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Review

Concentrations of bisphenol-A in adults from the general population: A systematic review and meta-analysis

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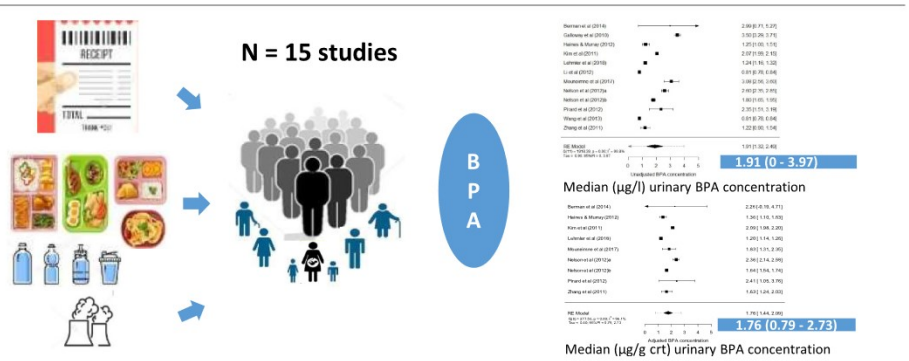
HIGHLIGHTS

- This first meta-analysis of BPA concentrations highlights widespread population exposure.
- BPA was detected in more than 90% of the recruited samples.
- No differences were found in BPA concentration by sex, geographic area or analytical technique.
- Larger sample sizes were associated with lower BPA concentrations.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Human bisphenol-A (BPA) exposure has been linked to adverse health effects even at low doses, which may be of potential public health concern.
Objective: To summarize BPA concentrations in general human population and their variability according to sex, geographic area, and analytical method.
Methods: Systematic review and meta-analysis of studies reporting BPA concentrations in adult human populations. Separate meta-analyses of median values were carried out for BPA in serum, creatinine-adjusted urinary

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BPA, and unadjusted urinary BPA concentrations using a random-effects model. Cochran's *Q*-statistic, I^2 index, 95% prediction intervals (PIs), between-studies standard deviation (τ), and forest plots were applied to verify study heterogeneity. Sensitivity and subgroup analyses and weighted ANOVAs and meta-regressions were conducted. Funnel plots and Egger's tests were used to examine publication bias.

Results: Fifteen studies were included in the meta-analysis, totaling 28,353 participants. BPA was detected in over 90% of participants. The pooled creatinine-adjusted urinary BPA concentration was 1.76 μg/g (95% PI: 0.79–2.73), with individual estimates ranging between 1.20 and 2.41. The pooled estimate for unadjusted urinary BPA was 1.91 μg/l (95% PI: 0–3.97), ranging between 0.81 and 3.50, while the pooled estimate for serum BPA was 1.75 μg/l (95% PI: 0–10.58), ranging between 0.34 and 3.76. No differences were found by sex, geographic area or analytical technique. Larger sample sizes were associated with lower BPA concentrations. There was large heterogeneity across studies, whereas data for urinary BPA levels suggested a publication bias affecting research in low exposed populations.

Conclusion: This first meta-analysis of human BPA concentrations highlights a widespread population exposure to BPA. Although there was high heterogeneity across studies, the expected range of estimated human BPA concentrations suggests that potential health risks are unlikely. Further studies are warranted to better characterize the epidemiology of human BPA exposure, accounting for ethnic, geographic, individual and environmental variability.

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1. Introduction

Bisphenol-A (BPA) is an endocrine-disrupting chemical widely used in the manufacture of polycarbonate plastics and epoxy resins to line food containers. Potential sources of human exposure are oral ingestion or contact through the air or the skin, but diet has been estimated to account for 95–99% of exposure (Miyamoto and Kotake, 2006; Wilson et al., 2007), mainly through foods in contact with BPA leached from packaging materials when exposed to heat (Geens et al., 2012). Since BPA is rapidly metabolized in the body within hours (Vandenberg et al., 2007), the quasi-universal distribution of BPA suggests that humans are continuously exposed. Detectable urinary BPA levels have been found in over 90% of the US, European and Asian populations (Calafat et al., 2008; CDC (Centers for Disease Control and Prevention)., 2015; Vandenberg et al., 2010).

As evidenced by *in vivo* and *in vitro* studies in animals and human tissues, BPA has the capacity to alter the function of the endocrine system by mimicking estradiol (E2) actions through binding to E2 receptors ER-α and ER-β, albeit with lower affinity than 17-β-estradiol (Acconcia et al., 2015; Kim et al., 2014). BPA is also able to disrupt the action of several other hormones, contributing to the development of a plethora of diseases such as obesity, hypertension, diabetes, cardiovascular diseases, and cancer, even at low doses (Melzer et al., 2012; Prins et al., 2019; Savastano et al., 2015; Shiue, 2014; Song et al., 2016; Zhang et al., 2020). These endocrine-disrupting abilities and their associated effects have garnered concern in regulatory agencies all over the world. Thus, European Food Safety Authority (EFSA) reduced the tolerable daily intake (TDI) of BPA from 50 μg/kg per day to 4 μg/kg per day in 2015, and a new re-evaluation is under way for 2020 (Cwiek-Ludwicka, 2015). In addition, in 2017 the General Court of the European Union and in 2010 the US Environmental Protection Agency (US EPA) confirmed

that BPA was a substance of very high concern (General Court of the European Union, n.d.; U.S. Environmental Protection Agency, 2010). Consequently, regulatory actions have been taken in different countries to reduce the population exposure to BPA by limiting its content in food containers, packaging materials, and thermal paper, whereas a ban on the use of BPA-based polycarbonate resins in baby bottles and infant formula packaging came into effect several years ago in regions such as Canada, Europe, several Latin-American countries or the US. In response to a stricter regulation on BPA, the industry has moved structurally similar alternatives such as BPS, BPF or BPAF, which exhibit similar or greater estrogenic or anti-androgenic activities (Chen et al., 2016; Mustieles et al., 2020).

Due to concerns about the widespread exposure to BPA in human populations, there has been a rapid increase in the number of human studies on BPA, most of which are cross-sectional biomonitoring studies (Covaci et al., 2015; Dunder et al., 2019; Huang et al., 2018; Kim et al., 2011; Lehmler et al., 2018; Vandenberg et al., 2010). BPA has been detected in human urine, blood, saliva, placental tissue, adipose tissue, and breast milk, among other human fluids (Vandenberg et al., 2010). Several biomonitoring studies have described differences in BPA concentrations according to the type of biological matrix, sex, age, socioeconomic level and ethnicity (Calafat et al., 2008). Thus, BPA concentrations in humans vary across studies even within the same country. For instance, reports from biomonitoring studies such as the National Health and Nutrition Examination Survey study (NHANES) showed that mean urinary BPA concentrations in several survey cycles ranged from 2.97 μg/l to 4.89 μg/l in the United States (Dunder et al., 2019) and from 0.81 μg/l to 3.23 μg/l in China (Li et al., 2012; Zhang et al., 2011), whereas mean serum BPA ranged from 0.58 μg/l to 1.19 μg/l in Spain (González et al., 2019; Salamanca-Fernández et al., 2020).

The aim of this study was to conduct a systematic review and meta-analysis of the available cross-sectional studies with at least one BPA measurement to estimate a pooled adult human BPA exposure in different populations, to evaluate potential differences by geographic region and to examine the influence of other potential variables.

2. Methods

This systematic review and meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Moher et al., 2009). Supplementary file 1 presents the PRISMA checklist for this study. The study protocol was registered at PROSPERO.org on April 28th, 2020 (registration code CRD4202015762).

2.1. Search strategy

A systematic search of published articles was conducted in PubMed, EMBASE, and the Web of Science until September 22nd, 2019 using the following search strategy: ("bisphenol A" OR "BPA" OR "endocrine disruptor" OR "endocrine disruption" OR "endocrine disrupting chemical" OR "EDs" OR "xenoestrogens" OR "chemical disruptors") AND ("concentrations" OR "levels" OR "biomonitoring" OR "exposure" OR "human exposure"). The search strategy is described in detail in Supplementary file 2. In addition, the reference lists of the selected articles were manually searched to detect any potential additional studies not found by the primary search.

2.2. Eligibility criteria

Inclusion criteria were as follows: (a) cross-sectional studies in the general population reporting BPA concentrations in adult humans (age: >18 years old), excluding specific populations such as pregnant women, women undergoing fertility treatments, students, *etc.*; and (b) articles published in English, French and Spanish. The search was restricted using the following exclusion criteria: a) studies in which the main objective was the validation of BPA detection techniques or to evaluate the exposure to controlled doses of BPA in an experimental or laboratory context; b) studies exclusively focused on child or teenager populations; c) *in vitro* or animal studies; and d) conference or congress presentations, posters, letters and reviews. No restrictions based on time period or ethnicity were applied.

2.3. Study selection criteria

Identified articles were independently evaluated by two reviewers. Titles and abstracts were checked to assess eligibility criteria, and potentially relevant studies were selected for a full-text review. When there were different studies that had analyzed the same population or had overlapping samples, only the study with the largest number of participants was selected. The selected articles were stored in Mendeley Reference Management Software. After the removal of duplicated studies, each paper was coded as 'included', 'excluded', or 'uncertain'.

2.4. Data extraction

The relevant information from each study was independently extracted by two researchers using a predefined data extraction form. A codebook was produced to describe how the study characteristics had to be extracted (see Supplementary file 3). The main study characteristics extracted were as follows: main author, year, geographical area (country and continent), sample size, the percentage of females in the sample, ethnic distribution, average age of participants, type of biological sample, and assessment analytical technique, limit of detection (LOD) and limit of quantification (LOQ).

To analyze the reliability of the data extraction process, two researchers coded the study characteristics independently. The interrater agreement between the two researchers was calculated using kappa coefficients for categorical variables and intraclass correlation coefficients for continuous variables. Inconsistencies between the two reviewers were solved by consensus or the involvement of a third researcher.

All of the categorical moderators achieved satisfactory kappa coefficients (over 0.60). Regarding continuous moderators, 94% of them obtained satisfactory intraclass correlation coefficients (over 0.60) and only 6% showed moderate agreement (0.41–0.60).

2.5. Assessment of study quality

The methodological quality of the included studies in this systematic review was assessed by two researchers independently using an adaptation of the Newcastle-Ottawa Scale (NOS) for cross-sectional studies (Modesti et al., 2016). This scale has a 'star system' to judge three subscales: selection, comparability, and exposure ascertainment. The comparability item was excluded as it did not apply to this study. Thus, the Newcastle-Ottawa Scale for this review consisted of 5 items for a total maximum score of 6 stars. Study quality was classified as 'high' (6 stars), 'medium' (3 to 5 stars), or 'low' (<3 stars).

2.6. Meta-analysis of BPA concentrations

The outcome measures in this meta-analysis were pooled BPA concentrations in serum or urine, both unadjusted (μg/l) and adjusted by creatinine (μg/g). The majority of the studies included in this meta-analysis reported medians or, to a lesser extent, geometric or arithmetic means. For consistency, the effect size was defined as the median BPA concentration. For this matter, an estimate of the standard error, SE_{Md}, was required together with the median value. As studies did not report the SE_{Md}, they were estimated by means of the formula $SE_{Md} = 1.253 x SD/\sqrt{N}$, where SD is the standard deviation of the BPA concentrations and N is the sample size (Hojo, 1931). For each study, the sampling variance of the median was calculated as: $V_{Md} = SE^2_{Md}$.

When studies did not report the *SD*, it was estimated through the median, 1st and 3rd quartiles and/or minimum and maximum values, as described elsewhere (McGrath et al., 2019; Wan et al., 2014). One study did not report medians but geometric means (Aekplakorn et al., 2015), and in this case, the geometric means were taken as estimates of the medians. Several studies reported BPA concentrations for male and female subsamples. In these cases, the medians (and SE_{Md}) of BPA concentrations were calculated separately for men and women. Supplementary file 4 presents a detailed description of how the medians and their standard errors were obtained or calculated from the different selected studies, and Excel Table S1 includes the Excel sheet elaborated by Wan (Wan et al., 2014) and used in this meta-analysis to estimate the *SD*s when they were not reported in the original studies.

2.7. Statistical analyses

Separate meta-analyses were carried out for the median serum and urinary (unadjusted and creatinine-adjusted) BPA concentrations with the use of random-effects models, as heterogeneity was expected in median BPA concentrations. In addition, separate meta-analyses were performed according to the biological sample used: serum, urine (unadjusted), or creatinine-adjusted urine. The inverse variance method was used to weight each median BPA concentration, being the variance equal to the sum of the sampling variance of the median (V_{Md}) and the between- study variance, τ^2, which was estimated by restricted maximum likelihood (Cooper et al., 2019). For each meta-analysis, a pooled BPA concentration was obtained, and a 95% CI was constructed using the improved method developed by Hartung and Knapp (Hartung and Knapp, 2001; Sánchez-Meca and Marín-Martínez, 2008). To check for heterogeneity between studies, Cochran's *Q*-statistic and the I^2 index, were used. I^2 is a relative index of the heterogeneity among the effect estimates that takes into account the within-study sampling variance, such that in meta-analyses that integrate a set of studies with large sample sizes the I^2 index will be large even in absence of large heterogeneity (Borenstein et al., 2017; Coory, 2010; IntHout et al., 2016). In addition, I^2 is a proportion and, as a consequence, it is not in the same metric that the effect estimates, such that it cannot quantify the absolute amount of heterogeneity. To assess the absolute amount of heterogeneity among the effect estimates, the between-studies standard deviation (τ) and a 95% prediction interval (PI) were calculated. A 95% PI is similar to a 95% CI in that both of them take the pooled estimate to calculate around it a lower and an upper limit. Whereas a 95% CI describes the expected range of values for the *true average effect*, a 95% PI takes into account the heterogeneity among the effect estimates, such that it qualifies the expected range of *true effects* (not the true average effect). Put in other words, a 95% PI describes the expected range of true effects if a new study was accomplished. As the between-studies standard deviation and the lower and upper limits of a 95% PI are in the same metric than the effect estimates, they can offer a reasonable description of the amount of heterogeneity (Borenstein et al., 2009; Higgins et al., 2020; IntHout et al., 2016; Stijnen et al., 2021). For each meta-analysis, a forest plot was also constructed in order to make explicit the individual median BPA concentrations obtained from the studies. A sensitivity analysis was conducted to assess whether the overall BPA concentration was substantially influenced by the presence of any individual study by systematically removing each study on a one-by-one basis and recalculating the significance of the overall result. To explain the heterogeneity among the median BPA concentrations, weighted ANOVAs and meta-regressions for categorical and continuous moderators were applied, respectively, with the use of mixed-effects models. An improved *F* statistic developed by Knapp and Hartung (Knapp and Hartung, 2003; Rubio-Aparicio et al., 2020) was applied to test the statistical significance of each moderator. The Q_E statistic was applied for testing the model misspecification and an estimate of the proportion of variance accounted for by each moderator was obtained by means of the formula $R^2 = 1 - \tau^2_{res}/\tau^2$, where τ^2_{res} and τ^2 were the residual and total between-study variances, respectively (López-López et al., 2014). To assess whether publication bias was a threat to the validity of the meta-analytic results, funnel plots were constructed and their asymmetry was examined with Egger's test (Rothstein et al., 2005). A statistically significant result for Egger's test ($p < 0.10$) was evidence of publication bias. In the case of asymmetry, the trim-and-fill method was applied to impute missing BPA concentrations (Duval and Tweedie, 2000). All statistical analyses were conducted with the *metafor* program in R (Viechtbauer, 2010).

3. Results

3.1. Characteristics of the included studies

A total of 1314 titles and abstracts were screened, of which 1013 records were excluded for not meeting the inclusion criteria. A total of 301 full-text papers were further reviewed for eligibility, and 283 were finally excluded either because the study population was not relevant to this review or because the same sample had already been included as part of a previous study. Thus, 18 articles were selected as potentially eligible. Four of them were finally excluded by consensus after it was confirmed that they did not fully meet all inclusion criteria. The flowchart of the search process is shown in Fig. 1.

One of the fourteen studies that fulfilled the inclusion criteria for this meta-analysis, published by Nelson et al. (2012), reported separate BPA concentrations for two NHANES survey cycles (2003–04 and 2005–06). Both of them were included in the meta-analysis, thus giving rise to a total of 15 independent studies for this meta-analysis. Excel Table S2, Excel Table S3, Excel Table S4 and Excel Table S5 include the final database of this meta-analysis. The 15 studies were based on a total sample size of 28,353 participants (Median = 1490, Minimum = 67, Maximum = 6003). The average age of the subjects ranged from 35.8 to 70 years (Mean = 50.3, *SD* = 50.0) and three continents were represented: Asia (8 studies), North America (4 studies), and Europe (3 studies). The type of biological sample used was urine in the majority of the studies (80%) or blood/serum (20%). The analytical technique most frequently used to measure BPA concentrations was HPLC-MS (10 studies) and, to a lesser extent, GC–MS (1 study) and ELISA (1 study).

The study quality was assessed according to the NOS score as previously described. Supplementary file 5 includes the scores achieved by each study in each item included, as well as its total quality score. In summary, half of the selected studies reached the maximum score (6 points), with a mean value of 4.9 and minimum score of 2.

3.2. Estimations of the BPA concentrations

Twelve studies reported median unadjusted urinary BPA concentrations (μg/l). The urinary medians reported varied between 0.81 μg/l (Li et al., 2012) and 3.50 μg/l (Galloway et al., 2010). The pooled unadjusted BPA concentration was $BPA_+ = 1.91$ μg/l, with 95% CI: 1.32, 2.49, 95% PI: 0, 3.97, and $\tau = 0.898$. The results are presented in a forest plot in Fig. 2. A sensitivity analysis was accomplished, consisting of the deletion of each median BPA concentration on a one-by-one basis and then the recalculation of the pooled BPA concentration. Table S1 includes the pooled BPA leaving out one study and their discrepancies with the original pooled BPA concentration. As shown, in urinary BPA studies none of the discrepancies reached 10%. A large relative heterogeneity among the median BPA concentrations was found, $Q_{11} = 1918.39$, $p < 0.0001$, $I^2 = 99.8\%$.

Nine studies reported median urinary BPA concentration adjusted by creatinine (μg/g). The medians reported in the studies varied between 1.20 μg/g (Lehmler et al., 2018) and 2.41 μg/g (Pirard et al., 2012). The pooled adjusted BPA concentration was $BPA_+ = 1.76$ μg/g [95% CI: 1.44, 2.09; 95% PI: 0.79, 2.73; $\tau = 0.397$]. Fig. 3 presents the forest plot with the results. A *leave-one-out sensitivity analysis* was performed, and no *single* study had a substantial influence on the overall

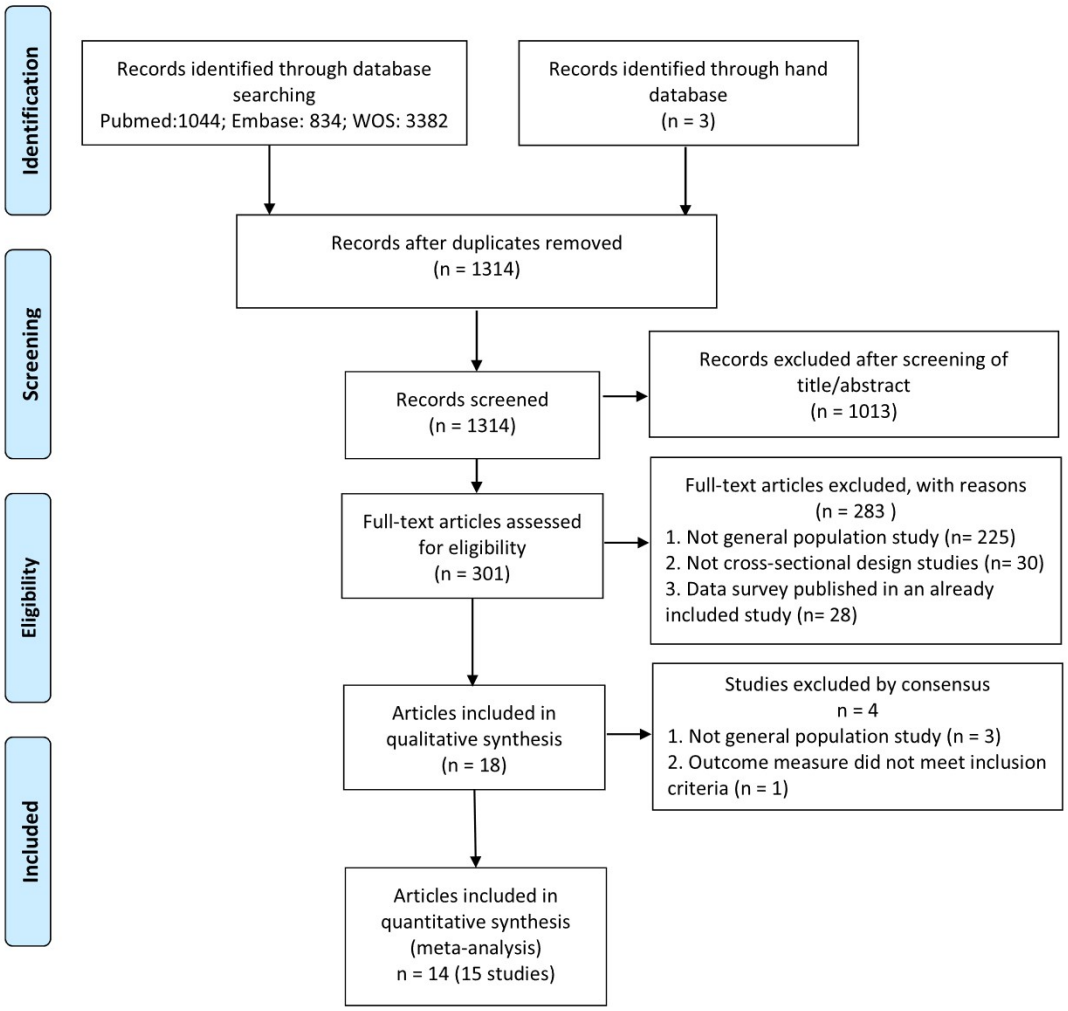

Fig. 1. PRISMA 2009 flow diagram.

BPA estimate (discrepancies lower than 10%; see Table S2). A large relative heterogeneity among the median BPA concentrations was found, $Q_8 = 277.56$, $p < 0.0001$, $I^2 = 96.1\%$.

Three studies reported median BPA concentrations from human serum samples. The medians reported varied between 0.34 μg/l (Aekplakorn et al., 2015) and 3.76 μg/l (Olsén et al., 2012). The pooled BPA concentration was $BPA_+ = 1.75$ μg/l [95% CI: 0, 6.18; 95% PI: 0, 10.58; $\tau = 1.78$]. A *leave-one-out sensitivity analysis* was performed, and its results showed a large influence of the three median BPAs, especially the Olsén et al. (2012) BPA estimate, as its deletion led to a reduction in the pooled BPA concentration of 57% (Table S3). The three BPA estimates obtained from serum samples exhibited a large relative heterogeneity [$Q_2 = 1003.88$, $p < 0.0001$; $I^2 = 99.9\%$]. In addition, note that the Aekplakorn et al. (2015) BPA estimate was a geometric mean instead of a median.

3.3. Analysis of publication bias

Publication bias was analyzed through the construction of a funnel plot and assessments of its asymmetry with Egger's test and the trim-and-fill method. Fig. 4 presents the funnel plot for the 12 median unadjusted BPA concentrations (μg/l) obtained from urine samples. The inspection of the funnel plot revealed certain asymmetry, with Egger's test being statistically significant, $t_{10} = 3.00$, $p = 0.013$, suggesting a publication bias affecting research in low exposed populations and the trim-and-fill method imputed three additional BPA estimates to symmetrize the funnel plot, leading to an overall BPA estimate of BPA_{adj} [95% CI] = 1.55 μg/l [0.96, 2.15]. Compared with the original overall BPA estimate ($BPA_+ = 1.91$ μg/l), the overall BPA concentration adjusted by publication bias decreased by 18.8%.

Fig. 5 shows the funnel plot for the 9 studies reporting creatinine-adjusted urinary BPA concentrations (μg/g). Although the funnel plot exhibited asymmetry, Egger's test did not reach statistical significance, $t_7 = 1.30$, $p = 0.235$. However, the trim-and-fill method imputed one BPA estimate to symmetrize the funnel plot, such that the pooled BPA concentration once corrected by publication bias was BPA_{adj} [95% CI] = 1.73 μg/g [1.44, 2.03]. Compared with the original overall BPA concentration obtained from the 9 studies ($BPA_+ = 1.76$ μg/g), the overall BPA concentration once adjusted by publication bias barely changed, with a negligible decrease of 1.7%.

3.4. Analysis of potential moderators

3.4.1. Unadjusted urinary BPA concentrations

The large heterogeneity found among the median BPA concentrations (μg/l) led to an analysis of influence of potential moderator variables. Table 1 presents the results of the weighted ANOVAs performed on several categorical moderators. Five studies separately reported median unadjusted urinary BPA concentrations and three median adjusted urinary BPA concentrations in samples from adult women and men

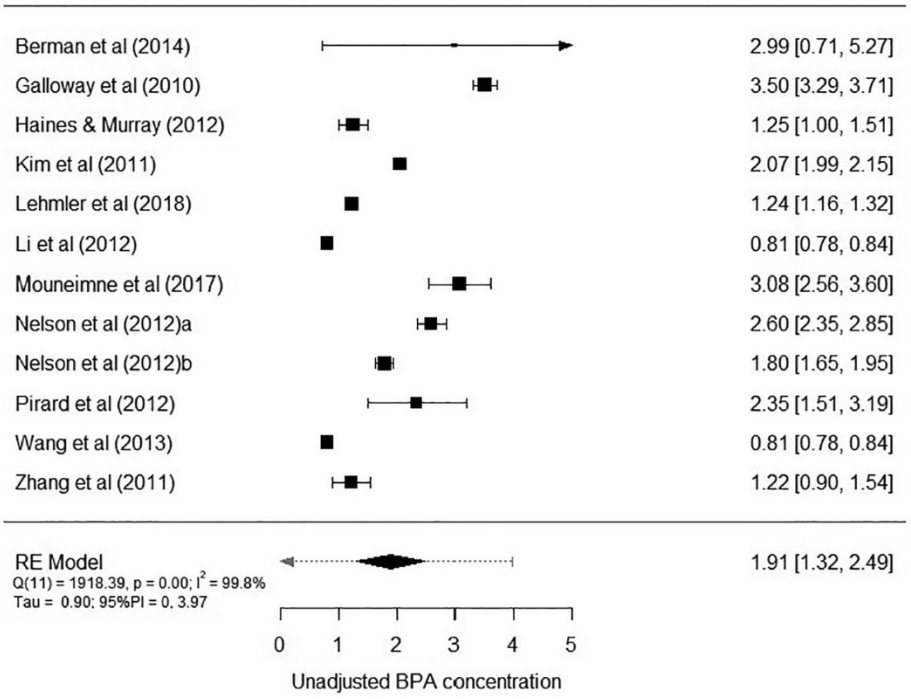

Fig. 2. Forest plot of the median unadjusted urinary BPA concentrations (μg/l) of 12 studies from urine biological samples. 'Nelson et al (a)' and 'Nelson et al (b)' corresponded to the '2003–04' and '2005–06' NHANES samples, respectively. Black squares represent median BPA concentrations extracted from each study, whereas lines represent the 95% confidence limits around them. Black diamond represents the average of the median BPA concentrations. Dotted lines from the black diamond represent the 95% prediction interval limits (95% PI). Tau = between-studies standard deviation (τ). RE model = random-effects model. Data in brackets are the lower and upper 95% confidence limits for the median BPA concentration and for its average.

(Excel Table S6 and Excel Table S7). Although men exhibited a higher pooled BPA concentration ($BPA_+ = 1.92$ μg/l) than women ($BPA_+ = 1.65$ μg/l), no statistically significant differences were found between them ($p = 0.709$). Fig. 6 presents the forest plot for these findings. The continent and the country where the study was done, as well as the analytical technique for BPA measurement, did not show a

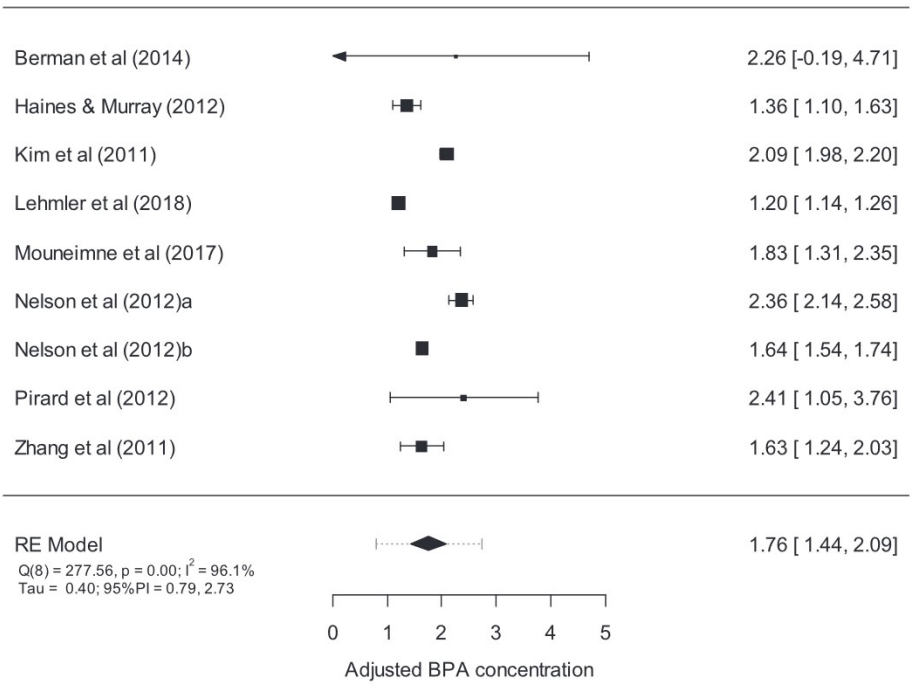

Fig. 3. Forest plot of the median urinary BPA concentrations adjusted by creatinine (μg/g) of 9 studies. 'Nelson et al. (2012)a' and 'Nelson et al. (2012)b' corresponded to the '2003–04' and '2005–06' NHANES samples, respectively. Black squares represent median BPA concentrations extracted from each study, whereas lines represent the 95% confidence limits around them. Black diamond represents the average of the median BPA concentrations. Dotted lines from the black diamond represent the 95% prediction interval limits (95%PI). Tau = between-studies standard deviation (τ). RE model = random-effects model. Data in brackets are the lower and upper 95% confidence limits for the median BPA concentration and for its average.

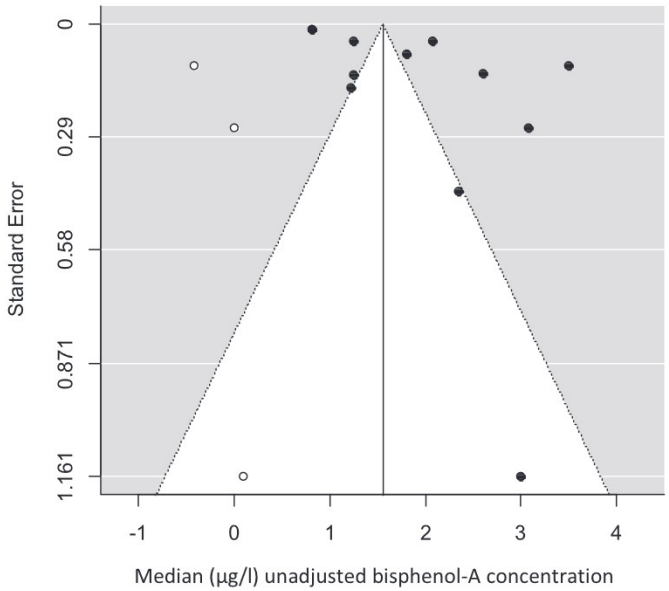

Fig. 4. Funnel plot of the median urinary unadjusted bisphenol-A (BPA) concentrations. Black circles represent the original median unadjusted BPA concentrations, whereas white circles represent the three BPA estimates imputed with the trim-and-fill method.

statistically significant relationship with the median BPA concentrations reported ($p > 0.05$). However, it is worth noting that the pooled BPA concentration obtained from European countries ($BPA_+ = 2.99$ μg/l) was slightly higher than that from Asian ($BPA_+ = 1.66$ μg/l) and North American study populations ($BPA_+ = 1.72$ μg/l).

Weighted ANOVAs were also applied on the items of the NOS (Table 2). No statistically significant association of sample representativeness, sample size adequacy, the number of non-respondents, or the adequacy of statistical tests with median BPA concentrations was observed. However, the pooled BPA concentration was systematically smaller when the studies fulfilled each of these quality items than when they did not.

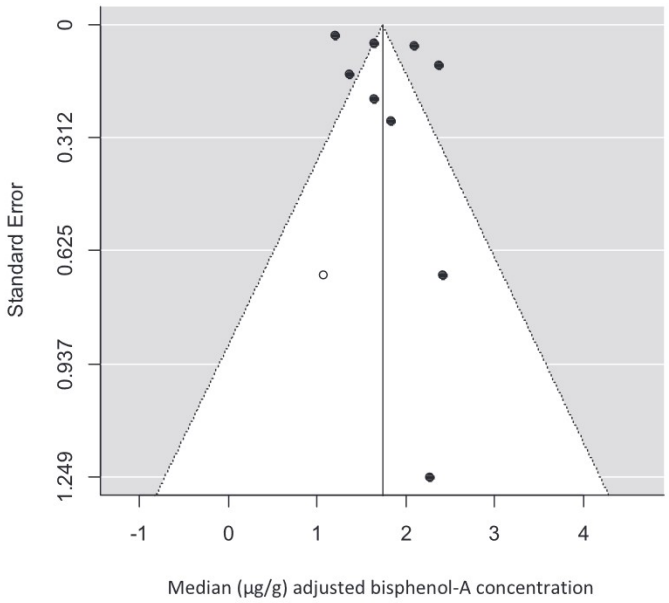

Fig. 5. Funnel plot of the median adjusted bisphenol-A (BPA) concentrations adjusted by creatinine. Black circles represent the original median adjusted BPA concentrations, whereas the white circle represents one BPA estimate imputed with the trim-and-fill method.

Several continuous moderators were also analyzed by means of meta-regression models (Table 3). The only moderator that exhibited a statistically significant relationship with median BPA concentrations was the sample size ($p = 0.015$), accounting for 41% of the variance. In particular, a negative relationship was found such that the larger the sample size, the lower the estimated BPA concentration.

3.4.2. Adjusted urinary BPA concentrations

The influence of several categorical moderators on the urinary median BPA concentrations extracted from 8 studies adjusted by creatinine (μg/g) was also analyzed. Three studies reported adjusted BPA concentrations in samples separately by sex. Although women exhibited higher median BPA concentrations than men ($BPA_+ = 1.71$ μg/g and 1.34 μg/g, respectively), the difference did not reach statistical significance ($p = 0.390$). A forest plot of the median creatinine-adjusted BPA concentrations by sex is presented in Fig. 7. As shown in Table 1, none of the categorical moderators reached a statistically significant association with median BPA concentrations. It is worth noting, however, that the pooled BPA concentration from European countries ($BPA_+ = 2.41$ μg/g) was slightly higher than those from Asian ($BPA_+ = 1.88$ μg/g) and North American populations ($BPA_+ = 1.63$ μg/g).

None of the items of the NOS reached statistical significance (Table 2). Finally, the results of the meta-regressions performed on several continuous moderators (Table 3) did not show any statistically significant association for any of the moderators studied with regards to median adjusted BPA concentrations.

4. Discussion

4.1. BPA exposure assessment

This is the first systematic review and meta-analysis to analyze BPA concentrations in different population-based studies and to evaluate potential differences by sex, geographic area, and analytical methodology. BPA was detected in more than 90% of the recruited samples (only one study had a lower detection percentage of 78%), which suggests widespread BPA exposure in the general population, consistent with previous studies in North America, Asia, and Europe (Kim et al., 2011; Lehmler et al., 2018; Salamanca-Fernández et al., 2020). The findings in this study are based on 28,353 adult subjects from three continents. The pooled unadjusted urinary BPA concentration was $BPA_+ = 1.91$ μg/l; the urinary creatinine-adjusted BPA concentration was 1.76 μg/g, and the pooled BPA concentration in serum samples was 1.75 μg/l. The biological matrix may have a substantial influence on the exposure assessment; however, in this meta-analysis, BPA concentrations were similar in urine and blood/serum, as well as in unadjusted or creatinine-adjusted measures. A review of the literature regarding the biomonitoring of BPA levels in adult populations from different countries and biological matrices (urine, blood, human tissues, and other fluid) found generalized BPA exposure, with the highest urinary BPA concentrations among the Korean population (mean 9.5 μg/l) and the highest blood/serum concentrations among Japanese women (mean 2.5 μg/l). Most of the studies included were not population-based and comprised only a small number of subjects (Vandenberg et al., 2010).

Although BPA threshold levels that define a potential health risk have not been defined universally, human biomonitoring-derived cut-offs of BPA or biomonitoring equivalents (BE) in urine have been suggested as convenient reference values for humans in order to contextualize the exposure level of different populations. Of note, the resulting urinary BPA concentrations in our meta-analysis were far below the reference HBM-I value of 200 μg/l (0.2 mg/l) for adults derived by the Human Biomonitoring Commission of the German Environmental Agency (HBM Commission) (Apel et al., 2017; German Human Biomonitoring Commission, 2020) and it is also much lower than the guidance value of 2000 μg/l (Aylward et al., 2013). HBM-I values define

Table 1
Results of the weighted ANOVAs of the categorical moderators on urinary BPA concentrations.

Moderator	N	k	BPA_+ (95% CI)	ANOVA results
Median unadjusted urinary BPA concentration (μg/l)				
Detection techniques:				$F_{2,8} = 0.32, p = 0.737$
GC–MS	246	1	2.99 (0, 6.48)	$R^2 = 0$
HPLC-MS	13,106	8	1.87 (1.07, 2.67)	$Q_E(8) = 1112.96, p < 0.0001$
Other	1937	2	2.20 (0.54, 3.85)	
Gender:				$F_{1,8} = 0.15, p = 0.709$
Women	6284	5	1.65 (0.40, 2.90)	$R^2 = 0$
Men	4973	5	1.92 (0.46, 3.37)	$Q_E(8) = 1407.73, p < 0.0001$
Continent:				$F_{2,9} = 1.89, p = 0.206$
Asia	9715	6	1.66 (0.85, 2.47)	$R^2 = 0.19$
Europe	787	2	2.99 (1.60, 4.38)	$Q_E(9) = 1094.09, p < 0.0001$
North America	8251	4	1.72 (0.79, 2.65)	
Country:				$F_{7,3} = 3.18, p = 0.185$
Belgium	67	1	2.35 (0.12, 4.57)	$R^2 = 0.65$
Canada	3465	1	1.25 (0, 3.05)	$Q_E(3) = 126.79, p < 0.0001$
China	6849	2	0.81 (0, 2.05)	
Israel	246	1	2.99 (0, 7.10)	
Italy	720	1	3.50 (1.72, 5.28)	
Korea	1870	1	2.07 (0.32, 3.82)	
Lebanon	501	1	3.08 (1.13, 5.02)	
USA	4786	3	1.87 (0.85, 2.89)	
Median creatinine-adjusted urinary BPA concentration (μg/g)				
Detection techniques:				$F_{2,5} = 0.73, p = 0.528$
GC–MS	246	1	2.26 (0, 5.35)	$R^2 = 0$
HPLC-MS	5535	5	1.72 (1.27, 2.18)	$Q_E(5) = 146.30, p < 0.0001$
Other	1937	2	2.15 (1.30, 3.01)	
Gender:				$F_{1,4} = 0.93, p = 0.390$
Women	3855	3	1.71 (0.23, 3.18)	$R^2 = 0$
Men	3279	3	1.34 (0.58, 2.09)	$Q_E(4) = 182.29, p < 0.0001$
Continent:				$F_{2,6} = 0.73, p = 0.519$
Asia	2866	4	1.88 (1.31, 2.46)	$R^2 = 0$
Europe	67	1	2.41 (0.61, 4.20)	$Q_E(6) = 146.95, p < 0.0001$
North America	8241	4	1.63 (1.16, 2.11)	
Country:				$F_{5,2} = 0.28, p = 0.891$
Belgium	67	1	2.41 (0, 6.29)	$R^2 = 0$
Canada	3456	1	1.36 (0, 3.92)	$Q_E(2) = 141.50, p < 0.0001$
Israel	246	1	2.26 (0, 8.20)	
Korea	1870	1	2.09 (0, 4.59)	
Lebanon	501	1	1.83 (0, 4.57)	
USA	4785	3	1.73 (0.28, 3.17)	

[a]In the analysis of the country, the Zhang et al.'s (2011) study was deleted because it included several countries.
[b]N = total sample size. k = number of studies. BPA_+ = average BPA concentration. 95% CI, 95% confidence interval for BPA_+. F = F statistic for testing the statistical significance of the moderator. R^2 = proportion of variance accounted for by the moderator. Q_E = Chi-square statistic for testing the model misspecification. GC–MS, Gas chromatography mass spectrometry. HPLC-MS, Liquid chromatography–mass spectrometry. BPA, Bisphenol-A.

the threshold below which the concentration of BPA would pose no risk for adverse health effects and, consequently, would not warrant preventive actions. It should be noted, however, that exposure guidance values published by environmental regulatory agencies are subject to revision as further scientific data on acceptable or tolerable concentrations of BPA in human accrues.

The vast majority of studies reported BPA measurements in urine, whereas studies measuring BPA in blood (serum) were more limited in general, particularly when considering studies on population-based samples. Biomonitoring studies measuring BPA provide the best exposure assessment possible by integrating different routes of exposure in the population. It is important to remark that studies that have measured BPA in urine have mainly used spot urine samples rather than 24-h urine samples or multiple spot measurements (only one study among those included in this meta-analysis collected 24-h urine samples). BPA is a non-persistent compound that is rapidly removed from the body; thus, exposure distributions from spot urine samples are generally shifted to the left with respect to average distributions based on 24-h urine samples and tend to underestimate the BPA concentration (Aylward et al., 2017). In addition, spot sample measurements are subject to greater intra- and inter-individual variability than those from 24-h samples. However, BPA exposure seems to occur on a daily basis and the studies included in this meta-analysis were of relatively large sample size; therefore, any potential underestimation bias derived from the use of spot urine samples would be of minor importance.

Large I^2 indices were found in the three meta-analyses (over 90%), indicating a high relative heterogeneity of the median BPA concentrations across studies. However, it is important to note that the I^2 index can offer a distorted picture of the true heterogeneity when the studies have large samples sizes, as it was the case. In particular, I^2 will be very large although true heterogeneity across studies is not large (Borenstein et al., 2017; Coory, 2010; IntHout et al., 2016). In place of I^2, the between-studies standard deviation and the 95% PI are more informative and clinically relevant methods to assess the amount of heterogeneity, as they are in the same metric than the effect estimates (Borenstein, 2019; Higgins et al., 2020; Stijnen et al., 2021). For unadjusted urinary BPA concentrations (μg/l), the between-studies standard deviation was 0.898 and the 95% PI enables us to predict that the expected range of BPA concentrations if a new study was accomplished should be between 0 and 3.97. Taking into account the urinary BPA thresholds of 200 and 2000 μg/l proposed by the German HBM Commission and Aylward et al., respectively, as concentrations potentially harmful to human health, the results of our meta-analysis reveal a range of BPA exposure in general human population clearly under these thresholds, even in the presence of heterogeneity across studies. Further, if we compare the upper limits of the 95% CIs reported in the forest plot (Fig. 2) for

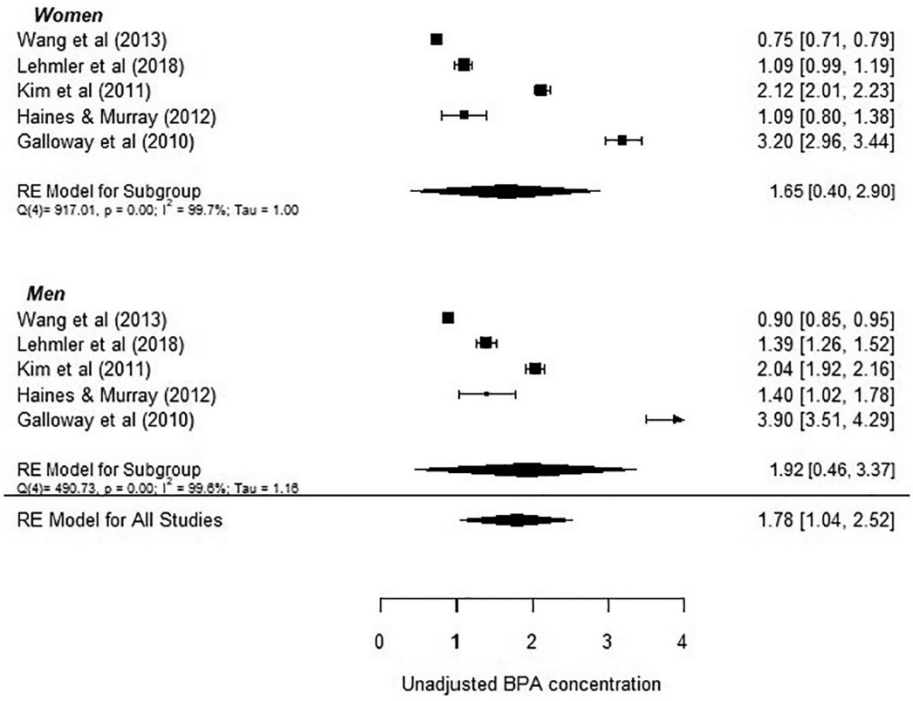

Fig. 6. Forest plot of the 5 studies that reported separate median unadjusted urinary BPA concentrations (μg/l) for women and men (adults only). Black squares represent median BPA concentrations extracted from each study, whereas lines represent the 95% confidence limits around them. Black diamonds represent the average of the median BPA concentrations. Tau = between-studies standard deviation (τ). RE model = random-effects model. Data in brackets are the lower and upper 95% confidence limits for the median BPA concentration and for their averages.

each median BPA concentration across studies, all of them are clearly under these thresholds (range: 0.84 and 5.27). Regarding urinary BPA concentrations adjusted by creatinine (μg/g), the between-studies standard deviation was 0.397, such that the 95% PI enables us to predict that the expected range of BPA concentrations in a new study should vary between 0.79 and 2.73. In addition, the upper confidence limits of each median BPA concentration reported in the forest plot (Fig. 3) ranged between 1.26 and 4.71. And regarding human serum BPA

Table 2
Results of the weighted ANOVAs of the Newcastle-Ottawa Scale items on urinary BPA concentrations.

Moderator	N	k	BPA_+ (95% CI)	ANOVA results
Median unadjusted urinary BPA concentration (μg/l)				
Sample represent.:				$F_{1,10} = 0.01, p = 0.922$
Yes	18,191	9	1.89 (1.20, 2.59)	$R^2 = 0$
No	562	3	1.96 (0.57, 3.36)	$Q_E(10) = 1909.67, p < 0.0001$
Sample size:				$F_{1,10} = 1.79, p = 0.211$
Yes	15,601	7	1.64 (0.91, 2.36)	$R^2 = 0.06$
No	3152	5	2.35 (1.41, 3.28)	$Q_E(10) = 713.67, p < 0.0001$
Non-respondents:				$F_{1,10} = 0.80, p = 0.391$
Yes	17,690	8	1.76 (1.05, 2.46)	$R^2 = 0$
No	1063	4	2.29 (1.16, 3.42)	$Q_E(10) = 1875.51, p < 0.0001$
Statistical test:				$F_{1,10} = 0.20, p = 0.663$
Yes	18,686	11	1.87 (1.23, 2.51)	$R^2 = 0$
No	67	1	2.35 (0.09, 4.60)	$Q_E(10) = 1907.73, p < 0.0001$
Median creatinine-adjusted urinary BPA concentration (μg/g)				
Sample represent.:				$F_{1,7} = 0.10, p = 0.761$
Yes	10,612	6	1.74 (1.35, 2.13)	$R^2 = 0$
No	562	3	1.87 (1.02, 2.70)	$Q_E(7) = 276.19, p < 0.0001$
Sample size:				$F_{1,7} = 0.97, p = 0.356$
Yes	8742	5	1.66 (1.26, 2.07)	$R^2 = 0$
No	2432	4	1.96 (1.37, 2.55)	$Q_E(7) = 149.50, p < 0.0001$
Non-respondents:				$F_{1,7} = 0.14, p = 0.719$
Yes	10,111	5	1.73 (1.31, 2.15)	$R^2 = 0$
No	1063	4	1.85 (1.19, 2.51)	$Q_E(7) = 274.58, p < 0.0001$
Statistical test:				$F_{1,7} = 0.80, p = 0.399$
Yes	11,107	8	1.73 (1.39, 2.08)	$R^2 = 0$
No	67	1	2.41 (0.67, 4.14)	$Q_E(7) = 275.78, p < 0.0001$

[a]N = total sample size. k = number of studies. BPA_+ = average BPA concentration. 95% CI, 95% confidence interval for BPA_+. F = F statistic for testing the statistical significance of the moderator. R^2 = proportion of variance accounted for by the moderator. Q_E = Chi-square statistic for testing the model misspecification. BPA, Bisphenol-A.

Table 3
Results of the meta-regressions applied of continuous moderators on urinary BPA concentrations.

Moderator	k	b_j	F	p	Q_E	p	R^2
Median unadjusted urinary BPA concentration (μg/l)							
Publication year	12	−0.024	0.04	0.845	1898.08	< 0.0001	0
Mean age	10	−0.013	0.1	0.763	831.41	< 0.0001	0
% of women	9	−0.081	2.97	0.129	1034.65	< 0.0001	0.18
Sample size	12	−0.0005	8.65	0.015	455.69	< 0.0001	0.41
NOS score	12	−0.188	0.83	0.385	1017.41	< 0.0001	0
Median creatinine-adjusted urinary BPA concentration (μg/g)							
Publication year	9	−0.071	2.02	0.198	63.67	< 0.0001	0.15
Mean age	7	−0.022	0.48	0.52	74.99	< 0.0001	0
% of women	6	−0.004	0.02	0.898	127.88	< 0.0001	0
Sample size	9	−0.0002	1.17	0.315	265.22	< 0.0001	0
NOS score	9	−0.092	0.58	0.469	191.62	< 0.0001	0

[a]k = number of studies. b_j = regression coefficient. F = F statistic to test the statistical significance of the moderator. Q_E = Chi-square statistic for testing the model misspecification. R^2 = proportion of variance accounted for by the moderator. p = probability level. NOS score = total score obtained in the Newcastle-Ottawa Scale to assess the study quality. BPA, Bisphenol-A.

concentrations (μg/l), the between-studies standard deviation was 1.776, and the 95% PI gave lower and upper limits of 0 and 10.58. In all cases, even in presence of heterogeneity, BPA concentrations found in the studies and in our meta-analyses seem to be clearly under thresholds for potential health risk.

4.2. Publications bias

A large heterogeneity was found in median BPA concentrations for all the meta-analyses performed (blood/serum, unadjusted urine, and creatinine-adjusted urine). Regarding the studies that measured BPA in urine samples, none reported a discrepancy greater than 10%; however, the Olsen study using blood samples showed a large discrepancy (57%). This later study reported the highest BPA concentration and mean age, as well as the highest standard error (SE), compared with all other studies, which could contribute particularly to the observed heterogeneity. In addition, it should also be noted that the study by Aekplakorn et al., (2015) reported the geometric mean of serum BPA instead of the median, which could also introduce some variation. Median unadjusted urinary BPA concentrations varied between 0.81 μg/l and 3.50 μg/l, whereas creatinine-adjusted values ranged between 1.20μg/g and 2.41 μg/g. BPA concentration in serum samples varied between 0.34 μg/l (Aekplakorn et al., 2015) and 3.76 μg/l (Olsén et al., 2012). The observed heterogeneity was not attributable to differences in study design, year of publication, sex, country, or biological matrix, since our results showed no differences for any of these potential moderators. Thus, other factors need to be invoked to account for the heterogeneity found, including individual characteristics (*e.g.*, age, education, social class, ethnic group, dietary and lifestyle habits) and environmental factors (*e.g.*, environmental and occupational exposure to BPA). Egger's test indicated publication bias for unadjusted urinary BPA concentrations only. The trim-and-fill method imputed three additional BPA concentrations to symmetrize the funnel plot, and the overall BPA concentration adjusted by publication bias decreased by 18.8%. No indication of publication bias was found for results based on blood or creatinine-adjusted urine levels.

4.3. Influence of potential moderators

Our results did not exhibit statistical significance in BPA concentrations by sex. This finding is in line with current literature that has evidenced the lack of significant differences in BPA concentration between men and women (Aekplakorn et al., 2015; Olsén et al., 2012; Zhang et al., 2011).

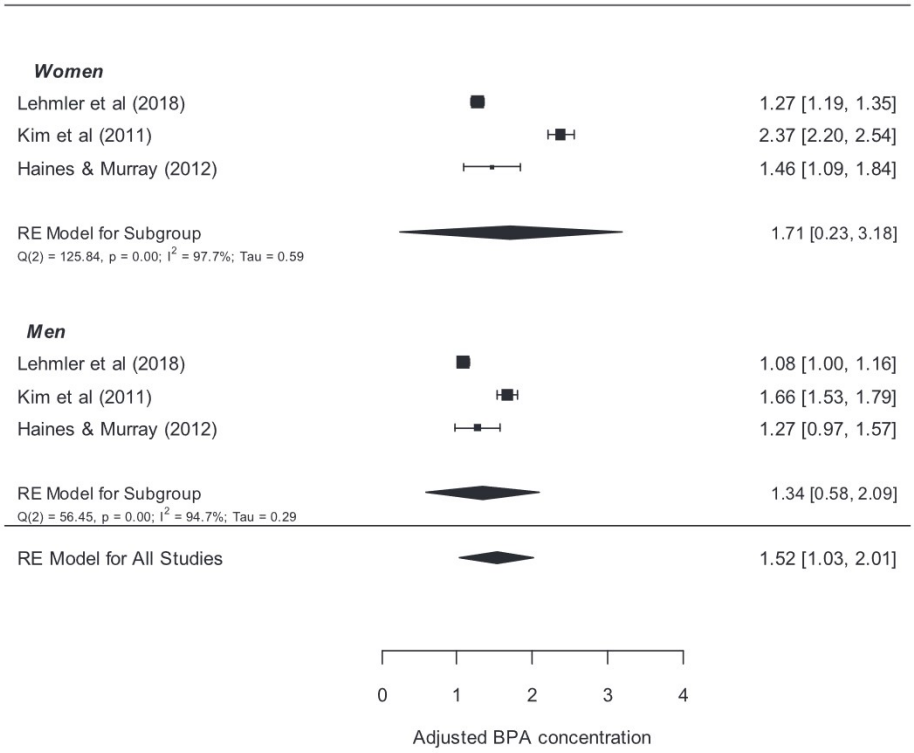

Fig. 7. Forest plot of the 3 studies that reported separate median adjusted BPA concentrations (μg/g creatinine) for women and men from adult samples. Black squares represent median BPA concentrations extracted from each study, whereas lines represent the 95% confidence limits around them. Black diamonds represent the average of the median BPA concentrations. Tau = between-studies standard deviation (τ). RE model = random-effects model. Data in brackets are the lower and upper 95% confidence limits for the median BPA concentration and for their averages.

According to data from the studies included, no differences in BPA concentrations were found by geographical area (continent). It is worth noting that while our analysis included mainly Caucasian populations, a considerable number of Asian subjects were also included. However, no data on other ethnic groups, such as Hispanics or Blacks, were available. Further studies including other population settings and ethnicities would be required to provide data that would help to elucidate whether variables such as country or ethnic group would account for part of the variability in human BPA concentrations, as previously suggested (Berman et al., 2014).

Although different analytical detection techniques to measure BPA were used, the most frequent was HPLC-MS/MS (high-performance liquid chromatography with tandem mass spectrometry), which is considered the gold standard (Calafat et al., 2015). No differences in median urinary BPA concentrations were found according to the different analytical techniques used, suggesting that the method used to measure BPA in the included studies did not affect their results.

The only moderator that exhibited a statistically significant relationship with the median BPA concentrations was the sample size of the study, showing an inverse association such that the larger the sample size, the lower the BPA concentration estimate. Although BPA concentrations were not influenced by any of the NOS items, it is worth noting that systematically, the average BPA concentration was smaller when the studies fulfilled each of these quality items than when they did not fulfill them.

4.4. Limitations and strengths of the study

Some limitations are worth considering. First, the number of studies included was low, which may affect the generalizability of the results found and the analysis of moderator variables. In particular, the limited number of studies that reported BPA concentrations adjusted by creatinine (eight studies only) impairs the generalizability of our findings. Second, another limitation refers to missing data regarding relevant moderator variables, such as sex, ethnicity, rural or urban setting, or age groups. For this reason, it was not possible to analyze differences in the BPA concentrations according to these variables. Another limitation was that most studies included had only one single BPA measurement obtained from spot urine samples. Only the study by Galloway et al. collected 24-h urine samples (Galloway et al., 2010). Given the short half-life of BPA in the body (less than 6 h) (Volkel et al., 2002), the use of spot samples may not fully capture the intraday variability in BPA concentrations within individuals and might not reflect the actual short-term exposure. Furthermore, the lack of repeated measurements did not allow us to evaluate exposures in the longer term by accounting for day-to-day variability in sources of BPA such as diet. It could be argued that this limitation would be less important for studies with larger sample sizes, where the intra-individual variability would have a lower impact on the pooled estimates (Ye et al., 2011). Finally, as in any meta-analysis, the validity of these results greatly depends on the quality of the original studies included. Of note, in our assessment of study quality using the Newcastle-Ottawa Scale, most of them received a high score. Furthermore, our study evaluated the role of heterogeneity in median BPA concentrations and the potential publication bias to adjust the overall BPA concentration estimates, approaches that are not routinely assessed in most meta-analyses, despite being strongly recommended (Moher et al., 2009).

The major strength of this study is that it represents the first systematic review and meta-analysis of BPA concentrations in population-based adult human samples. Thus, it provides the most accurate summary estimates of BPA exposure in general adult human populations available so far. Furthermore, two researchers independently performed the systematic review of articles, data extraction, and quality assessment. The interrater agreement between researchers was high, reducing potential biases. In addition, a comprehensive assessment of heterogeneity, study quality and publication bias was carried out. Of note, although the number of studies that fulfilled the inclusion criteria was not high, the final results are based on a large number of participants, including both men and women from different geographic areas, and age groups.

4.5. Future research and implications for practice

The potential health risks associated with daily human BPA exposure represent an important challenge for the scientific community. The first step in the assessment of potential health hazards associated with BPA is the evaluation of the level of exposure of human populations to this endocrine-disrupting chemical compound. Remarkably, none of the studies included in this meta-analysis presented BPA concentrations above, or even close, to the reference HBM-I value of 200 μg/l defined by German Human Biomonitoring Commission, or greater than the biomonitoring equivalent (BE) value of 2000 μg/l urine defined by the US EPA, corresponding to the intake of a tolerable reference dose (RfD) of 50 μg/kg·d (Aylward et al., 2013; Kannan et al., 2010). Of note, the German Human Biomonitoring Commission defined reference values based on a TDI of 50 μg/kg·d, before the 2015 BPA safety re-assessment, which led the EFSA to temporarily reduce the tolerable threshold (t-TDI) to 4 μg/kg·d. Thus, HBM reference values might be revised in the future to reflect such stricter criteria.

Although there are many toxicological (Prins et al., 2019) and biomonitoring studies on BPA exposure in different populations (Covaci et al., 2015; Dunder et al., 2019; Vandenberg et al., 2010), epidemiological studies assessing BPA concentrations in large, representative population samples are still insufficient, and publication bias is a concern. Further studies are needed to update the BPA safety reference values to clarify uncertainties about continued exposure to BPA and adverse health effects at low doses.

In addition, it is of major importance to widen our knowledge about BPA exposure in representative population-based samples in diverse study settings (different countries from different continents) to identify highly exposed groups. A good approach is that of the NHANES study, which measured urinary BPA in several survey cycles throughout two decades in the general US population, but there is a lack of similar data from other countries. Additionally, separate data for population subgroups defined by sex or ethnicity are either sparse or non-existent in many regions. Future studies should also consider standardizing the analytical procedures and the reporting of BPA results, including standardized urine concentration adjustment methods when using spot urine samples (Barr et al., 2005). Since BPA concentrations are largely influenced by differences in food consumption patterns, as diet is the main source of BPA exposure, future studies should consider including a short-term evaluation of diet to account for geographical and cultural differences in BPA concentrations. It would be interesting to design longitudinal studies with repeated BPA measurements at different time points to assess changes in exposure over time. This type of study design has been used in a few studies from the US and Canada, which could be an inspiration for future research initiatives (Bushnik et al., 2010; Dunder et al., 2019; van Woerden et al., 2019). Of note, these studies suggested that BPA concentrations are decreasing over time in some population groups (van Woerden et al., 2019), probably due to an adaptive response of the chemical industry to increased population concerns about potential health risks of BPA, which has fostered the production of "BPA-free" materials. However, BPA is frequently being replaced by structurally similar chemicals, such as bisphenol-S and bisphenol-F, which also exert endocrine-disrupting effects (Rochester and Bolden, 2015; Warner and Flaws, 2018). The lack of strong scientific evidence on the safety of BPA and its substitutes for human health supports the continued use of the precautionary principle as a justified measure.

5. Conclusions

In conclusion, this first systematic review and meta-analysis of human BPA concentrations supports the widespread exposure of general

population of different origins to this endocrine-disrupting chemical. This study provides summary measures of human BPA concentrations, but does not deal with potential health risks associated to BPA exposure.

Although our study had sufficient power to assess the potential differences between BPA concentration and sex, geographic area, or analytical technique, no statistically significant differences were found. We found an inverse association between study size and BPA concentrations. Further studies with repeated measurements on large representative population samples are warranted to address the information gaps in the literature, and particularly to evaluate the relationship between environmental low-dose BPA exposure and health. Furthermore, such data should provide reference values of BPA exposure for populations of different geographic and ethnic origins to inform regulatory agencies and stakeholders. Whether such levels of environmental BPA exposure pose a risk for the health of human populations still warrants investigation.

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CRediT authorship contribution statement

Sandra Colorado-Yohar: Conceptualization; Methodology; Validation; Formal analysis; Investigation; Data Curation; Writing - Original Draft; Writing - Review & Editing; Visualization.

Ana C Castillo-González: Conceptualization; Investigation; Data Curation; Writing - Review & Editing.

Julio Sánchez-Meca: Methodology; Software; Validation; Formal analysis; Investigation; Data Curation; Writing - Original Draft; Writing - Review & Editing; Visualization.

María Rubio-Aparicio: Methodology; Software; Validation; Formal analysis; Investigation; Data Curation; Writing - Original Draft; Writing - Review & Editing; Visualization.

Diego Sánchez-Rodríguez: Data Curation; Writing - Review & Editing.

Elena Salamanca-Fernández: Writing - Review & Editing.

Eva Ardanaz: Writing - Review & Editing.

Pilar Amiano: Writing - Review & Editing.

Mariana F. Fernández: Writing - Review & Editing.

Jaime Mendiola: Writing - Review & Editing.

Fernando Navarro-Mateu: Conceptualization; Methodology; Validation; Formal analysis; Investigation; Data Curation; Writing - Original Draft; Writing - Review & Editing; Visualization; Supervision; Project administration.

María Dolores Chirlaque López: Conceptualization; Methodology; Validation; Formal analysis; Investigation Data Curation; Writing - Original Draft; Writing - Review & Editing; Visualization; Supervision; Project administration.

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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