Leone A, Ravasenghi S, Bulzomì M, Ravella S, Battezzati A, De Amicis R, Bertoli S, 'Bisphenol A exposure and symptoms of anxiety and depression among women of reproductive age' (2023) 1 EJPLT.
DOI: .....

EJPLT
ISSN 2704-8012

# Bisphenol A exposure and symptoms of anxiety and depression among women of reproductive age

Alessandro Leone [1], Stefano Ravasenghi [1,2], Marina Bulzomì [3], Simone Ravella [1], Alberto Battezzati [1,2], Ramona De Amicis [1,3], Simona Bertoli [1,3]

[1] ICANS-DIS, Department of Food Environmental and Nutritional Sciences, University of Milan, Milan, Italy.
[2] Clinical Nutrition Unit, Department of Endocrine and Metabolic Medicine, IRCCS Istituto Auxologico Italiano, 20100 Milan, Italy.
[3] IRCCS Istituto Auxologico Italiano, Obesity Unit and Laboratory of Nutrition and Obesity Research, Department of Endocrine and Metabolic Diseases, 20145 Milan, Italy.

## Abstract

*Bisphenol A (BPA) is a chemical compound used in multiple areas, including the manufacture of food packaging and containers. Dietary exposure accounts for >90% of total exposure. It is considered an endocrine disruptor, as it is suspected to adversely affect fetal development during intrauterine life and contribute to the development of obesity, diabetes and cardiovascular disease and mental health in adulthood. European law (Regulation (UE) 321/2011) banned BPA from polycarbonate infant feeding bottles, but it remains authorized for all other products with a tolerable daily intake of 4 µg/kg body weight/day (EFSA2015). We conducted a cross-sectional study of 56 women aged 18-40y to investigate the association between BPA exposure and the presence of anxiety and depressive symptoms. Subjects, recruited at ICANS, University of Milan, completed the STAI2 and QD questionnaires to investigate anxiety and depressive symptoms, respectively. A blood sample was taken to determine exposure to total and unconjugated-BPA (metabolically active form). After adjustment for age, BMI, smoking and physical activity, total BPA (log-transform for linearity) was not associated with anxiety and depression, whereas unconjugated-BPA (transformed in square root for linearity) was significant associated with depression score (β (√BPA) = 0.11, 95% CI: 0.01, 0.21; p=0.042). Our data suggest that BPA exposure is associated with depressive symptoms in women in reproductive age.*

Keywords: Bisphenol A; Anxiety; Depression; Women.



## Introduction.

Bisphenol A (BPA) is a chemical compound used in the manufacture of polycarbonate, a plastic material used in several fields including food packaging, epoxy resins used in the inner lining of cans to prevent direct contact between the metal wall of the container and food or beverages, thermal paper, dental materials, medical devices, and sales receipts [1,2]. Due to its mass production and widespread applications, the presence of BPA is ubiquitous in the environment. Indeed, due to an incomplete polymerization process, significant amounts of BPA residues can migrate from the containers to food and beverage or from materials to the environment. The mean concentrations in food vary mainly due to food processing, and storage methods in different regions [2]. BPA enters organisms predominantly through the digestive tract, but the exposure can also occur through the respiratory tract and skin contact [3,4]. The dietary route is the main route of BPA exposure, accounting for more than 90% of total exposure [4]. Once ingested, BPA is glucoronidated (conjugated-BPA) in the liver and excreted with urine. However, abnormalities in the activity of the enzymes involved in the glucoronidation process cause the increase in levels of unconjugated-BPA (the form metabolically active) concentration in blood [5].

BPA is a known endocrine disruptor, as it is able to interact with various biological receptors [6], such as those for estrogen, androgen, and thyroid hormones, thus interfering with the normal function of the reproductive, nervous, and endocrine-metabolic systems [2,7,8]. Indeed, several epidemiological studies have reported an

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association between BPA exposure and the risk of infertility [9]obesity [10]cardiovascular disease [11], diabetes [12] and cognitive impairment [13] . In 2015, based on these studies, the European Food Safety Authority (EFSA) lowered the tolerable daily intake (TDI), initially set at 50 µg/kg body weight/day, to 4 µg/kg body weight/day.

Several studies reported BPA exposure also associated with behavioral problems and mental disorders, like anxiety and depression in children. In particular, exposure to BPA during pregnancy could disrupt brain development in offspring by increasing the risk for unusual behavior in preschool children [14], and depression and anxiety, especially in boys [15]. At the same time, postnatal exposure would also appear, although with mixed results, to be associated with the development of children's behavioral outcomes. Some studies reported an association between exposure to BPA during the first 5-10 years of life, with the development of anxiety and depression in both boys and girls [16,17,18].

However, the number of studies analyzing BPA exposure in adulthood in relation to depressive or anxious symptoms are limited. Only one study found a positive relation between BPA exposure and depression in elder [19]. Hence, the aim of this study was to investigate the association between the total and unconjugated-BPA exposures and continuous anxious and depression in young women of reproductive age.

## 1. Material and methods.

*Study design*

We carried out a cross-sectional study of 56 voluntary women aged 18-40 years recruited at the International Center for Nutritional Status Assessment (ICANS),

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[19] K Hao, J Luo, H Ge, Z Wang, 'Associations of urinary bisphenol A and its alternatives bisphenol S and F concentrations with depressive symptoms among adults' (2021) 279 Chemosphere, 130573.

University of Milan, between January 2018 and December 2019. Women underwent a clinical examination to obtain information about patient's medical history, chronic drug therapies, smoking and weekly structured physical activity and to measure blood pressure. Anthropometric measurements and a blood sample were taken. Inclusion criteria were: age 18-40 years, no previous diagnosis of diabetes, cardiovascular disease, cancer within the past 5 years, neurological, gastrointestinal, cardiac, renal, liver and pulmonary failure, and mental disorders. The study was conducted following the guidelines laid down in the Declaration of Helsinki and the Ethics Committee of the University of Milan gave a positive opinion on study procedures (protocol n. 25/2017). Patients gave signed informed consent for the use of their data for research purposes.

*Anthropometric measurements*

Anthropometric measurements were taken following International standard procedure [20]. Body weight, height, circumferences and skinfolds were measured on subjects wearing only light underwear. Body weight was measured by an electronic scale to 100 g. Body height was measured to the nearest 0.1 cm using a vertical stadiometer. Body mass index was then calculated using the formula: BMI= weight(kg)/height(m). Waist circumference was measured with a non-stretch tape applied horizontally midway between the lower rib margin and the superior anterior iliac spine taken to the nearest 0.5 cm. Bicipital, tricipital, subscapular and suprailiac skinfold thicknesses were measured by Holtain Tanner/Whitehouse skinfold calliper (Holtain Ltd, Crymych, Wales). Body density and fat mass were then calculated by the Durnin and Womersley method [21] and by the Siri's formula [22] respectively.

*Biochemical analysis and BPA exposure*

A fasting blood sample was drawn between 08:30 and 09:00 AM for the measurement of BPA exposure. The measurement of total and unconjugated-BPA was made through ELISA sandwich test (MyBioSource ELISA kit).

*Psychological questionnaires*

Anxious symptoms were evaluated using the Italian version of Spielberg et al.'s State-Trait Anxiety Inventory (STAI). Anxiety was defined as a STAI2 (trait anxiety) score ≥95th percentile of reference values. Depression was evaluated using the Italian Depression Questionnaire (QD). Depression was defined as a QD score ≥95th percentile of reference

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values [23, 24].

*Statistical analysis*

Continuous variables are reported as median and interquartile range, while discrete variable as count and percentage. Total and unconjugated BPA exposures were log- and square root-transformed, respectively, to reach normality. Linear regression model was used to assess the association between BPA exposure and anxiety and depression scores. Potential confounders were sex, age, BMI, smoking and physical activity. A P value < 0.05 was considered statistically significant.

## 2. Results.

The characteristics of the women are reported in Table 1.

Women had a median age of 29 years (IQR: 25-34) and a median BMI of 24.2 kg/$m^2$ (IQR: 21.2-27.2). Among the participants, 57.1% of women had a normal weight, 33.9% of women had overweight and 8.9% of women had obesity. The prevalence of anxiety and depression were both 3.6%. About BPA exposure, all volunteers were found exposed to total BPA, and 98.2% of women presented measurable amounts of unconjugated BPA. Median total BPA exposure was 2.8 ng/ml (IQR: 0.8-5.3), while median unconjugated-BPA concentration was 424 pg/ml (IQR: 332.8-585.7).

When we investigated the association between BPA exposure and the scores obtained from psychological questionnaires (Figure 1), we did not find any association of total BPA with the anxiety score (β (logBPA) = -0.78, 95% CI: -2.55, 0.98; p=0.377) and depressive score (β (logBPA) = 0.09, 95% CI: -0.71, 0.89; p=0.822). However, we observed that unconjugated-BPA was associated with the depressive score (β (√BPA) = 0.11, 95% CI: 0.01, 0.21; p=0.042), but not with the anxiety score (β (√BPA) = 0.14, 95% CI: -0,10, 0,38; p=0,243).

Table 1: Characteristics of the women

| | Median | Interquartile range |
|---|---|---|
| Age (years) | 29 | 25-34 |
| **Anthropometric measurements** | | |
| BMI (kg/m2) | 24.2 | 21.2-27.2 |
| Waist circumference (cm) | 80.8 | 73.5-87.5 |
| Body fat (%) | 32.1 | 26.7-36.1 |
| **Psychological profile** | | |

[23] E. Sanavio, Le scale CBA. Cognitive Behavioural Assessment: un modello di indagine psicologica multidimensionale (Raffaello Cortina Editore 2002)

[24] M Balsamo, A Saggino, 'Test per l'assessment della depressione nel contesto italiano: un'analisi critica' (2007) 13 Psicoter Cogn e Comportamentale, 167-99

| | | |
|---|---|---|
| Anxiety score | 38.5 | 33.5-44 |
| Depressive score | 3 | 0.5-6 |
| **BPA exposure** | | |
| Total BPA (ng/ml) | 2.8 | 0.8-5.3 |
| Unconjugated BPA (pg/ml) | 424 | 332.8-585.7 |
| | N | % |
| Smoking | | |
| Non-smoker | 34 | 60.7 |
| Ex-Smoker | 18 | 32.1 |
| Smoker | 4 | 7.2 |
| Physical activity | | |
| Sedentary | 17 | 30.4 |
| Physically active | 39 | 69.6 |
| Psychological symptoms | | |
| Major Depressive symptoms | 2 | 3.6 |
| Major Anxious symptoms | 2 | 3.6 |

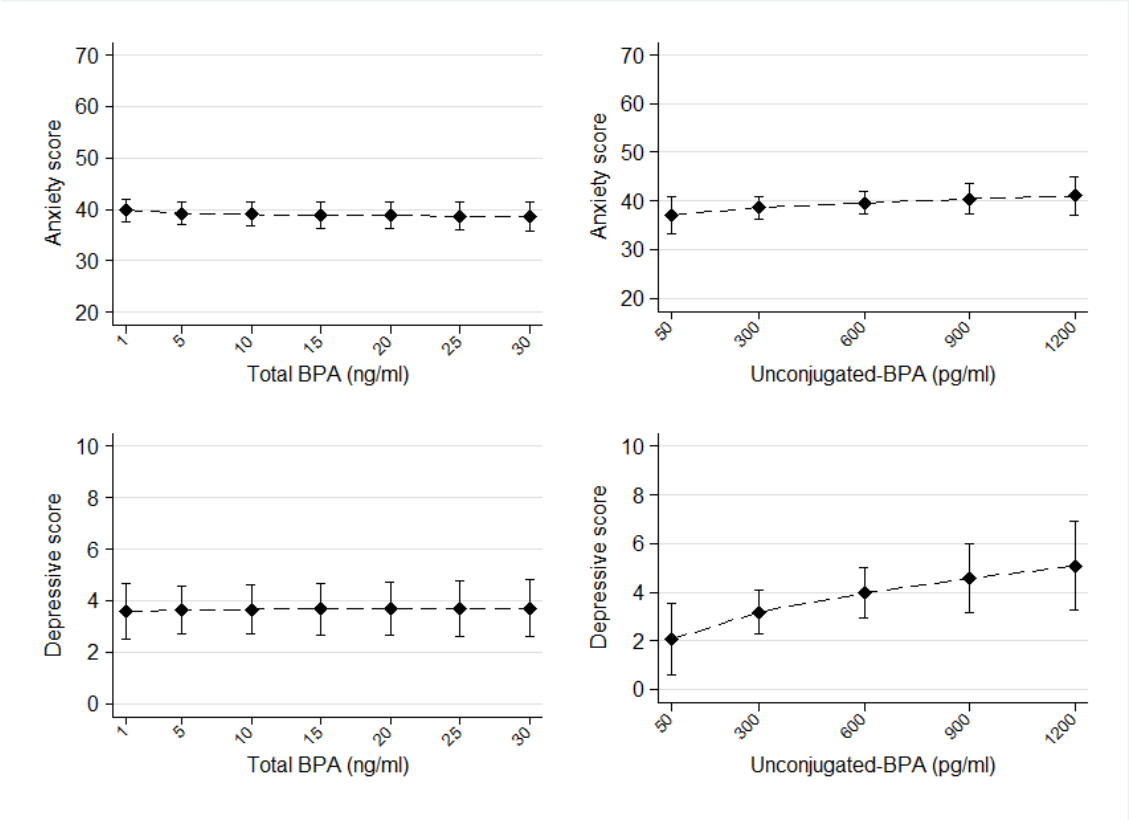


Figure 1. Association of total and unconjugated-BPA exposures with continuous anxiety and depression. Model were adjusted for age, BMI, smoking and physical activity.

## 3. Discussion.

The aim of this study was to assess the associations between BPA exposure and continuous measures of depression and anxiety in a group of women in reproductive age. We observed that all women were exposed to BPA. Moreover, we observed a positive association between blood unconjugated BPA concentrations and self-reported

symptoms of depression among women in reproductive age. In contrast we did not observed any association with anxiety. This suggests that BPA exposure in young adults may be a potential risk factor for the development of mental disorders such as depression. The investigation of this association is very important in the nutritional field, on one hand because BPA exposure is predominantly dietary, and on the other hand because mental disorders are frequently found in the nutritional clinical setting. In fact, depression is diagnosed more often among individuals with obesity [25].

In recent years, mental disorders have proven to be important contributors to the total burden of disease and disability [26]. Their determinants are multiple: emotions, interactions with others, social, cultural and economic factors, quality of life, working conditions, stress, genetics, nutrition, exposure to environmental hazards [27]. Thanks to progress in scientific research, it was hypothesized that exposure to environmental pollutants, such as BPA, could also contribute to the development of mental disorders. Our result seems confirms such hypothesis.

Previous studies found prenatal BPA exposure significantly associated with the development of depressive-like behaviors during childhood in a sex-dependent manner. Indeed, three different studies found the association only in boys but not in girls [15, 16, 18]. On the other hand, further studies found that BPA exposure during childhood was associated with depression in both boys and girls. Our results add information that BPA exposure during adulthood is also associated with greater depressive symptoms in young women. These results are in apparent contrast to recent findings observed in the NANHES population. Hao et al. [19] found no association between BPA exposure and depression risk in a sample of 7000 men and women aged 18 years or older. They found BPA exposure associated with depression risk only in older men (age >60 years). However, it should be noted that the authors only considered total BPA exposure and not the concentration of unconjugated BPA. Since this is the metabolically active form, it is therefore able to interact with the receptors of several hormones, it is possible that it is more associated with the risk of mood alteration. Additional reasons for discordance between the results are to be found in the body fluid used to determine BPA exposure (blood vs. urine), the instrument used to investigate the presence of depressive symptoms, in the different population recruited.

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[15] F Perera, 'Bisphenol A exposure and symptoms of anxiety and depression among inner city children at 10-12 years of age' (n 15), 890-99.

[16] KG Harley, 'Prenatal and early childhood bisphenol A concentrations and behavior in school-aged children' (n 16), 43-50.

[18] EL Roen , 'Bisphenol A exposure and behavioral problems among inner city children at 7-9 years of age' (n 18), 739-45.

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We are still far from fully understanding the mechanisms linking BPA to depression. However, some hypotheses can be put forward. BPA con promote the production of inflammatory cytokines such as interleukin (IL-6)-1 β and IL-7 like BPA [28]. This increases the inflammatory response, leading to continuous changes in neurotransmitter function and behavior, which can lead to depression [29]. In addition, BPA can significantly increase intracellular reactive oxygen species (ROS) levels and induce oxidative stress [30] , which is also a potential mediator of depression [31]. Moreover, BPA seems to able to affect the level of gamma-amino-butyric acid (GABA) (A) α2 receptors, a central inhibitory neurotransmitter system in the brain that is involved in depressive symptoms.

Our study has several strengths. First, this is one of the few studies to have investigated the association between BPA exposure in adulthood and anxiety and depression, Second, unlike previous studies, we measured both total BPA exposure and unconjugated BPA exposure. Third, we used a questionnaire specifically developed for the Italian population to define the presence of depressive symptoms.

However, the study is not without limitations. First, the small sample size. Second, the presence of anxiety and depressive symptoms was identified only through the use of questionnaires, without confirmation by a psychologist. Third, we recruited only young women, which limits the generalizability of our results. Fourth, we had no information on prenatal and childhood exposure to BPA. Fifth, we had no information on social, cultural and economic factors, quality of life, working conditions, stress, and familiarity for mental illness. Finally, Finally, as in any observational study, potential residual confounding could not be ruled out.

## 4. Conclusion.

In conclusion, our results indicated that BPA exposure, in particular the unconjugated-BPA exposure, was positively related to symptoms of depression in young women. In contrast, BPA was not associated with symptoms of anxiety. Considering the wide use of BPA, further studies are needed to confirm these results.

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## Interdisciplinary Dialogue Chart

By Emiliano Troisi

| Issues covered: | Legal relevance profiles: |
|---|---|
| Exposure to Bisphenol A and its impact on health; particularly, association between BPA exposure and anxious and depressive symptoms in women of reproductive age | 1. Protection of human health and the interests of consumers in relation to the placing on the market in the Community of materials and articles intended to come into contact directly or indirectly with food<br>2. Food safety and restrictions for contaminants in food contact materials.<br><br>***Law***<br>• Reg. (EC) 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety.<br>• Reg. (EC) No 1935/2004 of the European Parliament and of the Council of 27 October 2004 on materials and articles intended to come into contact with food and repealing Directives 80/590/EEC and 89/109/EEC<br>• Reg. (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH)<br><br>• Reg. (EU) 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food.<br>• Reg. (EU) 2018/213 of 12 February 2018 on |

| | |
|---|---|
| | the use of bisphenol A in varnishes and coatings intended to come into contact with food and amending Regulation (EU) No 10/2011 as regards the use of that substance in plastic food contact materials<br>• Dir. (EU) 2020/2184 of the European Parliament and of the Council of 16 December 2020 on the quality of water intended for human consumption.<br>• Commission Implementing Regulation (EU) 321/2011 of 1 April 2011 amending Regulation (EU) No 10/2011 as regards the restriction of use of Bisphenol A in plastic infant feeding bottles<br><br>• Decreto del Ministero della Salute 16 febbraio 2011 'Recepimento della direttiva 2011/8/UE della Commissione del 28 gennaio 2011 che modifica la direttiva 2002/72/CE per quanto riguarda le restrizioni d'impiego del bisfenolo A nei biberon di plastica (11A03727)<br><br>***Soft law***<br>• REACH Restrictions List, or Annex XVII (link to European Chemicals Agency – ECHA: https://echa.europa.eu/it/substances-restricted-under-reach)<br>• EFSA Scientific Opinion 'Re-evaluation of the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs' (https://doi.org/10.2903/j.efsa.2023.6857) |