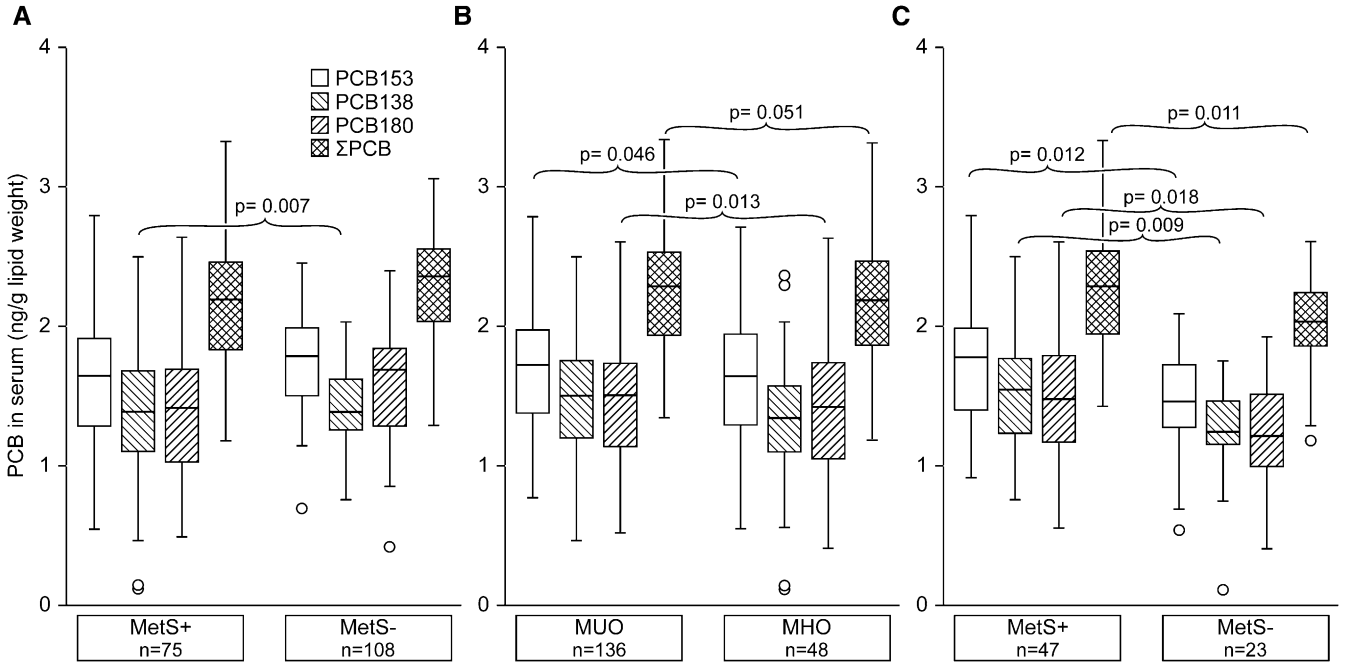

FIGURE 2 Serum concentrations of PCBs of individuals with the metabolic syndrome compared with individuals without the metabolic syndrome and of metabolically healthy individuals compared with metabolically unhealthy individuals at baseline (see Methods for criteria). Serum PCB concentrations were logarithmically transformed for normality. ΣPCB is sum of 27 measured PCB congeners (see Methods for details). Differences between groups were tested with the use of an independent samples t test. Significant results are represented in the figure with their respective P values. Values are shown for the entire study population (n = 184) (A and B) and for the study population with follow-up data available (n = 71) (C). Open circles indicate values within 3 SDs. *Value outside 3 SDs. MetS−, metabolic syndrome according to Adult Treatment Panel III criteria absent; MetS+, metabolic syndrome according to Adult Treatment Panel III criteria present; MHO, metabolically healthy obese; MUO, metabolically unhealthy obese; PCB, polychlorinated biphenyl.

Follow-up data at 6 and 12 mo were available for a subgroup of patients (Table 1). BMI, waist, triglycerides, and CRP concentrations were significantly higher in the subgroup ($P < 0.05$) than in the complete baseline group.

PCB concentrations

The most-prevalent PCB congeners identified in our study population were PCB153, PCB138, and PCB180 both in serum and in adipose tissue samples. Detailed information on the serum and adipose tissue concentrations of all measured congeners, the limit of quantification, and the detection frequency has been published previously (22, 23). PCB153, PCB138, and PCB180 made up 60% of the total PCB profile. Therefore, we limited additional statistical analyses of individual PCBs to these 3 PCBs. PCB concentrations, both in serum and adipose tissue, increased significantly with age (serum concentrations are shown in **Figure 1**). Because absolute PCB concentrations did not differ between visceral and subcutaneous adipose tissues, as described previously (23), additional statistical analyses were restricted to visceral adipose tissue concentrations.

Differences in serum PCB concentrations at baseline

Subjects with the MetS ($n = 75$) had significantly higher serum concentrations of PCB138 than those in subjects without the MetS (median: 31.3 compared with 21.4 ng/g lw, respectively) (**Figure 2**A). MUO ($n = 136$), compared with MHO, had significantly higher serum concentrations of PCB153 (median: 60.7 compared with 43.1 ng/g lw, respectively), PCB180 (48.4 compared with 24.9 ng/g lw, respectively), and ΣPCB (228.4 compared with 155.7 ng/g lw, respectively) (Figure 2B). There was a significant age difference between individuals with or without the MetS (44 ± 13 compared with 39 ± 12 y, respectively; $P = 0.014$), whereas this was not the case for MUO compared with MHO subjects (41 ± 10 y compared with 41 ± 13 y, respectively).

These analyses were repeated in the subgroup of patients ($n = 71$) of whom follow-up data were available. Serum concentrations of PCB153, PCB138, PCB180, and ΣPCB were significantly higher in MetS+ subjects ($n = 47$) than in MetS− subjects ($n = 23$) (40 ± 32 compared with 98 ±127, 22 ± 15 compared with 56 ± 74, 24 ± 20 compared with 59 ± 82, 138 ±105 compared with 365 ± 481 ng/g lw, respectively; $P < 0.02$ for all) (Figure

TABLE 2
Descriptive statistics of the subgroups with adipose tissue sampling[1]

	Entire population ($n = 50$)	MetS+ ($n = 30$)	MetS− ($n = 20$)	MUO ($n = 45$)	MHO ($n = 5$)
Sex, M:F, *n*	17:33	12:18	5:15	17:28	1:4
Age, y	40 ± 12[2]	43 ± 11[3]	34 ± 12	40 ± 12	38.4 ± 14
Active smoker, yes:no, *n*	7:43	6:24	1:19	6:39	1:4
BMI, kg/m^2	42.1 ± 3.8	42.5 ± 4.2	41.4 ± 2.9	42.4 ± 3.8	39.8 ± 1.7
Waist, cm	122 ± 12	126 ± 12	117 ± 8	124 ± 12	112.8 ± 4.7
Men	131 ± 10	135 ± 11	124 ± 4	132 ± 10	NA
Women	118 ± 10	121 ± 10	114 ± 8	119 ± 10	113 ± 5
Fasting glucose, mg/dL	98 ± 42	109 ± 52	83 ± 10	100 ± 44	82 ± 8
HOMA-IR	4.3 ± 2.7	4.9 ± 2.8	3.5 ± 2.3	4.5 ± 2.8	3.3 ± 1.7
Glucose-tolerance status, *n*					
NGT	22	9	13	17	5
IFG	1	0	1	1	0
IGT	17	12	5	17	0
IFG + IGT	3	2	1	3	0
T2DM	7	7	0	7	0
Blood pressure, mm Hg					
Systolic	126 ± 19	131 ± 21	118 ± 12	127 ± 19	118 ± 11
Diastolic	76 ± 11	78 ± 10	72 ± 12	76 ± 11	71 ± 11
Triglycerides, mg/dL	169 ± 103	214 ± 108	101 ± 36	177 ± 105	99 ± 32
HDL, mg/dL	47 ± 17	41 ± 14	57 ± 17	45 ± 17	68 ± 8
Men	35 ± 11	32 ± 7	44 ± 16	36 ± 11	NA
Women	53 ± 17	47 ± 15	61 ± 16	51 ± 17	68 ± 8
CRP, mg/dL	0.85 ± 0.67	0.84 ± 0.70	0.87 ± 0.63	0.87 ± 0.69	0.75 ± 0.45
PCB adipose tissue concentrations,[4] ng/g lipid weight					
PCB153	66.8 (9.1, 268.2)	78.8 (13.1, 268.2)[3]	36.9 (9.1, 207.5)	70.1 (10.0, 268.2)	57.4 (9.1, 96)
PCB138	33.3 (5.9, 141.9)	42.4 (8.1, 141.9)[3]	21.9 (5.9, 92.9)	35.8 (7.2, 141.9)	29.7 (5.9, 33.6)
PCB180	44.2 (4.9, 186.5)	58.3 (6.4, 162.9)[3]	23.1 (4.9, 186.5)	45.8 (5.4, 186.5)	35.7 (4.9, 68.6)
ΣPCB	284.6 (44.7, 1232.8)	337.1 (56.9, 1232.8)[3]	154.6 (44.7, 807.2)	298.6 (50.1, 1232.8)	224.3 (44.7, 350.0)

[1]Diabetes was classified according to the American Diabetes Association definition. Differences between groups were assessed with the use of the Mann-Whitney *U* test. CRP, C-reactive protein; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; MetS−, metabolic syndrome according to Adult Treatment Panel III criteria absent; MetS+, metabolic syndrome according to Adult Treatment Panel III criteria present; MHO, metabolically healthy obese; MUO, metabolically unhealthy obese; NA, not applicable; NGT, normal glucose tolerance; PCB, polychlorinated biphenyl; T2DM, type 2 diabetes mellitus.
[2]Clinical data are presented as mean ± SD.
[3]Significant difference between MetS+ and MetS− at baseline, $P < 0.05$.
[4]Values presented as median (minimum, maximum) given their not-normal distribution.

2C). Compared with MHO subjects (n = 7), MUO subjects (n = 61) did not have significantly different serum PCB concentrations. Age was not significantly different between subjects with MetS+ compared with MetS− and MUO compared with MHO groups.

Differences in adipose tissue PCB concentrations at baseline

Subjects with the MetS had significantly higher adipose tissue concentrations of PCB153, PCB138, PCB180, and ΣPCB, whereas this was not the case for MHO compared with MUO (**Table 2**). MetS+ subjects were significantly older than MetS− subjects, whereas this was not the case for MUO compared with MHO (Table 2).

Differences in serum PCB increments during weight loss

The increment in serum concentrations of PCB153, PCB138, PCB180, and ΣPCB (expressed as percentages) did not differ significantly between individuals with or without the MetS or between MUO and MHO at baseline (**Table 3**, **Figure 3**). Weight loss (expressed as a reduction in BMI) between the 2 groups did not differ significantly either (−16% ± 7% compared with −17% ± 10% at 6 mo, respectively, and −20% ± 13% compared with −19% ± 14% at 12 mo, respectively).

Differences in serum PCB increments between persistent MetS and MUO and resolved MetS and MUO subjects after weight loss

After 6 and 12 mo, 18 and 15 subjects, respectively, were identified as persistent MetS patients. Twenty-seven and 20 subjects were identified as resolved MetS patients. We did not detect a significant difference in the percentage increment in serum concentrations of PCB153, PCB138, PCB180, or ΣPCB at either time (**Table 4**). At 6 mo, the group in which the MetS persisted had a significantly lower weight loss (−13% ± 8% compared with −19% ± 11%, respectively; P = 0.046), but this was not the case at 12 mo. After 6 and 12 mo, 46 and 40 subjects, respectively, were considered persistent MUO, whereas 11 and 3 individuals, respectively, were identified as resolved MUO. We detected no difference in the percentage increment in serum concentrations of PCB153, PCB138, PCB180, or ΣPCB at either moment.

Predictive power of PCB serum concentrations for the resolution of the MetS or metabolically unhealthy status after weight loss

We performed a binary logistic regression to assess the effects of age, smoking behavior, BMI, and PCB serum concentrations at baseline on the likelihood of having persistent or resolved MetS or being MUO. In this regression analysis, serum concentrations of PCB153, PCB138, PCB180, or ΣPCB were not identified as significant factors in distinguishing between a persistent or resolved MetS or MUO. In addition, in regression analyses, ΔPCB serum concentrations could not be identified as significant predictors in the change of the individual components of the MetS and MUO.

TABLE 3
BMI and PCB serum concentrations at baseline and follow-up in metabolically healthy and unhealthy individuals[1]

	Baseline				6-mo follow-up,[2] value, % change			12-mo follow-up,[2] value, % change		
	MetS+	MetS−	MUO	MHO	MetS+ at baseline	MetS− at baseline		MetS+ at baseline		MetS− at baseline
n	47	23[3]	61	7	47	23		34		16
BMI	40.3 (31.5, 51.4)[4]	39.6 (27.4, 50.5)	40.3 (29.9, 51.4)	38.0 (27.4, 42.2)	34.2 (22.5, 48.9)	−18 (−41, 7)	33.0 (23.6, 46.3)	−17 (−27, −4)	31.7 (20.3, 46.7)	−21 (−5, 3)	31.2 (23.8, 48.1)	−19 (−39, 0)
Serum PCB153	59.2 (7.3, 624.0)	28.4 (2.5, 122.3)	48.5 (2.5, 624.0)	33.3 (3.9, 89.3)	71.3 (10.4, 276.5)	58 (−87, 385)	40.5 (7.8, 213.5)	43 (−10, 4972)	81.4 (19.6, 364.6)	37 (−87, 985)	66.8 (17.3, 196.5)	63 (1, 5170)
Serum PCB138	34.4 (4.8, 317)	16.9 (0.3, 56.5)	29.3 (0.3, 317)	21.0 (4.7, 45.5)	43.1 (6.4–151.9)	50 (−88, 304)	21.2 (4.7, 103.3)	24 (−24, 24800)	43.2 (12.8, 162.7)	27 (−87, 620)	28.0 (9.6, 90.5)	31 (−23, 22003)
Serum PCB180	29.4 (2.6, 404.0)	15.4 (1.6, 84.6)	27.4 (2.1, 404.0)	16.8 (1.6, 51.7)	53.2 (4.6–204.6)	76 (−85, 532)	22.9 (3.5, 181.8)	45.9 (−22, 3244)	63.3 (11.4, 252.5)	54 (−86, 1203)	42.9 (9.9, 166.6)	76 (14, 3261)
Serum ΣPCB[5]	215 (27, 2189)	107 (14, 409)	178 (14, 2189)	117 (19, 302)	264 (41–1249)	58 (−87, 422)	142 (32, 740)	43 (−13, 3144)	314 (77, 1572)	31 (−87, 984)	240 (66, 703)	69 (−2, 3171)

[1]See Methods for criteria of MUO and MHO designations. MetS−, metabolic syndrome according to Adult Treatment Panel III criteria absent; MetS+, metabolic syndrome according to Adult Treatment Panel III criteria present; MHO, metabolically healthy obese; MUO, metabolically unhealthy obese; PCB, polychlorinated biphenyl.
[2]Differences between groups were assessed with the use of the Mann-Whitney U test, but no significant differences were detected.
[3]Data were missing for one subject
[4]Data are presented as median (minimum, maximum).
[5]Sum of 27 PCB congeners (see Methods for details).

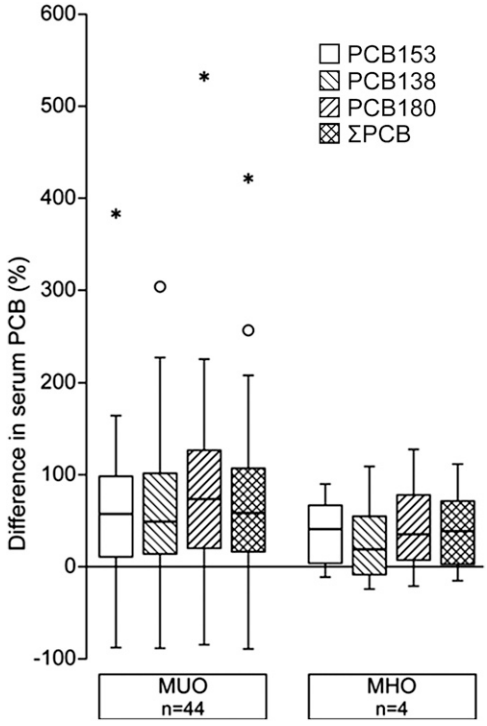

FIGURE 3 Increments in serum PCB concentrations after 12 mo of weight loss at baseline (see Methods for criteria). Differences between groups were assessed with the use of the Mann-Whitney *U* test, but no significant differences were detected. Open circles indicate values within 3 SDs. *Value outside 3 SDs. MHO, metabolically healthy obese; MUO, metabolically unhealthy obese; PCB, polychlorinated biphenyl.

DISCUSSION

Exposure to chemicals with endocrine-disrupting properties such as PCBs has been brought forward in several studies as a contributing factor in the increasing prevalence of obesity and related metabolic disorders such as insulin resistance and type 2 diabetes mellitus (10, 11, 26, 27). Our study is in line with these previous studies indicating higher serum concentrations of PCBs in individuals with the MetS and MUO subjects. The biochemical persistence of PCBs causes a significant accumulation within the human body throughout the lifetime. This trend was also present in our cohort. Because MetS+ subjects were significantly older than their MetS− counterparts, it could be argued that the significance in serum and adipose tissue concentrations was attributable to this age difference. However, in the entire baseline group (n = 184), MHO were not significantly younger than MUO, and nonetheless, MHO displayed significantly lower PCB serum and adipose tissue concentrations. The absence of this difference in the subgroup with follow-up data (n = 71) and with adipose tissue sampling might have been due to the very small number of MHO (n = 7 and 5, respectively). The interpretation if these results should be done with caution. However, our findings are in line with the few available studies that have also established higher serum PCB concentrations in patients with the MetS or who are MUO (9, 28). In a recent Korean study, serum PCB concentrations were predictive of the development of the MetS during a 4-y follow-up (29). Note that PCBs have recently been linked to trunk and visceral adipose tissue, which is the fat compartment that exerts a crucial role in the negative metabolic consequences of obesity (30, 31). Because of the variety of possible endocrine-disrupting mechanisms of different groups of PCB congeners (e.g., dioxin-like compared with nondioxin-like), it is particularly interesting to try to identify the specific group of PCB congeners that are responsible for the metabolically detrimental effect. However, because of a very high intercorrelation between the different PCB congeners in our study ($r > 0.7$ and $P < 0.01$ for most congeners), a detailed analysis of separate PCB groups was statistically not feasible.

Weight loss is a powerful method to reduce or abolish obesity associated comorbidities. However, during weight loss, lipophilic PCBs are released from the adipose tissue into the bloodstream, which causes a rise in PCB serum concentrations (16–18, 22) To our knowledge, no investigations have yet been carried out to determine whether this rise in PCB serum concentrations is different depending on the metabolic status and whether this rise is capable of blunting the beneficial effects of weight loss. In our study, no difference was detected in the percentage increase in PCB serum concentrations in MetS+ compared with MetS− subjects or in MUO compared with MHO. There were also no differences in serum PCB-concentration increments between persistent compared with resolved MetS or MUO subjects. In addition, PCB serum concentrations at baseline were not predictive for the persistence of resolution of a metabolically unfavorable state.

From a clinical point of view, individuals with the MetS or the MUO phenotype are considered at elevated risk of cardiovasculair morbidity and mortality. Several studies have investigated the link between cardiovascular disease and PCBs. In the NHANES study, PCB serum concentrations increased risk of cardiovascular mortality only in elderly subjects with a low fat mass (32). Another subanalysis of the NHANES indicated increased mortality risk in individuals >40 y of age with higher dioxin exposure (33). A review by Humblet et al. (34) also suggested increased risk of cardiovascular mortality with higher dioxin exposure but was not powered to control for other confounding factors. Moreover, it has also been suggested that PCB exposure can modulate traditional risk factors such as cigarette smoking (35).

Although we reported very detailed data on PCBs and metabolic health, we could not rule out the possibility of reverse causality because of the cross-sectional design of the study. Other chemicals of a less-persistent nature, such as phthalates and their metabolites, have also been linked to obesity and disturbances of glucose metabolism but were not taken into account (36). In addition, factors such as diet, parity, and breastfeeding may influence serum concentrations of PCBs as well. However, this information was not collected in our study.

In conclusion, for now, the concept of metabolically healthy obesity has not been clearly defined (37), but nonetheless, studies have indicated that a large number of these MHO individuals are still at increased risk to develop the MetS or type 2 diabetes mellitus after several years (38–40). Our study seems to suggest that, despite increased serum concentrations of PCBs during and immediately after weight loss, the beneficial health effects of weight reduction still far outweigh the possible risks associated with an elevated exposure to these endocrine-disrupting chemicals. This study raises the question of whether subjects with high PCB concentrations might have a higher chance of a relapse of obesity after weight loss or a higher chance of evolving from an MHO state into an MUO state. Indeed, PCB release has been

TABLE 4
BMI and PCB serum concentrations at baseline and follow-up in persistent and resolved metabolically healthy and unhealthy individuals[1]

	Baseline				6-mo follow-up, value, % change								12-mo follow-up, value, % change							
	MetS+	MetS−	MUO	MHO	Persistent MetS		Resolved MetS		Persistent MUO[2]		Resolved MUO		Persistent MetS		Resolved MetS		Persistent MUO		Resolved MUO	
n	47	23[3]	61	7	20		27		46		11		15		20		40		3	
BMI	40.3 (31.5, 51.4)[4]	39.6 (27.4, 50.5)	40.3 (29.9, 51.4)	38.0 (27.4, 42.2)	36.5 (28.2, 43.6)	−12 (−24, −3)[5]	31.8 (22.5, 48.9)	−20 (−41, 7)	34.3 (24.3, 48.9)	−16 (−30, 7)	31.9 (25.8, 39.8)	−20 (−41, −1)	33.3 (26.7, 44.6)	−14 (−35, 0)	29.2 (20.3, 46.7)	−21 (−53, 3)	32.2 (23.8, 48.1)	−18 (−39–3)	27.4 (20.3, 27.9)	−32 (−53, −30)
Serum PCB153	59.2 (7.3, 624.0)	28.4 (2.5, 122.3)	48.5 (2.5, 624.0)	33.3 (3.9, 89.3)	88.2 (15.3, 276.5)	40 (−85, 141)	67.4 (10.4, 201.4)	76 (−87, 385)	71.8 (10.4, 276.5)	43 (−85, 4972)	46.6 (14.4, 213.5)	62 (−86, 385)	79.4 (25.0, 364.6)	26 (−87, 154)	98.6 (19.6, 223.4)	57 (−82, 985)	80.9 (17.3, 364.6)	40 (−8, −5170)	41.8 (19.6, 150.9)	84 (73, 985)
Serum PCB138	34.4 (4.8, 317)	16.9 (0.3, 56.5)	29.3 (0.3, 317)	21.0 (4.7, 45.5)	52.2 (10.5, 151.9)	40 (−86, 116)	35.4 (6.3, 83.4)	68 (−88, 304)	43.1 (6.4, 151.9)	43 (−87, 24800)	32.2 (10.1, 103.3)	53 (−88, 304)	40.9 (15.5, 162.7)	24 (−87, 94)	49.2 (−83, 620)	50 (−83, 620)	42.1 (9.6, 162.6)	22 (−87, 22003)	23.3 (12.8, 64.1)	94 (43, 620)
Serum PCB180	29.4 (2.6, 404.0)	15.4 (1.6, 84.6)	27.4 (2.1, 404.0)	16.8 (1.6, 51.7)	54.9 (9.6, 204.6)	55 (−86, 180)	53.1 (4.6, 150)	95 (−86, 532)	44.9 (4.6, 204.6)	56 (−8, −3244)	34.0 (7.3, 181.8)	95 (−85, 532)	51.2 (17.9, 252.5)	39 (−86, 196)	65.4 (11.4, 180.5)	70 (−79, 1203)	52.6 (9.9, 252.5)	59 (−8, −3261)	21.9 (11.4, 113.3)	93 (79, 1203)
Serum ΣPCB[6]	215 (27, 2189)	107 (14, 409)	178 (14, 2189)	117 (19, 302)	341 (71, 1249)	47 (−87, 145)	260 (41, 681)	83 (−8, 422)	262 (41, 12479)	49 (−87, 3144)	205 (55, 740)	58 (−87, 422)	272 (99, 1572)	21 (−88, 148)	351 (76, 795)	56 (−82, 984)	288 (65, 1572)	39 (−88, 3172)	156 (77, 574)	86 (75, 984)

[1]See Methods for criteria of MUO and MHO designations. The Mann-Whitney *U* test was performed to assess differences between Persistent MetS and Resolved MetS or between Persistent MUO and Resolved MUO. MetS−, metabolic syndrome according to Adult Treatment Panel III criteria absent; MetS+, metabolic syndrome according to Adult Treatment Panel III criteria present; MHO, metabolically healthy obese; MUO, metabolically unhealthy obese; PCB, polychlorinated biphenyl; Persistent MetS, metabolic syndrome at baseline and still present after 6 or 12 mo of follow-up; Persistent MUO, metabolically unhealthy present at baseline and still present after 6 or 12 mo of follow-up; Resolved MetS, metabolic syndrome no longer present after 6 or 12 mo of follow-up; Resolved MUO, metabolically unhealthy no longer present after 6 or 12 mo of follow-up.

[2]Significant differences between Persistent MetS and Resolved MetS, $P < 0.05$.

[3]Data were missing for one subject.

[4]Data are presented as median (minimum, maximum).

[5]Difference between Persistent MUO and Resolved MUO was NS.

[6]Sum of 27 PCB congeners (see Methods for details).

shown to negatively affect the resting metabolic rate after weight loss, which possibly makes individuals more prone to weight regain (41). It would require a large scale follow-up study to answer these issues. Because of the current worldwide epidemic of obesity associated conditions such as the MetS, the possible effects of endocrine-disrupting chemicals such as PCBs on metabolic health are an imperative field of future research.

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