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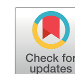
Adipose tissue concentrations of non-persistent environmental phenols and local redox balance in adults from Southern Spain



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ABSTRACT

The aim was to evaluate the associations of environmental phenol and paraben concentrations with the oxidative microenvironment in adipose tissue. This study was conducted in a subsample (n = 144) of the GraMo cohort (Southern Spain). Concentrations of 9 phenols and 7 parabens, and levels of oxidative stress biomarkers were quantified in adipose tissue. Associations were estimated using multivariable linear regression analyses adjusted for potential confounders.

Benzophenone-3 (BP-3) concentration was borderline associated with enhanced glutathione peroxidase (GPx) activity [$\exp(\beta) = 1.20$, $p = 0.060$] and decreased levels of reduced glutathione (GSH) [$\exp(\beta) = 0.55$, $p = 0.070$]. Concentrations of bisphenol A (BPA) and methylparaben (MeP) were associated to lower glutathione reductase (GRd) activity [$\exp(\beta) = 0.83$, $\exp(\beta) = 0.72$, respectively], and BPA was borderline associated to increased levels of oxidized glutathione (GSSG) [$\exp(\beta) = 1.73$, p-value = 0.062]. MeP was inversely associated to both hemeoxygenase-1 (HO-1) and superoxide dismustase (SOD) activity, as well as to the levels of thiobarbituric acid reactive substances (TBARS) [$0.75 < \exp(\beta) < 0.79$].

Our results suggest that some specific non-persistent pollutants may be associated with a disruption of the activity of relevant antioxidant enzymes, in addition to the depletion of the glutathione stock. They might act as a tissue-specific source of free radicals, contributing to the oxidative microenvironment in the adipose tissue.

1. Introduction

During the last decades, humans have been increasingly exposed to a wide variety of synthetic chemicals, some of which have been suspected to exert potential adverse effects on humans, *e.g.*, obesity, diabetes mellitus, hypertension, or cancer (Lakind et al., 2014). Particularly, increasing concern has recently arisen regarding environmental phenols and parabens, widely used in, *e.g.*, cosmetic products, food packaging, or pesticides. Consequently, humans are continuously exposed to these chemicals, mainly through dermal or ingestion routes (Soeborg et al., 2014). In contrast to other more persistent pollutants (*e.g.* organochlorine pesticides or polychlorinated biphenyls), environmental phenols and parabens exert a relatively low persistence in living organisms and, therefore, are known as non-persistent environmental pollutants (npEPs).

Environmental phenols include bisphenol A (BPA), used in the manufacture of polycarbonates and epoxy resins for a wide range of plastic products (Vandenberg et al., 2007), and UV filters

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[benzophenone-3 (BP-3)], antiseptic agents [triclosan (TCS) and triclocarban (TCCB)], pesticides [polychlorophenols (2,4-DCP, 2,5-DCP, and 2,4,5-TCP)], or fungicides [phenylphenols (2-PP and 4-PP)] (Frederiksen et al., 2014). Parabens are widely used as antimicrobial preservatives in cosmetic products and food packaging (SCCS, 2013).

Certain npEPs are known, or suspected, to disrupt the endocrine system at different levels (Boberg et al., 2010; Bonefeld-Jorgensen et al., 2007; Li et al., 2012). In addition, other complementary mechanisms of action have been identified, such as the promotion of an inflammatory milieu and/or the misbalance of the redox equilibrium (Choi et al., 2017; Thompson et al., 2015). In this regard, these chemicals have been identified as potential enhancers of the generation of reactive oxygen species (ROS) in *in vitro* (Perez-Albaladejo et al., 2017; R. Zhang et al., 2016), but also by using *in vivo* models (Elswefy et al., 2016; Hassan et al., 2012; Kazemi et al., 2016; Quan et al., 2017).

Considering that npEPs are rapidly metabolized and mainly excreted in conjugated forms, mainly as glucuronide and sulfate metabolites (facilitating their urinary excretion and reducing their bioactivity), urine is acknowledged as the preferable matrix for human biomonitoring purposes, and therefore, the majority of biomonitoring studies have assessed urinary levels of npEPs. Nevertheless, the log of the octanol–water partition coefficient (K_{ow}) of the abovementioned phenols and parabens typically ranges from 1 to 5 (Shelby, 2008). Therefore, these compounds (or at least some of them) might be also distributed in lipid-rich body compartments, such as adipose tissue, liver or brain, as previously suggested (Artacho-Cordon et al., 2017; Artacho-Cordon et al., 2018; Darbre et al., 2004; Fernandez et al., 2007; Geens et al., 2012; Wang et al., 2015).

Therefore, human-based evidence on the relationship between oxidative stress and internal levels of npEPs has been mainly explored by assessing associations of urinary pollutant concentrations with systemic levels of oxidative stress biomarkers (measured in the urine) (Asimakopoulos et al., 2016; Ferguson et al., 2016; Kang et al., 2013; Lv et al., 2016; Watkins et al., 2015). However, measures of oxidative stress biomarkers in urine or serum might not accurately reflect the oxidative microenvironment in specific body compartments (Arguelles et al., 2004; Frijhoff et al., 2015). In this regard, there is a lack of knowledge regarding the local oxidizing effect of environmental phenols and parabens in adipose tissue, a highly relevant compartment given the increasing evidence of increased oxidative stress in adipose tissue as an early pathogenic mechanism of obesity-related diseases, *e.g.* metabolic syndrome (Furukawa et al., 2004). The present study aims to shed light on the potential local redox unbalance caused by npEPs. Therefore, here we explore the potential associations of adipose tissue concentrations of npEPs with the *in situ* oxidative microenvironment in a cohort of adults from Southern Spain.

2. Materials and methods

2.1. Study population

The study population (n = 144) is a subsample of the GraMo cohort stablished in Southern Spain, which has been extensively described elsewhere (Arrebola et al., 2013; Arrebola et al., 2010; Arrebola et al., 2009). Participants were recruited between July 2003 and June 2004 among patients undergoing non-cancer-related surgery [hernias (41%), gallbladder diseases (21%), varicose veins (12%), and other conditions (26%)], at two public hospitals: San Cecilio University Hospital (Granada, urban area) and Santa Ana Hospital (Motril, semirural area), separated by 70 km. At recruitment, participants were over 16 years old, and had lived in one of the two study areas for > 10 years. Out of 409 individuals who were contacted, 387 (94.6%) agreed to participate in the study. The final subpopulation (n = 144, 35.2%) included those with adequate adipose tissue sample available in proper conditions for both the analyses of environmental phenols and oxidative stress. No statistically significant differences in baseline characteristics were found between the present subcohort and the excluded participants, except a higher proportion of patients living in urban areas found in the latter (Supplementary Table S1). All subjects signed an informed consent form, and the study was approved by the Ethics Committee of Granada (Comité de Ética de la Investigación Biomédica de Granada).

2.2. Chemical analyses

Adipose tissue samples were intraoperatively collected [front abdominal wall (67, 46.5%), pelvic waist (64, 44.4%) and limbs (13, 9.0%)] and immediately coded and stored in aliquots at −80 °C until analyses. A total of nine environmental phenols [bisphenol-A (BPA), benzophenone-3 (BP-3), triclosan (TCS), three chlorophenols (2,4-DCP, 2,5-DCP and 2,4,5-TCP) and two phenylphenols (2-PP and 4-PP), triclocarban (TCCB)] and seven parabens (sum of unconjugated, deglucuronidated and desulfated compounds) [methyl- (MeP), ethyl- (EtP), propyl- (n-PrP and i-PrP), butyl- (n-BuP and i-BuP) and benzyl-paraben (BzP)] were isolated from about 100 mg of adipose tissue samples and analyzed by TurboFlow liquid chromatography-tandem mass spectrometry (LC-MS/MS) following a previously validated methodology (Artacho-Cordon et al., 2017). Chemical analysis of phenols and parabens were performed at Department of Growth and Reproduction, Rigshospitalet, University of Copenhagen, Denmark.

Samples were analyzed in 4 batches during a period of 6 weeks. Each batch included standards for calibration curves (injected at beginning and end of each batch), 30–40 unknown samples, two blanks, two adipose tissue pool controls and two adipose tissue pool controls spiked at low and high level. The inter-day variation (expressed as the relative standard deviation) and the recovery of spiked samples was < 10% and > 85%, respectively for all analytes at low and high spike levels. Additionally, analyses were performed twice in a subset of samples to identify and track unintended contamination with the target analytes, as previously reported (Ye et al., 2013). Reagents and standards used were shipped as described previously (Artacho-Cordon et al., 2017). All reagents and solvents were of analytical, HPLC, or MS grade, and all chemicals and labwares were tested for contamination before use.

2.3. Measurement of oxidative stress biomarkers

A total of nine oxidative stress biomarkers were quantified in adipose tissue samples using commercially available kits (Enzo Life Sciences, Inc., Farmingdale, NY, USA), and an automatic microplate reader (TRIAD MRX II series, Dynex Technologies Inc., Chantilly, Virginia, USA), as previously detailed elsewhere (Artacho-Cordon et al., 2016; Leon et al., 2019). Hence, total superoxide dismutase (SOD) (U/mg protein), glutathione peroxidase (GPx) (nmol/min·mg protein) and glutathione reductase (GRd) activities (nmol/min·mg protein), as well as hemeoxygenase-1 (HO-1) levels (ng/mg protein) were measured. Moreover, concentrations of reduced glutathione (GSH) (nmol/min·mg protein) and oxidized glutathione (GSSG) (nmol/min·mg protein) was determined, and total glutathione (GST) (nmol/min·mg protein) and the ratio GSSG/GSH were then calculated. Finally, levels of lipid peroxidation (TBARS) (μM/mg protein) were also quantified.

2.4. Statistical analyses

A descriptive analysis was carried out and qualitative covariates were expressed as n (%). Levels of npEPs and oxidative stress biomarkers in adipose tissue were expressed as n (%) > LOD, mean, standard deviation (SD) and percentiles (25th, 50th and 75th). Because ANOVA assumptions were not always fulfilled, bivariate analyses for comparisons of the subsample with the total cohort were carried out using the nonparametric Mann–Whitney *U* test and Kruskal–Wallis test.

The shapes of the relationships between independent and dependent variables were visually evaluated through locally weighted scatterplot

smoothing (LOWESS) and generalized additive models (GAM). The associations of npEPs with oxidative stress biomarkers was assessed by means of multivariable linear regression analyses. Thus, we firstly created unadjusted linear regression analyses and then we built multivariable models with different levels of adjustment. The selection of confounders was based on significant associations with exposure or outcomes and on previous reports (Artacho-Cordon et al., 2018; Block et al., 2002; Furukawa et al., 2004). Given the limited sample size, models were sequentially adjusted for age (years), gender (male/female), body mass index (kg/m^2) and residence (urban/semirural). Other potential confounders, such as smoking habits, occupational class or adipose tissue source were additionally explored, showing no relevant influence or effect modification on the associations found. Concentrations of phenols and oxidative stress biomarkers were log-transformed and β coefficients are also presented as exp(β). Concentrations of selected phenols with a detection frequency of 20–75% were entered as dichotomous variables (< LOD/ > LOD) (*i.e.* TCS, EtP and n-PrP), while those phenols detected in < 20% of samples were excluded for analyses (*i.e.*, TCCB, 2,4-DCP, 2,5-DCP, 2,4,5-TCP, 2-PP, 4-PP, i-PrP, i-BuP, n-BuP and BzP).

We also estimated the combined effect of npEP concentrations on oxidative stress/glutathione system biomarkers using Weighted Quantile Sum (WQS) regression (Carrico et al., 2015), which calculates a weighted index from the individual associations of the exposure variables (chemical concentrations) with each oxidative stress marker, and in which each chemical has a specific weight. The WQS analyses were performed with quartile-scored pollutant concentrations, using a training set defined as a 40% random sample of the dataset, being the remaining 60% used for model validation. Only npEPs with a detection frequency > 75% were included in the WQS analyses. We further explored the associations between each WQS index and its corresponding outcome using multivariable linear regression, adjusting for the same confounders as the models with individual chemical concentrations. It has been reported that WQS regression is a highly accurate method to address collinearity and high-dimensionality (Carrico et al., 2015).

The significance level was set at p = 0.05 and all tests were two-tailed. Data analyses were performed with R statistical computing environment 3.0 (R Core Team, 2018), with gWQS package v1.0.0 for the calculation of WQS index (Renzetti et al., 2018).

3. Results

Table 1 summarizes the baseline characteristics of the study participants. Mean (± SD) age and BMI of the participants were, respectively, 52.3 (± 17.8) years and 27.5 (± 4.8) kg/m^2. There was a higher proportion of women *vs* men (61.1 *vs* 38.9%), as well as urban residents (77.8 *vs* 22.2%). Out of 144 participants, 33 (22.9%) had at least secondary studies, 112 (77.8%) were manual workers, and 55 (38.2%) declared to be smokers at recruitment. Adipose tissue concentrations of selected npEPs and levels of oxidative stress biomarkers in GraMo cohort have previously been reported (Artacho-Cordon et al., 2018; Artacho-Cordon et al., 2016). In our subsample, we detected levels of BPA, BP-3 and MeP in > 75% of samples, whereas TCS, EtP, and n-PrP were found in 45.8%, 20.1% and 54.2%, respectively. Regarding oxidative stress biomarkers, we found detectable levels of selected biomarkers of oxidative stress in 100% (GRd, HO-1 and SOD), 96.5% (GPx), 92.4% (TBARS), 81.9% (GST), 75.7% (GSH), 46.5% (GSSG), and 41.7% (GSSG/GSH) of the samples (Supplementary Table S2). No tissue-specific differences were found in levels of oxidative stress biomarkers, with the exception of GRd activity, which was higher in adipose tissue from the pelvic waist (Supplementary Table S3).

The results from multivariable linear regression analyses assessing the associations of adipose tissue npEPs with the glutathione cycle markers are shown in Table 2, while models for other antioxidant enzymes and lipid peroxidation are displayed in Table 3. Given that associations did not change substantially along different levels of adjustment, Tables 2 and 3 only show those results from the last (full) model (adjusted for age, gender, BMI and residence). Analyses to explore the potential effect modification of gender, BMI and adipose tissue source were also carried out, with null results (Supplementary Tables S4–6).

Table 1
Characteristics of the study population (n = 144).

	N (%)
Age (years)	52.3 ± 17.8[a]
Sex	
Male	88 (61.1)
Female	56 (38.9)
Body mass index (kg/m^2)	27.5 ± 4.8[a]
Residence	
Urban	112 (77.8)
Semi-rural	32 (22.2)
Educational level	
< Primary	42 (29.2)
Primary	69 (47.9)
Secondary/university	33 (22.9)
Current smoker	55 (38.2)
Occupational class	
Non-manual worker	32 (22.2)
Manual worker	112 (77.8)
Adipose tissue source	
Pelvic waist	64 (44.4)
Front abdominal wall	67 (46.5)
Limbs	13 (9.0)

[a] Mean ± standard deviation.

We detected a positive borderline-significant association between BP-3 adipose tissue concentrations and the activity of GPx (antioxidant enzyme), while GRd activity was inversely associated with both BPA and MeP adipose tissue levels. Regarding glutathione compounds, BP-3 levels were inversely associated with GSH levels, while BPA levels were positively associated with GSSG levels, although the associations found were close to the statistical significance (p-values = 0.070 and 0.062, respectively). GST levels were also related to higher BPA concentrations (Table 2). Moreover, when all the three chemicals were included in the multivariable analyses, only MeP remained significantly associated with the GRd activity [exp(β) 0.75, 95% CI (0.58, 0.98); p-value 0.032] (data not shown in tables).

Adipose tissue concentrations of npEPs were also negatively associated to other antioxidant enzymes such as HO-1 and SOD (Table 3). In this regard, BPA concentrations were associated to lower activity of SOD, while MeP concentrations were associated to lower HO-1 and SOD activities. When BPA and MeP were simultaneously included in the multivariable analysis, only BPA was significantly associated with SOD activity [exp(β) 0.82, 95% CI (0.68, 0.97); p-value 0.025] (data not shown in tables). Finally, the oxidative damage to the lipids (measured as TBARS) was inversely related to MeP concentrations in the adipose tissue. Similarly, lower TBARS levels were observed in participants with detectable levels of EtP in their adipose tissue. As shown in Fig. 1, we also observed significant associations of tertiles of BPA with SOD levels; BP-3 with GPx and GSH; and MeP with GRd, HO-1, and TBARS.

WQS analyses were additionally performed to assess the contribution of the potential combined effect of environmental phenols in the disruption of adipose tissue oxidative stress biomarkers (Table 4). The WQS index was inversely associated with GRd activity and TBARS levels, being the latter only marginally significant. In both oxidative stress biomarkers, MeP was found to be the main contributor to the index (52.3% and 90.6% for GRd and TBARS, respectively). In the models for GRd activity, BPA (22.6%) and BP-3 (25.4%) showed relatively modest but non-negligible contributions, although the influence of these chemicals on the index for TBARS was very low (9.4% and < 0.01%, respectively).

Table 2
Adipose tissue concentrations of environmental phenols and status of the glutathione cycle. Multivariate analysis.

	GPx										GRd				
	Unadjusted model					Adjusted model					Unadjusted model				
	β	exp(β)	95% CI		p-Value	β	exp(β)	95% CI		p-Value	β	exp(β)	95% CI		p-Value
Environmental phenols															
BPA (ng/g tissue)	0.05	1.05	0.86	1.28	0.653	0.10	1.10	0.90	1.35	0.337	−0.22	0.80	0.67	0.96	0.018
TCS (> LOD *vs* ≥LOD)	0.23	1.26	0.83	1.90	0.274	0.29	1.33	0.89	2.00	0.160	−0.04	0.96	0.66	1.41	0.849
BP-3 (ng/g tissue)	0.09	1.09	0.90	1.32	0.377	0.18	1.20	0.99	1.45	0.060	−0.01	0.99	0.83	1.18	0.915
Parabens															
MeP (ng/g tissue)	−0.21	0.81	0.62	1.05	0.115	−0.20	0.82	0.63	1.06	0.133	−0.36	0.70	0.55	0.88	0.003
EtP (> LOD *vs* ≥LOD)	−0.20	0.82	0.49	1.37	0.439	−0.13	0.88	0.53	1.45	0.610	0.03	1.03	0.64	1.64	0.905
PrP (> LOD *vs* ≥LOD)	−0.20	0.82	0.54	1.23	0.335	−0.15	0.86	0.58	1.29	0.472	−0.03	0.97	0.66	1.41	0.858

	GRd					GST									
	Adjusted model					Unadjusted model					Adjusted model				
	β	exp(β)	95% CI		p-Value	β	exp(β)	95% CI		p-Value	β	exp(β)	95% CI		p-Value
Environmental phenols															
BPA (ng/g tissue)	−0.19	0.83	0.69	1.00	0.045	0.68	1.97	1.18	3.26	0.009	0.65	1.91	1.13	3.25	0.016
TCS (> LOD *vs* ≥LOD)	−0.01	0.99	0.68	1.45	0.957	−0.09	0.91	0.32	2.63	0.863	−0.19	0.83	0.28	2.47	0.732
BP-3 (ng/g tissue)	0.05	1.05	0.88	1.26	0.602	0.09	1.09	0.90	1.32	0.377	−0.17	0.84	0.50	1.42	0.521
Parabens															
MeP (ng/g tissue)	−0.33	0.72	0.57	0.91	0.006	0.06	1.06	0.54	2.10	0.866	0.05	1.05	0.52	2.11	0.898
EtP (> LOD *vs* ≥LOD)	0.07	1.08	0.67	1.72	0.760	0.26	1.30	0.35	4.84	0.697	0.08	1.08	0.28	4.20	0.911
PrP (> LOD *vs* ≥LOD)	0.01	1.01	0.70	1.47	0.946	0.66	1.93	0.67	5.56	0.219	0.58	1.79	0.61	5.23	0.287

	GSH										GSSG				
	Unadjusted model					Adjusted model					Unadjusted model				
	β	exp(β)	95% CI		p-Value	β	exp(β)	95% CI		p-Value	β	exp(β)	95% CI		p-Value
Environmental phenols															
BPA (ng/g tissue)	0.14	1.15	0.59	2.24	0.687	0.14	1.16	0.58	2.30	0.679	0.59	1.81	1.04	3.15	0.037
TCS (> LOD *vs* ≥LOD)	−0.09	0.91	0.23	3.59	0.893	0.01	1.01	0.25	4.09	0.992	0.16	1.18	0.37	3.72	0.778
BP-3 (ng/g tissue)	−0.38	0.69	0.36	1.30	0.244	−0.61	0.55	0.28	1.05	0.070	−0.16	0.85	0.50	1.47	0.564
Parabens															
MeP (ng/g tissue)	0.35	1.42	0.59	3.42	0.432	0.37	1.45	0.59	3.54	0.412	0.05	1.05	0.50	2.19	0.901
EtP (> LOD *vs* ≥LOD)	−0.17	0.84	0.15	4.61	0.840	−0.30	0.74	0.13	4.23	0.737	0.23	1.26	0.30	5.28	0.747
PrP (> LOD *vs* ≥LOD)	0.54	1.71	0.44	6.72	0.439	0.49	1.64	0.41	6.48	0.480	0.64	1.90	0.60	5.94	0.270

Table 2 (*continued*)

	GSSG					GSSG/GSH									
	Adjusted model					Unadjusted model					Adjusted model				
	β	exp(β)	95% CI		p-Value	β	exp(β)	95% CI		p-Value	β	exp(β)	95% CI		p-Value
Environmental phenols															
BPA (ng/g tissue)	0.55	1.73	0.97	3.09	0.062	−0.47	0.63	0.32	1.23	0.175	−0.41	0.66	0.33	1.32	0.241
TCS (> LOD *vs* ≥LOD)	−0.05	0.95	0.29	3.11	0.933	0.15	1.17	0.29	4.71	0.829	0.34	1.41	0.35	5.74	0.630
BP-3 (ng/g tissue)	−0.18	0.84	0.47	1.47	0.531	−0.24	0.79	0.41	1.53	0.483	−0.44	0.64	0.33	1.26	0.199
Parabens															
MeP (ng/g tissue)	0.06	1.06	0.50	2.26	0.874	0.57	1.77	0.73	4.30	0.205	0.59	1.80	0.74	4.40	0.193
EtP (> LOD *vs* ≥LOD)	0.09	1.10	0.25	4.78	0.899	−0.29	0.75	0.13	4.22	0.742	−0.27	0.76	0.13	4.35	0.760
PrP (> LOD *vs* ≥LOD)	0.60	1.82	0.57	5.80	0.307	0.19	1.21	0.30	4.87	0.790	0.21	1.23	0.31	4.91	0.770

LOD: limit of detection; multivariate analyses were adjusted for age (years), gender (male/female), body mass index (kg/m^2) and residence (rural/semirural).

4. Discussion

To the best of our knowledge, this study represents the first epidemiological evidence reporting associations of specific npEPs and *in situ* oxidative stress in the adipose tissue, suggesting that these chemicals might induce small but potentially long-lasting disruption of the local redox balance. Hence, in contrast to the inverse associations found with SOD or HO-1 antioxidant enzyme activities, we have detected that those participants with higher levels of some npEPs in the adipose tissue had an increased GPx activity, which is crucial for maintaining intracellular homeostasis as well as redox balance. Furthermore, our results also indicate that glutathione turnover might be affected by certain npEPs, based on the positive associations found with GSSG and the inverse associations with GRd activity and GSH levels. Nevertheless, the lack of associations with TBARS levels suggests that the studied npEPs in adipose tissue are not related to oxidative damage in tissue macromolecules. However, previous studies in other populations have reported positive associations of human internal levels of, *e.g.* BPA, parabens, TCS and benzophenones, with systemic oxidative stress (Asimakopoulos et al., 2016; Ferguson et al., 2016; Huang et al., 2017; Watkins et al., 2015; T. Zhang et al., 2016), supporting a potential oxidation of macromolecules by these chemicals.

Total antioxidant status (TAS) is comprised by a wide variety of both enzymatic and non-enzymatic antioxidants (Teixeira et al., 2013) which are responsible for converting free radicals into less harmful molecules. The prominent enzymes in this system are GPx, SOD, HO-1, and catalase (CAT) (Jones et al., 2000). A previous *in vivo* study using rats found that an exposure to 10–50 mg/kg of BPA (once daily for four weeks) caused a decrease in the liver SOD and CAT activities (Macczak et al., 2017). Similarly, another study reported lower SOD activity levels in the liver after daily doses of 50 mg/kg of BPA during eight weeks (Elswefy et al., 2016). Ozaydin et al. (2018) also evidenced decreased levels of GSH, SOD, GPx, and CAT in old male wistar rats after 8 weeks of treatment with 5, 50, and 500 μg/kg body weights/day of BPA. Furthermore, an experimental study using rats revealed reduced GRd activity and GSH levels after a mid-term exposure to 10–50 mg/kg of BPA (once daily for four weeks) (Hassan et al., 2012). However, comparisons between adipose tissue and liver should be made with care.

The influence of npEPs exposure on HO-1 activity has been scarcely addressed in previous research. Kazemi et al. (2016) reported increased gene expression of HO-1 in male wistar rats after administration of increasing doses of BPA (5, 25, and 125 μg BPA/kg) during 35 consecutive days, although protein levels or enzyme activity was not reported in this study. However, comparison between gene and protein expression profiles should be made with care, given that (i) gene expression may not be always translated into protein, (ii) may be translated incorrectly, and (iii) protein folding may be inadequate.

As abovementioned, there is a scarcity of epidemiological studies assessing the influence of npEPs on neither systemic nor *in situ* antioxidant system activity. Our results suggest a role of GPx in the detoxification of npEP-derived ROS, at least in the context of adipose tissue with daily baseline concentrations of npEPs. In addition to this increased GPx activity, BPA-enhanced GSSG levels also indicate that the glutathione cycle is detoxifying ROS production. Furthermore, GRd, which reduces GSSG into GSH, was inversely associated with levels of specific npEPs (BPA and MeP), in agreement with the detected GSSG accumulation and the reduced availability of GSH levels, which probably indicates a depletion of GSH (Fig. 2). In addition to the potential induction of the free radical production, previous studies have reported associations between the exposure to npEPs and the disruption of enzyme biosynthesis and, even more, alterations in protein folding of the antioxidant enzymes (R. Zhang et al., 2016). Likewise, Kim et al. (2016) reported a potential effect of BPA exposure and TT genotype at rs4880 on the SOD2 isoform among patients with abnormal liver function. It was previously reported that the T allele at rs4880 of SOD2 disrupts the alpha-helix structure of SOD2, causing protein retention at the

Table 3
Adipose tissue concentrations of environmental phenols and levels of oxidative stress in the tissue. Multivariate analysis.

	HO1										SOD				
	Unadjusted model					Adjusted model					Unadjusted model				
	β	exp(β)	95% CI		p-Value	β	exp(β)	95% CI		p-Value	β	exp(β)	95% CI		p-Value
Environmental phenols															
BPA (ng/g tissue)	0.00	1.00	0.87	1.15	0.992	0.00	1.00	0.87	1.16	0.986	−0.23	0.79	0.68	0.93	0.004
TCS (> LOD *vs* ≥LOD)	0.13	1.14	0.85	1.52	0.370	0.12	1.13	0.84	1.51	0.410	0.22	1.24	0.90	1.72	0.191
BP-3 (ng/g tissue)	0.00	1.00	0.88	1.15	0.975	0.04	1.04	0.91	1.20	0.539	−0.02	0.98	0.84	1.14	0.786
Parabens															
MeP (ng/g tissue)	−0.28	0.75	0.63	0.90	0.002	−0.29	0.75	0.63	0.90	0.002	−0.24	0.79	0.64	0.97	0.025
EtP (> LOD *vs* ≥LOD)	0.16	1.17	0.82	1.67	0.391	0.13	1.14	0.80	1.64	0.465	−0.17	0.84	0.56	1.27	0.406
PrP (> LOD *vs* ≥LOD)	0.08	1.08	0.81	1.44	0.594	0.08	1.08	0.81	1.44	0.603	−0.13	0.88	0.63	1.22	0.432

	SOD					TBARS									
	Adjusted model					Unadjusted model					Adjusted model				
	β	exp(β)	95% CI		p-Value	β	exp(β)	95% CI		p-Value	β	exp(β)	95% CI		p-Value
Environmental phenols															
BPA (ng/g tissue)	−0.24	0.78	0.67	0.92	0.003	0.11	1.11	0.96	1.29	0.160	0.12	1.13	0.97	1.32	0.117
TCS (> LOD *vs* ≥LOD)	0.24	1.27	0.91	1.78	0.163	−0.05	0.95	0.70	1.30	0.752	−0.03	0.97	0.71	1.33	0.853
BP-3 (ng/g tissue)	0.02	1.02	0.86	1.19	0.854	0.02	1.02	0.88	1.18	0.779	0.04	1.04	0.89	1.20	0.634
Parabens															
MeP (ng/g tissue)	−0.24	0.78	0.63	0.97	0.025	−0.23	0.79	0.65	0.96	0.019	−0.24	0.78	0.64	0.96	0.016
EtP (> LOD *vs* ≥LOD)	−0.18	0.83	0.55	1.27	0.396	−0.43	0.65	0.45	0.95	0.027	−0.45	0.64	0.43	0.93	0.021
PrP (> LOD *vs* ≥LOD)	−0.15	0.86	0.62	1.20	0.381	−0.26	0.77	0.57	1.05	0.095	−0.25	0.78	0.57	1.06	0.108

LOD: limit of detection; multivariate analyses were adjusted for age (years), gender (male/female), body mass index (kg/m^2) and residence (rural/semirural).

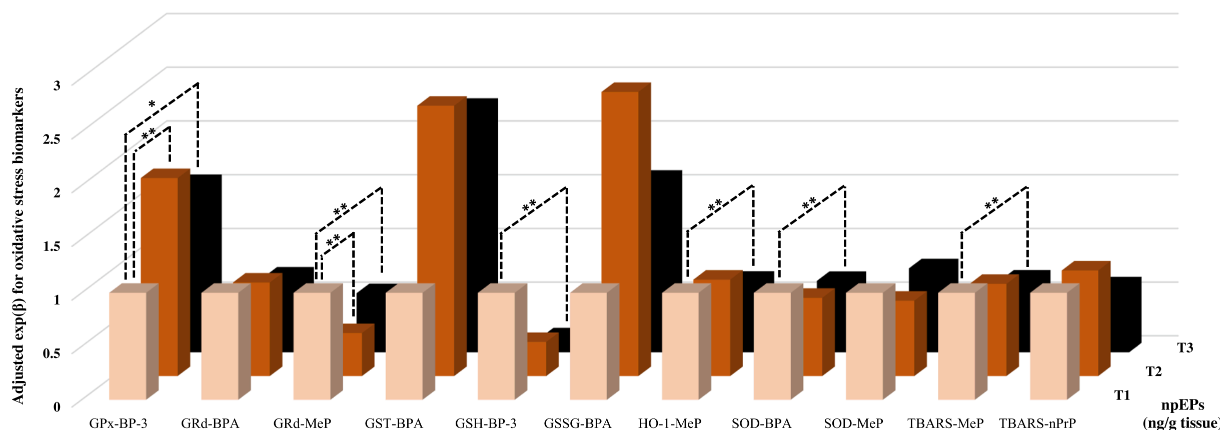

Fig. 1. Adjusted exp(β) for levels of oxidative stress biomarkers in the tertiles (T) of adipose tissue concentration of npEPs. Models were adjusted for age (years), gender (male/female), body mass index (kg/m^2) and residence (urban/semi-rural). *p < 0.10; **p < 0.05.

Table 4
(1) Individual weights of each pollutant in the Weighted Quantile Sum (WQS) regression index, and (2) associations between WQS index and each oxidative stress biomarker.

	(1) WQS regression index weights[a]			(2) WQS index		
	BPA	BP-3	MeP	β	SE	p-Value
GPx	n.c.	n.c.	n.c.	0.071	0.057	0.218
GRd	0.226	0.254	0.523	−0.205	0.061	0.001
GST	n.c.	n.c.	n.c.	0.219	0.216	0.315
GSSG	n.c.	n.c.	n.c.	−0.129	0.239	0.590
GSH	n.c.	n.c.	n.c.	−0.026	0.161	0.872
GSSG/GSH	n.c.	n.c.	n.c.	−0.024	0.171	0.889
SOD	n.c.	n.c.	n.c.	0.008	0.006	0.181
TBARS	0.094	0.000	0.906	−0.064	0.034	0.063
HO-1	n.c.	n.c.	n.c.	−0.058	0.038	0.126

n.c. "not calculated". Analyses were adjusted for age (years), gender (male/female), body mass index (kg/m^2) and residence (rural/semirural).
[a] Weights of specific compounds were only estimated in those models where WQS associated with the outcome.

mitochondrial inner membrane, which leads to enhanced susceptibility to oxidative stress (Hiroi et al., 1999).

Two previous pharmacodynamic studies in rats reported slightly higher half-time elimination rates of npEPs in adipose tissue compared to those in serum (Aubert et al., 2012; Doerge et al., 2012). This is in agreement with our previous findings of absence of correlation between npEP concentrations in serum/urine and those in the adipose tissue of 14 volunteers (Artacho-Cordon et al., 2017). Thus, and given that only a residual fraction of npEPs remains in the adipose tissue after 24 h (Aubert et al., 2012; Doerge et al., 2012), there might be temporal daily fluctuations in the npEP adipose tissue burden. These repetitive recent exposures are more prone to activate TAS, while chronic and stable exposures are more related to tissue oxidative damage due to the TAS capacity decline (Possamai et al., 2007). Hence, our results indicate that, whereas long-term accumulated persistent chemicals in the adipose tissue lead to oxidative damage (Artacho-Cordon et al., 2016), low exposures of some npEPs were associated with disturbances in the antioxidant system in the adipose tissue, at least at the exposure levels of our population.

In contrast to the abovementioned lack of studies assessing the potential influence of circulating npEP levels on the antioxidant defense, previous epidemiological studies have widely addressed npEP-derived oxidative damage of macromolecules. In this regard, previous researches found associations of urinary levels of npEPs with higher systemic levels of oxidative damage, either considering lipid peroxidation (Ferguson et al., 2016; Kang et al., 2013; Kim and Hong, 2017; Watkins et al., 2015) or DNA damage (Asimakopoulos et al., 2016; Ferguson et al., 2016; Lv et al., 2016; T. Zhang et al., 2016). Interestingly, the inverse associations between adipose tissue MeP concentrations and TBARS levels seem not in agreement with previous findings. However, given that urinary concentrations of several npEPs are some orders of magnitude higher in comparison with the adipose tissue levels (Vandenberg et al., 2007), it appears reasonable that systemic, but not adipose tissue burden of npEPs would lead to a generalized collapse of antioxidant system and thus, to macromolecule oxidation. Moreover, it has been previously demonstrated that repeated stress leads to biological systems to an up-regulation of protective mechanisms, such as their proteasome proteolytic capacity, in order to replace oxidized proteins (Pickering et al., 2013). Similarly, an up-regulation of lipid turnover has been described after redox imbalance (Giron-Calle et al., 1997). Thus, a chronic up-regulation of lipid turnover might lead to an

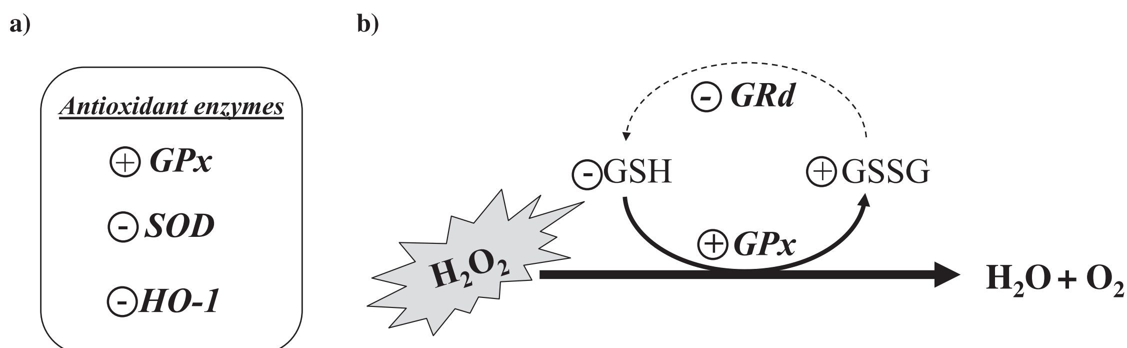

Fig. 2. Hypothesized influence of npEPs in redox balance in adipose tissue. (a) Low daily concentrations of npEPs in the adipose tissue may disrupt the antioxidant system, with only GPx enzyme detoxifying npEP-derived free radicals. (b) Low daily concentrations of npEPs in the adipose tissue may deplete glutathione turnover.

excess in damaged lipid clearance. In addition to that, it is worth to mention that systemic lipid peroxidation might not reflect status of lipids in specific tissues (Arguelles et al., 2004), and therefore, comparisons between systemic and local oxidative microenvironment should be made with care.

Our study has certain limitations that can hamper the assumption of causal associations. Our cross-sectional design hampers the elucidation of causal effects, considering the risk of reverse-causality in the associations found. In addition, we have observed relatively subtle associations that might not have immediate health consequences in our participants, but their long-term clinical implications warrant further research, particularly when the exposure occurs on a daily basis. Furthermore, this is a hospital-based study and the external validity of our results might be limited, although there is no reason to believe that these findings would not be reproduced in the general population, on the basis of the heterogeneous clinical background of the study participants. Moreover, the sample size was relatively small, which may have hampered the detection of a wider range of associations. Although a wide range of covariates were tested and associations remained significant at all levels of adjustment, we did not account for the influence of the use of cosmetics on the npEP levels or the potential confounding effect of physical exercise. Even more, in this study, oxidative stress was only estimated by quantifying lipid oxidation, but other tissue macromolecules are also susceptible to be affected, such as proteins and DNA. Thus, there is a need for further studies evaluating the influence of distributed npEPs in the adipose tissue on protein and/or DNA damage.

5. Conclusions

To the best of our knowledge, this study constitutes the first epidemiological evidence reporting associations of a group of npEPs distributed in the adipose tissue (*i.e.*, BPA, BP-3 and MeP) with the local redox disturbance. Hence, our results suggest that some npEPs may disrupt the activity of relevant antioxidant enzymes, in addition to the depletion of the glutathione stock. Thus, and despite tissue lipids seem to be undamaged, some npEPs might act as a tissue-specific source of free radicals. These chemicals, in combination with other previously identified exposures, such as persistent organic pollutants (Artacho-Cordon et al., 2016), may contribute to the oxidative microenvironment in the adipose tissue. Hence, we consider these results highly relevant to public health, considering that oxidative stress in adipocytes is acknowledged to contribute to the development of a number of chronic diseases (Manna and Jain, 2015), as well as the increasing importance of adipose tissue homeostasis misbalance in the development of chronic diseases (Kershaw and Flier, 2004). Further research is needed to confirm our findings as well as on the potential long-term clinical implications of the observed disturbance of adipose tissue microenvironment.

Declaration of competing interest

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

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2019.105118.

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