Received: 20 January 2023 | Revised: 21 January 2024 | Accepted: 13 February 2024

DOI: 10.1111/obr.13738

REVIEW

OBESITY Reviews WILEY

Associations of bisphenol A exposure with metabolic syndrome and its components: A systematic review and meta-analysis

Tianli Xiao[1,2] | Zehua Huang[1,2] | Chanjuan Zheng[1,2] | Binh Quach[3] | Yulian Zhu[4] | Feifei Li[3,5] | Wei Liang[6] | Julien Baker[3,5] | Christoph Reichetzeder[7,8] | Berthold Hocher[9,10,11] | Yide Yang[1,2]

[1]Key Laboratory of Molecular Epidemiology of Hunan Province, School of Medicine, Hunan Normal University, Changsha, China

[2]The Institute of Interdisciplinary Studies, Hunan Normal University, Changsha, China

[3]Centre for Health and Exercise Science Research, Hong Kong Baptist University, Hong Kong, China

[4]Hunan Prevention and Treatment Institute for Occupational Diseases, Changsha, China

[5]Department of Sport, Physical Education and Health, Hong Kong Baptist University, Hong Kong, China

[6]School of Physical Education, Shenzhen University, Shenzhen, China

[7]Institute of Nutritional Science, University of Potsdam, Potsdam, Germany

[8]HMU – Health and Medical University, Potsdam, Germany

[9]Fifth Department of Medicine (Nephrology/Endocrinology/Rheumatology), University Medical Centre Mannheim, University of Heidelberg, Mannheim, Germany

[10]Institute of Medical Diagnostics, IMD, Berlin, Germany

[11]Clinical Research Center for Reproduction and Genetics in Hunan Province, Reproductive and Genetic Hospital of CITIC-XIANGYA, Changsha, China

Correspondence
Yide Yang, School of Medicine, Hunan Normal University, Changsha, 410081, China.
Email: yangyide2007@126.com

Berthold Hocher, Fifth Department of Medicine (Nephrology/Endocrinology/Rheumatology), University Medical Centre Mannheim, University of Heidelberg, Theodor-Kutzer-Ufer 1–3, 68167 Mannheim, Germany.
Email: berthold.hocher@medma.uni-heidelberg.de

Funding information
Health Research Project of Hunan Provincial Health Commission, Grant/Award Number: 202112031516; National Natural Science Foundation of China, Grant/Award Number: 81903336; Hunan Provincial Natural Science Foundation of China, Grant/Award Number: 2019JJ50376; Scientific Research Fund of Hunan Provincial Education Department, Grant/Award Number: 22B0038; Open Project for Postgraduates of Hunan Normal University, Grant/Award Number: KF2022019; The

Summary

Mounting evidence shows that bisphenol A (BPA) is associated with metabolic risk factors. The aim of this study was to review related epidemiologic studies and conduct a meta-analysis to quantitatively estimate the association between BPA and metabolic syndrome. Four electronic databases were systematically searched to identify suitable articles. A total of 47 published studies were finally included. Two studies involved metabolic syndrome. Of the 17, 17, 14, and 13 studies on the relationship between BPA with abdominal obesity, blood pressure, fasting plasma glucose, and dyslipidemia, 10, 6, 3, and 4 studies were included in the meta-analysis, respectively. The results showed that the risk of abdominal obesity increased with the increase of BPA exposure, especially in the group with higher BPA exposure levels (Quartile 2 vs. Quartile 1, pooled $OR = 1.16$, *95%CI*: 1.01, 1.33; Q_3 vs. Q_1, pooled $OR = 1.31$, *95%CI*: 1.13, 1.51; Q_4 vs. Q_1, pooled $OR = 1.40$, *95%CI*: 1.21, 1.61). However, there was no significant correlation between BPA exposure and metabolic syndrome components including hypertension, abnormal fasting plasma glucose, and dyslipidemia. The present study found

Abbreviations: BPA, bisphenol A; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MetS, metabolic syndrome; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; WC, waist circumference.

Research Team for Reproduction Health and Translational Medicine of Hunan Normal University, Grant/Award Number: 2023JC101

that BPA exposure is significantly associated with a higher risk of abdominal obesity. However, the relationship between BPA with metabolic syndrome and its other components needs further longitudinal studies to verify.

KEYWORDS
abdominal obesity, bisphenol A, meta-analysis, metabolic syndrome, review

1 | INTRODUCTION

Metabolic syndrome (MetS) is a clinical syndrome composed of a cluster of metabolic disorders, including insulin resistance, obesity, atherosclerotic dyslipidemia, and high blood pressure and is a strong predictor for cardiovascular diseases and type 2 diabetes.[1] Actually, the incidence of MetS parallels that of obesity and type 2 diabetes (one of the MetS's consequences), and it is estimated that over a billion people worldwide have MetS.[2] A recent study has shown that the average prevalence of MetS is 31.0% worldwide.[3] According to the National Health and Nutrition Examination Survey (NHANES) in the United States from 2011 to 2016 with 17048 participants, the weighted prevalence of MetS was 34.7% (*95%CI*: 33.1%, 36.3%).[4] In China, a meta-analysis from 2016 has shown that the pooled prevalence of MetS was 24.5% (*95%CI*: 22.0%, 26.9%) among the investigated subjects (≥15 years).[5]

Mounting evidence implies that environmental chemicals, especially endocrine-disrupting chemicals, might play an important role in the increase of metabolic-related problems, such as obesity and type 2 diabetes.[6,7] Bisphenol A (BPA) is a chemical substance extensively used as a monomer in polycarbonate synthesis, plasticizer in the production of epoxy resins and other applications.[8–10] BPA has been shown to play a role in the pathogenesis of several endocrine disorders including female and male infertility, precocious puberty, hormone-dependent tumors such as breast and prostate cancers, and several metabolic disorders including polycystic ovary syndrome (PCOS).[8] Furthermore, various studies have shown associations between BPA exposure and MetS. Teppala et al demonstrated that urinary BPA levels are positively related to the risk of MetS in US adults.[11] Another cross-sectional study has discovered that plasma BPA levels were significantly associated with waist circumference (WC), triglycerides (TG), and markers of glucose homeostasis.[12] However, a Czech study could not find a significant association between BPA levels and main MetS components (diabetes, hypertension, and dyslipidemia).[13] More comprehensive systematic reviews and meta-analyses are needed to reconcile these inconsistent results. Therefore, we conducted a systematic review and meta-analysis to provide more reliable data regarding the associations between BPA and the risk of MetS or its components. Moreover, we tried to obtain more precise estimates such as odds ratio (*OR*) that describe this relationship quantitatively.

2 | METHODS

2.1 | Search strategy

A systematic online search on PubMed, Web of Science, Embase, and Medline databases was conducted to identify studies that were published until April 2021. The keywords metabolic syndrome, MetS, central obesity, central obese, abdominal obesity, abdominal obese, blood pressure, systolic blood pressure (SBP), diastolic blood pressure (DBP), hypertension, fasting plasma glucose (FPG), glucose, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride (TG), and total cholesterol (TC) were combined with the Boolean operators "OR". The key terms bisphenol A or BPA were inputted and combined with the former using the Boolean operator "AND". The complete electronic search strategy for the four English databases is reported in the supplementary files. References from acquired studies were manually searched to ensure that no relevant studies were missed.

2.2 | Inclusion and exclusion criteria

The inclusion criteria of studies on the associations of BPA exposure with MetS and its components[14,15] were defined as follows: (1) all study types except meta-analyses and systematic reviews; (2) human studies including both children and adults; (3) the exposure level of BPA was measured; (4) no restriction regarding the source of the sample, including urine, serum, or plasma; (5) outcome indices providing *OR* or relative ratio (*RR*) value and *95%* confidence interval (*CI*); (6) no restriction on sample size; and (7) studies published in English.

The inclusion criteria of studies regarding specific indicators of the associations between BPA exposure with MetS and its components were defined as follows: (1) BPA exposure levels given as a continuous variable or dividing the BPA exposure concentration into groups, and providing the number of subjects in each group; (2) outcome measures associated with MetS (i.e., abdominal obesity, hypertension, and dyslipidemia); and (3) at least one specific outcome variable, such as WC, SBP, DBP, TC, HDL, and LDL.

Exclusion criteria of studies on the associations of BPA exposure with MetS and its components[14,15] were defined as follows: (1) review, meta-analysis, animal and cell experimental studies, editorials, letters, comments, and conference papers; (2) studies without data or results unable to be extracted; (3) repeated publications; (4) full text unavailable; (5) articles published after April 2021; (6) studies published in

other languages than English; and (7) studies with a score lower than 7 after quality evaluation. All studies that met any of these exclusion criteria were excluded.

Exclusion criteria of studies regarding specific indicators of the associations between BPA exposure with MetS and its components were defined as follows: (1) no given BPA exposure concentrations; (2) no indication of the number of participants in each group; (3) studies without extractable indices such as sex, age, TC, WC, HDL, and LDL; and (4) no sample size, mean, and standard deviation of indices provided in the results.

2.3 | Quality assessment/risk of bias

The Newcastle–Ottawa scale (NOS) was used to evaluate the quality of cohort and case–control studies and scores of "0–3," "4–6," and "7–9" were defined as low, medium, and high quality, respectively.[16,17] The quality of cross-sectional studies was evaluated by the U.S. Agency for Healthcare Research and Quality (ARHQ) and scores of "0–3," "4–7," and "8–12" were defined as low, moderate, high quality, respectively.[16,18] The risk of bias (RoB) tool was used to evaluate the quality of randomized controlled trials and randomized crossover trials.[19]

2.4 | Selection and data extraction

To preliminarily exclude disqualified studies, two researchers (T.X. and Z.H.) independently reviewed citation information including title and abstract according to the inclusion and exclusion criteria. The full text of the included studies was downloaded and carefully read to evaluate the quality. During this process, any problems or disagreements would be solved through discussion or the judgment of a third researcher (Y.Y.). Details of all studies were collected as follows: author, year of publication or survey, study location and population, study type, sample size and source, sex ratio, BPA concentration assessment method, covariates, parameter concentration value, variable classification, and outcome. The effect values (i.e., *OR* and *RR*) and their *95%CIs* were extracted for meta-analysis. TG, HDL, LDL, and other indicators were incorporated to obtain the effect of BPA exposure on MetS and its components.

2.5 | Data analysis

Extracted data of included studies was used to build a database. Review Manager 5.3 (Review Manager, Cochrane Informatics and Knowledge Management Department) and R 4.2.2 were employed for meta-analysis. Forest plots were performed to visually assess the individual study's *OR*s and overall *OR*s, with corresponding *95% CIs*. Heterogeneity between studies was assessed by the Cochrane *Q* statistic test and I^2 statistical analysis.[20] I^2 statistical indicators divide studies into three heterogeneity levels: low (25%), medium (26%–50%), and high (51%–75%).[21] $P < 0.05$ and $I^2 > 50\%$ indicated heterogeneity of included studies.[15] Random-effects models were used if the pooled study showed significant heterogeneity. Otherwise, fixed-effects models were used. *OR*, 95%*CI*, and correlation coefficient (*r*) were obtained from the involved studies for meta-analysis. Sensitivity analysis was performed to evaluate the stability and reliability of meta-analysis results. Only when the number of included studies was at least 5, publication bias was evaluated by the funnel plot and Egger test.[22] $P < 0.05$ was considered significant. A study protocol with accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines was registered on PROSPERO (https://www.crd.york.ac.uk/PROSPERO, CRD42021244658) on April 23, 2021.

3 | RESULTS

3.1 | Study selection

A total of 4197 published studies were initially screened from four electronic databases including PubMed using the English search conditions and search time period with the publication deadline of April 2021. Among them, 2435 duplicates were excluded manually or automatically; then, the remaining 1762 articles were preliminarily screened on the basis of their titles and abstracts, and 498 articles were deleted. After screening based on the inclusion and exclusion criteria, a total of 47 studies were finally included in the systematic review and meta-analysis. Two studies[23,24] investigating the association between BPA exposure and the risk of MetS were only used for the systematic review due to the lack of relevant data for further meta-analysis. Seventeen studies[12,25–40] explored the association between BPA and the risk of abdominal obesity, 10 of which[12,25–27,32–35,39,40] provided sufficient data to be included in the meta-analysis. Seventeen studies[12,23,28,29,33,41–52] explored the relationship between BPA and blood pressure, 6 of which[23,41–44,51] were included in the meta-analysis, whereas the remaining studies were solely included in the systematic review. Fourteen studies[12,29,33,39,53–62] exploring the relationship between BPA and blood glucose were included in the systematic review, of which three[12,33,53] were included in the meta-analysis. Thirteen studies[12,23,28,29,33,49,53,63–68] examining the association between BPA and dyslipidemia were included in the systematic review, of which four[12,33,53,63] were included in the meta-analysis. The screening flow chart is shown in Figure 1.

3.2 | Study characteristics

The overall characteristics of the included studies are shown in Table 1, with 47 related studies published between 2011 and 2021 and sample sizes ranging from 45 to 4320. The study populations included children and adults (ages from 2.5 to 79 years). Among the 47 relevant studies, 27 were cross-sectional studies, 16 were cohort

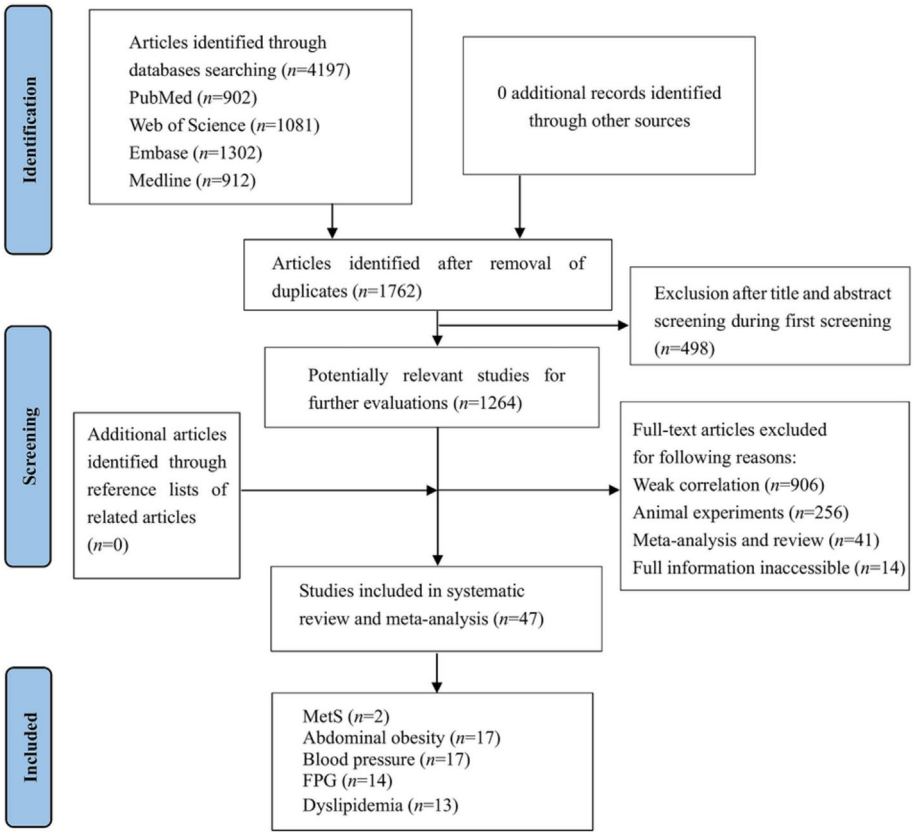

FIGURE 1 Flow diagram of the study selection process. FPG, fasting blood glucose, MetS, metabolic syndrome.

studies, 2 were randomized crossover trials, 1 was a repeated measures study, and 1 was a case–control study. These relevant studies were conducted in China (13), the United States (8), South Korea (7), Canada (3), Thailand (2), and a few other countries. Details of the country distribution are provided in Supplementary Table S1. Adjusted covariates included age, sex, ethnicity, education levels, family income, physical activity, smoking status, and alcohol consumption. Details of the covariates extracted from the included studies are provided in Supplementary Table S1. The results of the article quality assessment are shown in Supplementary Tables S2–S3. The results showed that the 47 articles included in the present study were of medium or high quality. The Agency for Healthcare Research and Quality (AHRQ) scale score (Supplementary Table S2) of the 27 cross-sectional studies ranged between 4 and 10. The 16 cohort studies and 1 case–control study had a score of 6–9 on the Newcastle-Ottawa Scale (NOS), and a repeated measures study was evaluated according to the NOS of the cohort study (Supplementary Table S3). The risk assessment results of the two randomized crossover trials are shown in Supplementary Figure S1. Publication bias (funnel plot) and sensitivity analysis of included studies are presented in Supplementary Table S4 and Figures S2, S3, and S4.

3.2.1 | MetS

Two studies investigating BPA and MetS were included in the systematic review.[23,24] Both studies were conducted in adults. A cross-sectional study[23] in urban Lebanese adults that examined the association between BPA and MetS by dividing BPA levels into tertiles did not find a statistically significant association between BPA and the risk of MetS. Another prospective cohort study in China,[24] which also classified BPA levels into low, middle, and high tertiles, showed no statistically significant association between BPA and MetS in all samples ($n = 1038$). However, among current smokers, it was found that compared with the low BPA level group, the middle BPA level group and the high BPA level group had a higher risk of MetS, with hazard ratios of 2.40 (*95%CI*: 1.13, 5.08) and 2.87 (*95%CI*: 1.38, 5.98), respectively, after adjusting for age, marital status, exercise, and drinking.

3.2.2 | Abdominal obesity

Seventeen studies[12,25–40] investigating the association between BPA and abdominal obesity were included in the systematic review. Of these studies, nine involved adults, and eight involved children.[26,28–31,33,38,40]

Three studies[29,37,38] categorized BPA into tertiles and considered tertile 1 as the reference category. The first study[29] ($n = 132$), a cross-sectional study of children in Iran, used WC as an outcome measure. This study showed that the mean WC increased significantly across the BPA tertiles (*P* for trend ≤0.001) in boys and girls.[29] The second study[37] ($n = 888$), a Chinese cohort study, defined central obesity based on WC (≥90 cm in men and ≥80 cm in women) and reported that compared to the lowest BPA tertile, tertiles 2 and 3 were

TABLE 1 The general characteristics of studies investigating the association between BPA with MetS and its components.

Characteristic	Number of studies	Percentages (%)
Total samples ($n = 47$)		
Location		
China	13	27.66
The United States	8	17.02
Korea	7	14.89
Canada	3	6.38
Thailand	2	4.26
Others	14	29.79
Study design		
Cross-sectional study	27	57.45
Cohort study	16	34.04
Randomized crossover trial	2	4.25
Repeated measures study	1	2.13
Case–control study	1	2.13
Age		
Children (<18 years)	33	70.21
Adults (≥18 years)	11	23.41
Children and adults	3	6.38
Sex		
All female	10	21.28
All male	3	6.38
Male and female	34	72.34
Classification of BPA		
Continuous	20	42.55
Two groups	2	4.26
Three groups	7	14.89
Four groups	12	25.53
Multiple groups	1	2.13
Continuous and categorical	5	10.64
Reference group		
Lowest BPA level	23	48.94
Others	24	51.06
Quality evaluation/risk of bias		
High quality	30	63.83
Moderate quality	17	36.17
Low quality	0	0.00

significantly associated with a higher risk of incident central obesity. The third study, another Chinese cohort study, did not find a significant association between BPA levels in early childhood and school-age children and the risk of central obesity in complete cases.[38]

Eight studies divided BPA levels into four groups, all using the first quartile as the reference group.[25–27,31,32,35,36,40] Two cross-sectional studies of children and adolescents in the United States did not find a significant association between BPA levels and the risk of abdominal obesity.[26,40] A cross-sectional study of Chinese adults ($n = 3390$) found that compared to the first BPA quartile group, the second, third, and fourth quartiles of BPA groups displayed a significantly higher risk of abdominal obesity, and the risk increased with increasing BPA quartiles.[35] A few studies found only one individual quartile group of BPA showing a significantly different risk of abdominal obesity compared with the reference group.[25,27,32] There were two studies[32,36] exploring the relationship between BPA and WC. A cross-sectional study of American adults ($n = 1521$) found a significant positive association between BPA concentration in the highest quartile and WC.[32] Another US cross-sectional study ($n = 2747$) showed a positive association between BPA levels and elevated WC in adults.[36] A cross-sectional study in American children, also categorizing BPA levels into quartiles, specifically suggested a positive association between BPA levels and the risk of abnormal waist circumference-to-height ratio.[31]

A total of 10 studies[12,25,28,30,33,34,37–40] used BPA level as a continuous variable to analyze the association between BPA and abdominal obesity. There were five studies involving adults and five studies involving children. Although no significant correlation was found in two Chinese studies[25,38] and one Greek study[28] ($n = 494$), a cross-sectional study of Italian adults[12] and another cross-sectional study involving Korean reproductive-aged women[39] showed a positive association between BPA levels and WC. In addition, four of the seven studies involving WC used correlation coefficients to explore the association between BPA levels and WC.[12,33,34,39] Although one case–control study among children in Saudi Arabia[33] ($n = 177$) and another cross-sectional study in Serbian women[34] ($n = 103$) did not show a significant association between BPA and WC, two cross-sectional studies among Italian adults ($n = 76$) and Korean reproductive-aged women ($n = 296$), respectively, demonstrated a significant association between BPA levels and WC.[12,39] Three studies[30,37,40] explored the relationship between BPA and abdominal obesity. Except for one cohort study in Chinese adults[37] ($n = 888$) demonstrating that increased BPA levels were significantly associated with increased risk of central obesity, neither a cohort study in Spanish boys[30] ($n = 298$) nor a cross-sectional study in American children[40] ($n = 1831$) found an association between BPA levels and abdominal obesity. A case–control study of children in Saudi Arabia[33] ($n = 177$) investigated the association of BPA with hip circumference and waist-to-hip ratio and found a positive association between BPA levels and waist-to-hip ratio only in children with obesity.

A total of 10 studies[12,25–27,32–35,39,40] were included in the meta-analysis. Six of them[25–27,32,35,40] divided BPA levels into quartiles with the first quartile (Q_1) being used as the control group. When the effect values of the second, third, and fourth quartiles (Q_2, Q_3, and Q_4) were combined respectively, it was found that individuals with higher BPA levels had a greater risk of abdominal obesity than those in Q_1 (Q_2: *OR* = 1.16, *95%CI*: 1.01, 1.33; Q_3: *OR* = 1.31, *95%CI*: 1.13, 1.51, and Q_4: *OR* = 1.40, *95%CI*: 1.21, 1.61, respectively; Figure 2). As observed in Supplementary Table S4 and Figure S2, the funnel plot did not exhibit an obvious risk of publication bias (Egger's test: Q_2, $P = 0.176$;

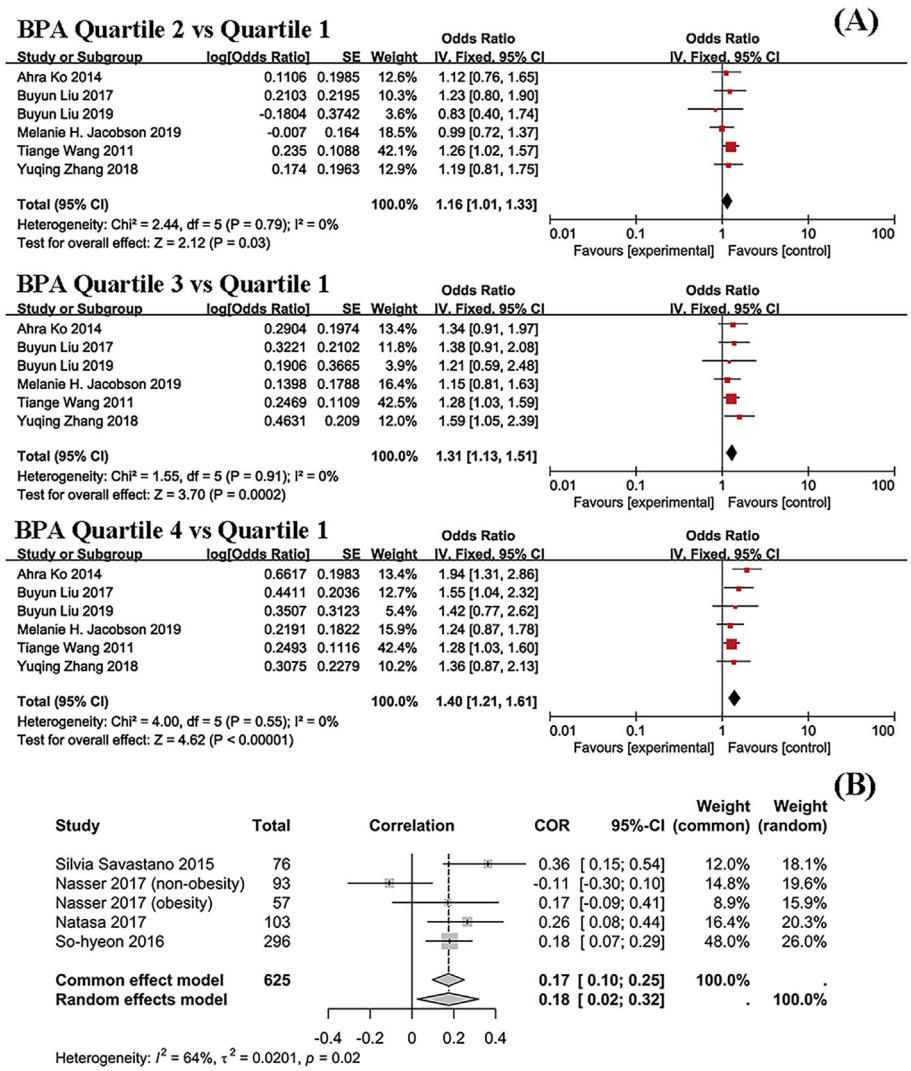

FIGURE 2 Forest plot of association between BPA and risk of abdominal obesity. (A) The forest plot of meta-analysis of studies categorizing BPA into quartiles; the BPA quartile 1 was the reference group (*OR* was pooled). (B) The forest plot of meta-analysis of studies of correlation analysis (coefficient was pooled). BPA, bisphenol A.

Q_3, $P = 0.710$; Q_4, $P = 0.385$). The remaining four studies[12,33,34,39] employed correlation analysis to explore the association between BPA and abdominal obesity. One of these studies[33] ($n = 150$) divided children into a non-obesity group ($n = 93$) and an obesity group ($n = 57$). For the meta-analysis, a total of five data from four studies were pooled, and the results demonstrated that BPA levels were positively correlated with the occurrence of abdominal obesity ($r = 0.18$, *95%CI*: 0.02, 0.32) (Figure 2). As observed in Supplementary Table S4 and Figure S2, the funnel plot did not exhibit an obvious risk of publication bias (Egger's test: $P = 0.975$).

3.2.3 | Blood pressure

Seventeen studies[12,23,28,29,33,41–52] describing the relationship between BPA levels and blood pressure were used in the systematic review. Twelve studies involved adults and five studies involved children.[28,29,33,49,52] Different factors such as age, sex, body mass index (BMI), and WC were used in the respective models as confounding factors.[12,23,28,29,33,41–52] In the three studies, BPA levels were divided into four groups.[41,42,44] Although a cohort study of Korean adults[44] ($n = 521$) found no significant association between BPA exposure with elevated blood pressure and hypertension, a cross-sectional study of Chinese adults ($n = 3246$) found a negative association between BPA exposure and hypertension in middle-aged and elderly Chinese adults.[41] In addition, another cross-sectional study of Thai adults ($n = 2588$) showed a greater risk of hypertension in the highest quartile of BPA compared with the first quartile.[42] Four other studies divided BPA levels into three groups to analyze the relationship between BPA levels and blood pressure.[23,29,43,51] Except for a cross-sectional study of adults in Lebanon[23] ($n = 486$) that did not find a significant association between BPA and the risk of hypertension, the other three studies had statistically significant findings.[29,43,51] The first study, a cross-sectional study in Iranian children[29] ($n = 132$) showed a consistently and statistically significant association between BPA levels with SBP and DBP. The second study, a cohort study of pregnant women in Canada[43] ($n = 1909$), demonstrated that BPA exposure in the second tertile of multiparous women was associated with a lower risk of gestational hypertension after parity stratification compared with the first tertile. The third study, a cross-sectional study

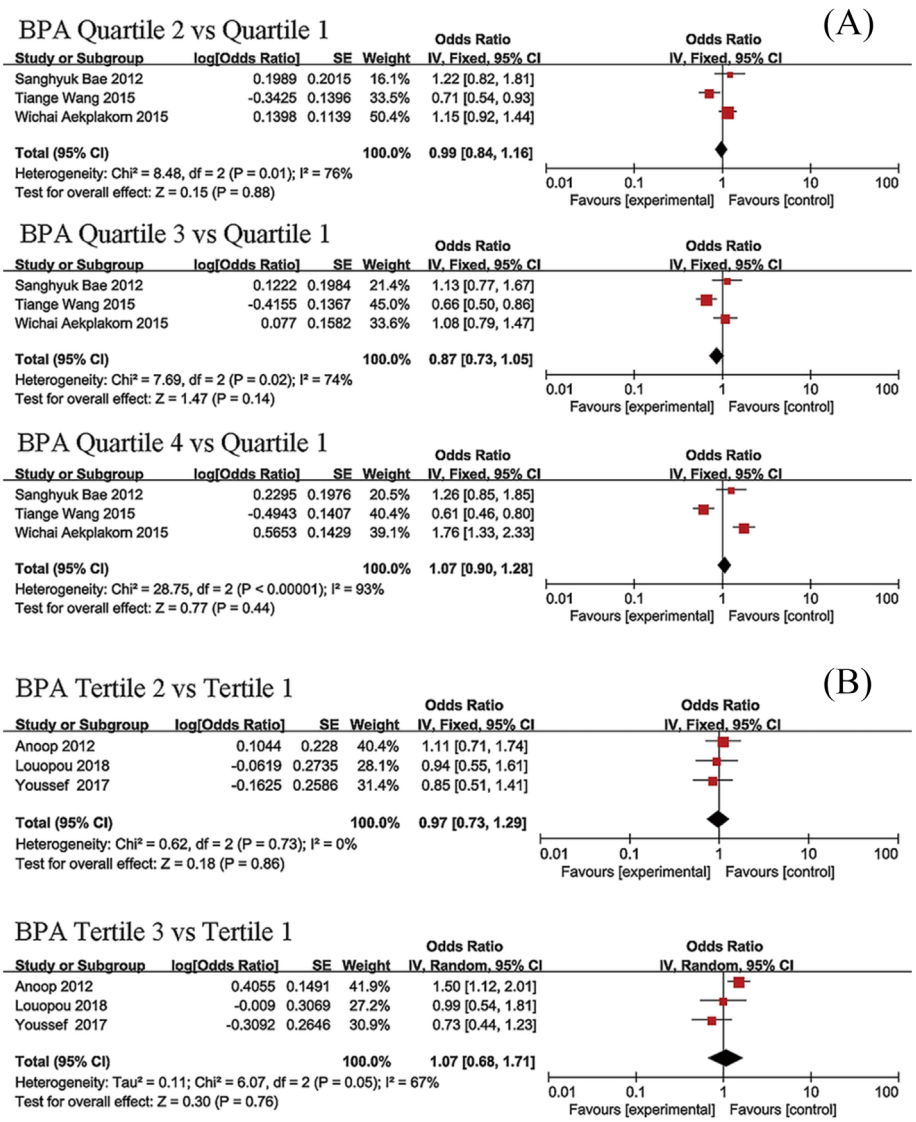

FIGURE 3 Forest plot of association between BPA and risk of hypertension. (A) The forest plot of meta-analysis of studies categorizing BPA into quartiles; the BPA quartile 1 was the reference group (*OR* was pooled). (B) The forest plot of meta-analysis of studies categorizing BPA into tertiles; the BPA tertile 1 was the reference group (*OR* was pooled). BPA, bisphenol A.

of US adults[51] ($n = 1380$) found a significant positive association between elevated BPA levels and the development of hypertension. The only study that divided BPA levels into two groups, a cross-sectional study of Chinese adults ($n = 90$), showed that DBP level was significantly higher in the high-BPA group than in the low-BPA group.[50] A total of 11 studies used BPA level as a continuous variable to analyze the relationship between BPA and blood pressure.[12,28,33,42,44–49,52] Seven studies included adults, and four studies involved children.[28,33,49,52] Except for three studies that did not find a relationship between BPA and blood pressure,[12,28,52] all the other studies had positive findings. The three studies with negative results consisted of a cohort study in Greek children ($n = 494$),[28] a cross-sectional study in Italian men ($n = 76$),[33] and a cross-sectional study in American children ($n = 538$).[52] In these two studies, correlation analysis was used to investigate the association between BPA with SBP and DBP.[28,33] A cross-sectional study of Thai adults[42] ($n = 2588$) found a significant association between logarithmic BPA levels and hypertension. A case–control study of children in Saudi Arabia[33] ($n = 177$) used correlation analysis to demonstrate that BPA exposure is associated with high SBP in a group of normal-weight children. A European cohort study ($n = 1277$) examining the association between environmental exposures and blood pressure in children early in life found that higher DBP was associated with higher maternal BPA levels.[45] One randomized crossover trial in Korean adults[46] ($n = 60$) and another randomized crossover trial in Korean adult women[48] ($n = 45$) found that BPA exposure is significantly associated with an increased SBP. However, a cross-sectional study of pregnant women in Europe ($n = 152$) showed that higher BPA levels during pregnancy were associated with lower SBP.[47] A cohort study of Dutch children[49] ($n = 471$) found that higher BPA levels in children aged 6 years were associated with lower DBP at baseline. The study furthermore showed that after follow-up, increased BPA levels at baseline were associated with a higher DBP change from 6 to 10 years of age. A cohort study of Korean adults[44] ($n = 521$) found that higher BPA levels were significantly associated with higher DBP.

A total of six studies were included in the meta-analysis of the relationship between BPA and hypertension.[23,41–44,51] Three of them[41,42,44] divided BPA levels into four groups, with the first quartile

being used as the control group. No statistically significant association was found between BPA level and hypertension after combining the results of these three studies (Q_2: *OR* = 0.99, *95%CI*: 0.84, 1.16; Q_3: *OR* = 0.87, *95%CI*: 0.73, 1.05, and Q_4: *OR* = 1.07, *95%CI*: 0.90, 1.28, respectively; Figure 3). The other three studies[23,43,51] divided BPA exposure levels from low to high into three groups, known as the tertile 1 (T_1), tertile 2 (T_2), and tertile 3 (T_3), and the lowest tertile was used as a reference group to explore the association between BPA and hypertension. Again, no statistical association was found between BPA levels and hypertension (T_2: *OR* = 0.97, *95%CI*: 0.73, 1.29; T_3: *OR* = 1.07, *95%CI*: 0.68, 1.71, respectively; Figure 3).

3.2.4 | FPG

Fourteen studies examining the relationship between BPA exposure and blood glucose were used for this systematic review.[12,29,33,39,53–62] Eleven studies included adults, and four studies involved children.[29,33,57,59] The 14 studies controlled for confounding factors including age, sex, physical activity, and BMI. Four studies divided BPA levels into four groups to analyze the relationship between BPA exposure and blood glucose.[56–58,62] Two of the studies found no statistically significant associations. A cross-sectional study of pregnant women in Canada[56] ($n = 1274$) that compared gestational diabetes and impaired glucose tolerance with normal glucose found no statistically significant results. The second study, a cross-sectional study of US adults[58] ($n = 1586$) did not find a significant association between BPA exposure and fasting glucose. Two other studies found significant associations. A cross-sectional study involving Thai children and adults[57] ($n = 2581$) showed that the risk of impaired fasting glucose was 1.7 times higher in the third quartile than in the first quartile of BPA levels. The second study, a cross-sectional study of Canadian adults[62] ($n = 2405$) showed that log-transformed glucose levels in the BPA third quartile (Q_3) were significantly higher compared with the BPA first quartile (Q_1). Four studies divided BPA exposure levels into three groups to investigate the relationship between BPA exposure and blood glucose.[29,55,59,60] One cohort study of pregnant women in China[55] ($n = 1841$) and another prospective birth cohort study of pregnant women in China[60] ($n = 620$) did not find an association between BPA tertiles and fasting glucose. Of the remaining two studies, a cross-sectional study of Iranian children[29] ($n = 132$) found a significant association between BPA levels and fasting blood glucose (*P* for trend <0.05). Similarly, the second study, a cohort study of preadolescent girls in South Korea[59] ($n = 80$), showed that BPA exposure was positively correlated with blood glucose levels. Nine studies used BPA exposure level as a continuous variable to analyze the relationship between BPA and blood glucose.[12,33,39,53–55,58,60,61] Except for three studies[12,53,61] that had significant findings, none of the other studies observed a significant association between BPA exposure and blood glucose. Among the studies with significant findings, a cross-sectional study of Italian adult men[12] ($n = 76$) and another cross-sectional study of Indian adults[53] ($n = 60$) showed a significant association between BPA levels and FPG. A repeated measures longitudinal study ($n = 1705$) from China found a positive association between BPA levels and FPG in women. The basic characteristics of the other six negative studies are summarized as follows: one case–control study of children in Saudi Arabia[33]; three Chinese adult cohort studies,[54,55,60] two of which involved pregnant women[55,60]; one cross-sectional study of American adults[58]; and one cross-sectional study of Korean reproductive-aged women.[39] None of the six studies concluded that BPA exposure was associated with FPG.

A total of three studies using correlation analysis to explore the relationship between BPA exposure and FPG were included in the meta-analysis.[12,33,53] One case–control study in Saudi Arabia divided children into a non-obesity group and an obesity group, and the correlation coefficients of each group were merged separately.[33] No statistically significant association was found between BPA level and FPG ($r = 0.15$, *95%CI*: −0.11, 0.40; Figure 4). The combined results are shown in Figure 4.

3.2.5 | Dyslipidemia

Thirteen studies that examined the relationship between BPA exposure and blood lipids were used in this systematic review.[12,23,28,29,33,49,53,63–68] Eight studies included adults, and five included children.[28,29,33,49,67] The 13 included studies were adjusted for confounding factors such as sex, age, physical activity, education level, smoking, and drinking status. Three studies divided BPA levels into three groups to analyze the association between BPA exposure and blood lipid levels.[23,29,67] One cross-sectional study of Danish children[67] ($n = 107$) found that the highest BPA tertile was significantly associated with lower triglyceride levels compared with the lowest BPA tertile. The other two studies, a cross-sectional study of Iranian children[29] ($n = 132$) and a cross-sectional study of Lebanese adults[23] ($n = 486$), found no association between BPA exposure and levels of TC, HDL, LDL, and TG. Ten studies used BPA level as a continuous variable to analyze the relationship between BPA and blood lipids.[12,28,33,49,53,63–66,68] Except for two studies that did not obtain statistically significant results,[28,63] the other studies all demonstrated statistically significant associations. The first study that did not observe an association between BPA exposure and blood lipids was a cross-sectional study[63] ($n = 300$) in Indian adults, which investigated the relationship between BPA with TG and HDL in patients with diabetes and healthy controls. The second study, a cohort study in Greek children[28] ($n = 494$), did not observe a significant association between BPA with TC or HDL. Among the eight studies with positive results,[12,33,49,53,64–66,68] one cross-sectional study[64] in an elderly Swedish population ($n = 1016$) found an association between BPA levels with LDL and HDL. A cohort study of Chinese adults[65] ($n = 1326$) showed that higher BPA levels were associated with higher LDL concentrations and lower HDL and TG concentrations. A repeated measures study ($n = 54$) of Korean adult women[66] found that BPA levels were negatively correlated with LDL and TC levels. A cohort study of Dutch children[49] ($n = 471$) found that increased BPA

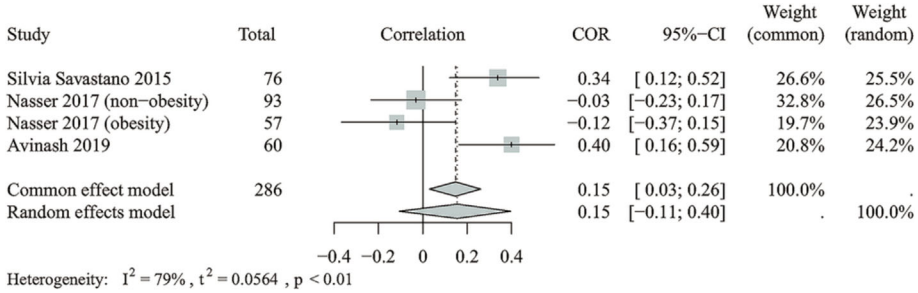

FIGURE 4 Forest plot of association between BPA and FPG. The figure presents the forest plot of meta-analysis of studies of correlation analysis (coefficient was pooled). BPA, bisphenol A; FPG, fasting blood glucose.

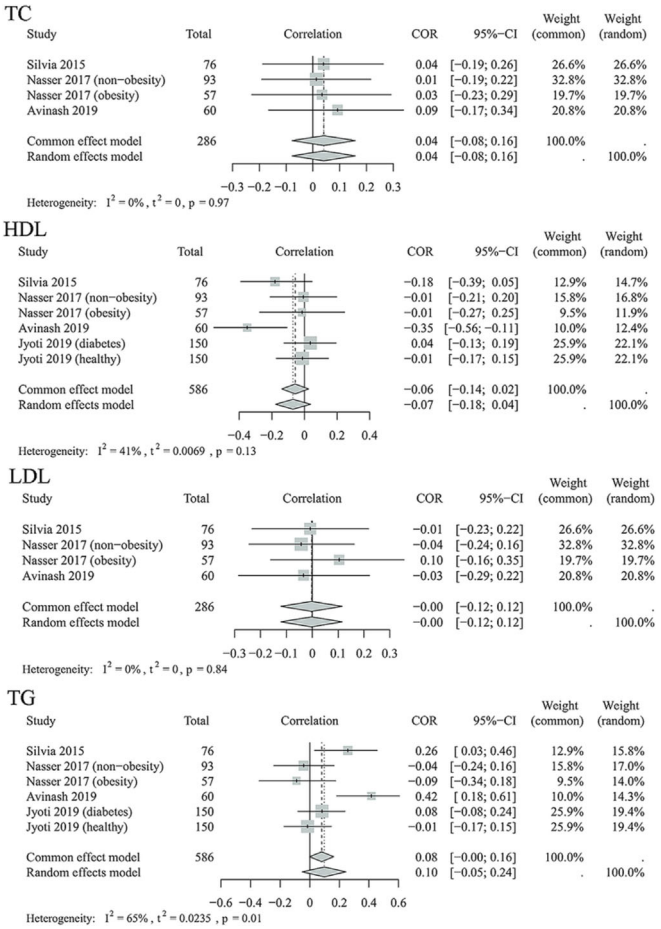

FIGURE 5 Forest plot of the association between BPA and blood lipids. The four plots represent the meta-analysis forest plots of correlation analysis studies of TC, HDL, LDL, and TG. BPA, bisphenol A; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride.

levels at 6 years were associated with elevated HDL. Of the eight studies with positive results, four used correlation analysis to investigate the association between BPA and blood lipid levels.[12,33,53,68] One cross-sectional study of Italian adult men[12] ($n = 76$) found a significant positive correlation between BPA levels and TG. A case–control study of Saudi Arabian children[33] ($n = 177$) found a significant positive association between BPA levels and TC in normal-weight girls, and the levels of BPA were positively correlated with LDL in girls both with non-obesity and obesity. A cross-sectional study of Indian adults[53] ($n = 60$) demonstrated that TG levels were positively correlated with BPA levels, whereas HDL levels were negatively correlated with BPA levels. A cohort study of Chinese adults[68] (baseline $n = 574$), which divided BPA exposure levels into three groups (three tertiles) showed that BPA levels were positively associated with LDL and negatively associated with HDL. In the analysis of baseline cross-sectional data, it was shown that subjects with higher BPA levels (the higher BPA tertile) had higher LDL levels and lower HDL levels.[68] In the analysis of follow-up data, each standard deviation (per SD) increase in baseline BPA was significantly associated with a higher incidence of low-HDL-cholesterolemia in subjects who did not have low-HDL-cholesterolemia at baseline.[68]

A total of four studies with results given as correlation coefficients were included in the meta-analysis.[12,33,53,63] The above-mentioned study by Li et al was not included because correlation coefficients were Z-transformed.[68] The first study ($n = 76$) was a cross-sectional study of plasma BPA in Italian adult males.[12] The second included study, a Saudi Arabian case–control study, divided children into a non-obesity group ($n = 93$) and an obesity group ($n = 57$), and the correlation coefficients of each group were combined separately.[33] The third study ($n = 60$) was a cross-sectional study of serum BPA in Indian adults.[53] The fourth study, a cross-sectional study of Indian adults, divided subjects into patients with diabetes ($n = 150$) and healthy controls ($n = 150$), and the correlation coefficients for each group were pooled separately.[63] Meta-analysis of these four studies[12,33,53,63] did not show a significant correlation between BPA with TG ($r = 0.10$, *95%CI*: −0.05, 0.24) or HDL ($r = -0.06$, *95%CI*: −0.14, 0.02). As observed in Supplementary Table S4 and Figure S2, the funnel plot did not exhibit an obvious risk of publication bias (Egger's test: TG, $P = 0.428$; HDL, $P = 0.140$). Study data allowing for the meta-analysis of TC and LDL were pooled.[12,33,53] No significant association was found between BPA with TC ($r = 0.04$, *95%CI*: −0.08, 0.16) or LDL ($r = 0.00$, *95%CI*: −0.12, 0.12). The above results are shown in Figure 5.

4 | DISCUSSION

4.1 | Summary of evidence

To the best of our knowledge, this is the first systematic review and meta-analysis to analyze the association between BPA exposure with

MetS and its components including abdominal obesity, high blood pressure, abnormal glucose, high TG, or low HDL levels.

With meta-analysis, we found that the risk of abdominal obesity increased with the increase of BPA exposure, especially in the group with higher BPA exposure levels. However, there was no significant correlation between BPA exposure and MetS components including hypertension, fasting blood abnormal glucose, and dyslipidemia. Our findings suggest the potential importance of early monitoring of BPA exposure levels to prevent and control the development and progression of abdominal obesity.

Abdominal obesity, as an important component of the MetS, plays an important role in the risk of cardiovascular diseases.[69] There are two possible mechanisms to explain the significant association between BPA exposure and the risk of abdominal obesity. In vitro data showed that the combination of BPA and insulin can accelerate the transformation of 3 T3–L1 fibroblasts into adipocytes.[70] In addition, the major metabolite of BPA, BPA-glucoside (BPA-g), which has previously been thought to be inactive, can actually induce preadipocyte differentiation and fat accumulation, thereby inducing the development of abdominal obesity.[71,72] Furthermore, a meta-analysis and systematic review published recently also found that the higher the level of BPA exposure, the greater the risk of WC increases.[73] This finding is similar to our results because abdominal obesity is generally defined by WC.[74] Another meta-analysis and systematic review[75] also found that BPA is associated with abdominal obesity in children and adults. Two cross-sectional studies regarding BPA and obesity in children, adolescents, and adults and in the United States[26,32] and another cross-sectional study in Korean adults[27] found an association between BPA exposure with the risk of abdominal obesity or WC.

Because only two articles[23,24] on the association between BPA and MetS were included in the present study, the number of studies is not sufficient to do a meta-analysis. Both studies divided BPA exposure levels into three groups, exploring the association between BPA tertiles and the risk of MetS, but no significant association was found. The first cross-sectional study of Lebanese adults[23] did not find significant results because the sample size was too small ($n = 486$) and the strength of the causal argument was insufficient. A second cohort study of adult Chinese males[24] ($n = 1038$) also did not find significant associations. Although neither of the two included studies on the relationship between BPA and MetS found a significant association, this does not mean that it can be concluded that there is no association between BPA and MetS—suitably designed prospective studies are still needed to comprehensively address this remaining open question.

The current meta-analysis found no statistically significant association between BPA with high blood pressure, abnormal blood glucose, and dyslipidemia. These results might have occurred due to heterogeneity among the included studies, differences in the definition of results, and discrepancies in the adjusted covariates. Although no positive findings were found in the current study, many previous studies,[41,64,73] such as Rancière et al,[73] found a significant positive correlation between urinary BPA levels with hypertension and diabetes; a cross-sectional study of middle-aged and elderly Chinese[41] showed that BPA exposure levels were inversely associated with hypertension. A 2020 meta-analysis by Fu et al[15] found that BPA exposure levels were negatively associated with HDL. However, possibly due to the insufficient evidence strength of the included cross-sectional study data, a meta-analysis from Dunder et al published in 2019[76] failed to demonstrate any associations between BPA levels and indicators of lipid metabolism such as TC, TG, HDL, and LDL.

4.2 | Advantages and limitations of the present study and included studies

In recent years, several studies on the association between environmental endocrine disruptors such as BPA, phthalates, and polychlorinated biphenyls with cardiovascular and metabolic diseases have been published. Similarly, elucidation of the mechanism and dose–response relationship between BPA and the MetS was the hot spot of current research. A systematic review of the epidemiological evidence linking BPA with the risk of cardiovascular and metabolic disorders was published by Rancière et al in 2014 and also included components such as hypertension and increased WC.[73] However, the current study included more comprehensive and updated literature and focused on the relationship between BPA with MetS and its multiple components. In addition to combining the effective *OR* and *95% CI*, we also combined the correlation coefficients. Even though many cross-sectional studies were included, strict inclusion and exclusion criteria were conducive to identifying high-quality cross-sectional results.

The current study has the following limitations. First, a risk of publication bias cannot be completely excluded due to the heterogeneity among included studies and differences in adjusted confounders. Second, although the included cross-sectional studies are of high quality, the disadvantage that such studies cannot infer causality remains. Third, due to language constraints, only studies published in English were considered. This led to the exclusion of a small number of articles published in different languages. More than half of the studies included were cross-sectional studies and only a very limited number were prospective studies. Therefore, the results of this meta-analysis have limited ability to infer causality. In addition, there is some heterogeneity between different studies, and no study can be identical, whether it is study design, definition of outcome variables, or confounding factors of adjustment. Finally, many of the included studies used databases from the same source,[11,36] but different researchers employed different statistical models or different data conversion methods, which also may affect the results.

It is worth noting that this study showed a positive association between BPA exposure and abdominal obesity, but the studies included all defined the presence or absence of abdominal obesity based on physical measures such as waist circumference and waist-to-hip ratio. It is the trend of future research to employ dual-energy X-ray absorption to measure the distribution of body fat and muscle, so as to more accurately measure obesity by body fat percentage or body fat volume.[77–79]

5 | CONCLUSION

Overall, this study has demonstrated that the degree of BPA exposure in the general population is positively associated with the risk of abdominal obesity. However, no association was found between BPA with the MetS and its components except for abdominal obesity. More prospective studies are needed to clarify the relationship between BPA exposure and MetS to provide a scientific basis for standards of BPA use in daily life.

AUTHOR CONTRIBUTIONS

Tianli Xiao and Yide Yang drafted the manuscript and performed the statistical analysis. Yide Yang, Chanjuan Zheng, Binh Quach, and Wei Liang conceived of the study. Yide Yang, Zehua Huang, Yulian Zhu, and Feifei Li participated in its design and coordination and helped to draft the manuscript. Julien Baker, Christoph Reichetzeder, and Berthold Hocher revised the manuscript. All authors participated in critically revising and approving the final manuscript.

ACKNOWLEDGMENTS

This study was supported by the Health Research Project of Hunan Provincial Health Commission (No. 202112031516), the National Natural Science Foundation of China (No. 81903336), the Hunan Provincial Natural Science Foundation of China (No. 2019JJ50376), a project supported by Scientific Research Fund of Hunan Provincial Education Department (22B0038), Open Project for Postgraduates of Hunan Normal University (No. KF2022019), and The Research Team for Reproduction Health and Translational Medicine of Hunan Normal University (2023JC101). The funders had no role in the design, analysis, or writing of this article.

CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

ORCID

Berthold Hocher https://orcid.org/0000-0001-8143-0579

Yide Yang https://orcid.org/0000-0003-3297-1306

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Xiao T, Huang Z, Zheng C, et al. Associations of bisphenol A exposure with metabolic syndrome and its components: A systematic review and meta-analysis. *Obesity Reviews*. 2024;e13738. doi:10.1111/obr.13738