Mena *et al. J. Environ. Expo. Assess.* **2025**, *4*, 12
DOI: 10.20517/jeea.2025.03

Journal of Environmental Exposure Assessment

Systematic Review

Open Access

Exposure to bisphenols and their relation to diabetes mellitus: a systematic review

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How to cite this article: Mena, M. I.; Lopez-Moro, A.; Mariscal-Arcas, M. Exposure to bisphenols and their relation to diabetes mellitus: a systematic review. *J. Environ. Expo. Assess.* **2025**, *4*, 12. https://dx.doi.org/10.20517/jeea.2025.03

Received: 18 Jan 2025 **First Decision:** 18 Mar 2025 **Revised:** 9 Apr 2025 **Accepted:** 15 Apr 2025 **Published:** 8 May 2025

Academic Editor: Stuart Harrad **Copy Editor:** Ting-Ting Hu **Production Editor:** Ting-Ting Hu

Abstract

Background: Bisphenols (BPs), such as BPA, BPS, BPF, and BPAF, are endocrine disruptors associated with metabolic disorders like diabetes mellitus (DM). This study reviews high-caliber research to evaluate BP exposure's potential link to DM, examining mechanisms, patterns, and demographic differences to inform public health policies.

Methods: Following PRISMA guidelines, studies were sourced from PubMed and Web of Science. Recent human research on bisphenol exposure and diabetes was included, excluding animal and *in vitro* studies. Risk of bias was assessed using the Cochrane tool, and three reviewers selected articles. Ethical approval was not required as secondary data were analyzed.

Results: A total of 277 references were retrieved. After removing 55 duplicates, 126 for not meeting criteria, and 76 for irrelevance, 20 studies were selected**.** The study finds a moderate link between bisphenol exposure and diabetes, stronger in pregnant and obese individuals. Limitations include study design, biomarker variability, and small sample sizes.

Conclusion: This study suggests a potential link between bisphenol exposure and diabetes risk, particularly in obese individuals. Factors like sex, age, and family history may also play a role. However, inconsistencies highlight the need for more rigorous research with standardized methods and better biomarker assessments to confirm

these findings.

Keywords: Bisphenols, diabetes, endocrine disruptors, insulin resistance, hyperglycemia

INTRODUCTION

The endocrine system is fundamental for maintaining health, as it relies on hormones produced by various glands to regulate key body functions. Bisphenols (BPs), a group of endocrine disruptors (EDs), are compounds capable of interfering with hormonal signaling by mimicking natural hormones or blocking their receptors, which can lead to significant metabolic disorders, including diabetes mellitus (DM)[1,2]. Due to their widespread use and potential health impacts, BPs have become some of the most studied EDs, with growing evidence linking them to DM[3,4].

BPs, such as bisphenol A (BPA) and its analogs (BPS, BPF, BPAF), are chemical compounds commonly used in plastics, epoxy resins, and thermal papers. Recent studies have increasingly linked BP exposure to insulin resistance and impaired glucose metabolism, suggesting that BPs could play a key role in the development of DM[5,6].

Despite efforts to limit BPA usage due to safety concerns, its analogs have gained popularity, although their safety profiles remain uncertain. Some recent research suggests that BPA analogs may have similar or even greater endocrine-disrupting effects compared to BPA itself, raising concerns about their potential impact on metabolic diseases like DM. Growing evidence linking BPs to adverse metabolic effects, including their potential role as diabetogenic agents, underscores the clinical relevance of studying their association with DM[7-9].

Human exposure to BPs occurs through various pathways, including ingestion, inhalation, and dermal contact, as well as prenatal and lactational transfer[10,11]. In particular, BPA exposure is widespread due to its presence in everyday products, such as food containers, water dispensers, and thermal receipts[12]. Although BPA has a short biological half-life of approximately 6 h and is primarily excreted through urine, its ubiquitous presence results in constant exposure[13]. Recent advancements in biomonitoring methods have enabled more precise measurements of BP levels in humans, providing further evidence of their pervasive presence in the environment and the human body. In response to accumulating evidence of its adverse effects, regulatory authorities such as the European Food Safety Authority (EFSA) have drastically reduced the tolerable daily intake (TDI) of BPA, although concerns about its analogs persist[14].

DM represents a global health crisis, affecting over 537 million adults worldwide as of 2021, with projections exceeding 643 million by 2030[15]. This disease poses a significant health and economic burden, contributing to millions of deaths annually. While DM is recognized as a multifactorial disease influenced by genetic, lifestyle, and environmental factors, the role of EDs, including BPs, in its etiopathogenesis requires further investigation. While evidence regarding the role of BPs in obesity is more established, their impact on DM remains less clear but clinically significant[16,17].

This study aims to evaluate the association between BP exposure and the onset and progression of DM in human populations. By focusing on high-caliber research, this research aims to identify patterns, explore potential mechanisms, and assess differences among demographic groups, such as by age, sex, and geographical location. Understanding this relationship is crucial to determine whether BPs can be considered diabetogenic agents. This study is particularly important as it seeks to uncover the mechanisms

through which BPs may contribute to the development of DM, which is crucial for informing public health policies aimed at mitigating their impact.

METHODS

This review was conducted in accordance with the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist[18] and has been appropriately registered on Figshare (DOI: 10.6084/m9.figshare.26095504).

Data extraction

The literature search was carried out between February and July 2024. Data were obtained through direct consultation and online access to bibliographic databases in the health sciences, specifically MEDLINE (via PubMed) and Web of Science.

Information processing

To organize and improve the interpretation of the results, the articles were categorized based on study variables, including first author, year of publication, quality index, title, study type, objectives, and findings. The multiplatform program MENDELEY (bibliographic reference manager program) was utilized to refine duplicate records across multiple databases. The search terms were defined by consulting the Thesaurus of Health Sciences Descriptors (DeCS), developed by the Latin American and Caribbean Center for Medical Sciences Information (BIREME), and its equivalent, the Medical Subject Headings (MeSH) from the U.S. National Library of Medicine. Based on the analysis of the hierarchical structure of both the Thesaurus and their indexing records, the following search equations were deemed appropriate, following the PIO format.

Population

Humans (DeSC term): Members of the species Homo sapiens: (((humans[MeSH Terms]) OR (humanos[MeSH Terms])) OR (humans[Title/Abstract])) OR (humanos[Title/Abstract]).

Intervention

Bisphenol, bisphenol A, BPA, bisphenol S, BPS, bisphenol F, BPF, bisphenol AF, BPAF, there are no DeCS term or MeSH equivalence: (((((((Bisphenol[Title/Abstract]) OR (bisphenol A[Title/Abstract])) OR (BPA[Title/Abstract])) OR (bisphenol S[Title/Abstract])) OR (BPS[Title/Abstract])) OR (bisphenol F[Title/Abstract])) OR (BPF[Title/Abstract])) OR (bisphenol AF[Title/Abstract])) OR (BPAF[Title/Abstract]).

Outcomes

DM (DeSC term): Heterogeneous group of disorders characterized by hyperglycemia and glucose intolerance. Insulin Resistance (DeSC term): Decreased effectiveness of insulin in lowering blood sugar levels: 200 units or more of insulin per day are required to prevent hyperglycemia or ketosis. Hyperglycemia has no DeCS term: (((((((diabetes mellitus[MeSH Terms]) OR (Diabetes Mellitus[Title/Abstract])) OR (insulin resistance[MeSH Terms])) OR (Insulin Resistance[Title/Abstract])) OR (Resistencia a la Insulina[MeSH Terms])) OR (Resistencia a la Insulina[MeSH Terms])) OR (Resistencia a la Insulina[Title/Abstract])) OR (Hyperglycemia[Title/Abstract]). The final search query was formulated for use in the MEDLINE database via PubMed, employing the Boolean union (AND and OR) using the filters "Full Text" and "Last 5 Years": (((((humans[MeSH Terms]) OR (humanos[MeSH Terms])) OR (humans[Title/Abstract])) OR (humanos[Title/Abstract])) AND (((((((((Bisphenol[Title/Abstract]) OR (bisphenol A[Title/Abstract])) OR (BPA[Title/Abstract])) OR (bisphenol S[Title/Abstract])) OR (BPS[Title/Abstract])) OR (bisphenol F[Title/Abstract])) OR (BPF[Title/Abstract])) OR (bisphenol AF[Title/Abstract])) OR (BPAF[Title/Abstract]))) AND (((((((diabetes mellitus[MeSH Terms]) OR (Diabetes Mellitus[Title/

Abstract])) OR (insulin resistance[MeSH Terms])) OR (Insulin Resistance[Title/Abstract])) OR (Resistencia a la Insulina[MeSH Terms])) OR (Resistencia a la Insulina[MeSH Terms])) OR (Resistencia a la Insulina[Title/Abstract])) OR (Hyperglycemia[Title/Abstract])) Filters: in the last 5 years.

Final selection of articles

The risk of bias assessment was conducted using the Cochrane risk of bas tool, with assessors blinded to study outcomes[19]. Articles meeting the following criteria were chosen for review and critical evaluation, which was conducted by three of the authors of this manuscript. Data correction was managed through the use of dual tables, which facilitated the detection of discrepancies and their resolution by reconsulting the original sources. To obtain more specific information in the literature search, the inclusion and exclusion criteria applied were as follows: Inclusion criteria: All articles published in the last 5 years were included to use the most recent and up-to-date information possible. All searches were conducted in both English and Spanish to achieve comprehensive international knowledge for this study. Studies that mention some of the most relevant and significant symptoms of the disease, such as hyperglycemia and insulin resistance, were included. Reviews, systematic reviews, meta-analyses, and various observational studies on the effect of bisphenol exposure, measured in urine and/or serum, were included.

Exclusion criteria

Animal studies, *in vitro* research, studies with low methodological quality, those with non-representative samples of the human population, and those that do not control for important confounding factors such as diet or comorbidities will be excluded. Studies that do not distinguish between the different types of BPs (BPA and its analogs), those that do not specifically analyze the relationship between BP exposure and diabetes, and those with incomplete or insufficient results to assess this association will also be discarded. These criteria will ensure that only relevant high-caliber research is included.

Ethical considerations

All data were obtained from the articles selected for review. Therefore, in accordance with Law 14/2007 on biomedical research, ethics committee approval was not necessary for the use of secondary data.

RESULTS

After applying the search criteria, a total of 277 references were retrieved: 118 from MEDLINE (via PubMed) and 159 from Web of Science. After reviewing all the articles, we decided to eliminate 55 articles due to duplicates in the different search sources and 126 articles for not meeting the inclusion criteria or for meeting the exclusion criteria. On the other hand, we also decided to remove 76 articles that did not address the objective of the study, and finally selected 20 studies for results [Figure 1 and Table 1]. Regarding the population, 9 studies were conducted in Asia (mainly in Korea and China), 5 in Europe (Italy, France, and Sweden), 4 in North America (USA and Mexico), 1 in Australia/Oceania, and 1 with a global focus. Regarding the type of analysis, 12 studies assessed bisphenol levels in urine samples, 3 in serum, and the remaining 5 were reviews or meta-analyses. Thus, most of the research comes from Asia and Europe, with a predominant focus on urinary assessment to study bisphenol exposure.

Urine analysis

BPA

Several studies have analyzed the impact of exposure to BPA and its analogs through various pathways of urine measurements. Oliviero *et al.* (2022) found that urinary concentrations of BPS were associated with an increased risk of type 2 diabetes (T2DM), although no consistent associations were found between BPS/BPF and insulin resistance or hyperglycemia[20]. Moon *et al.* (2022), in a cross-sectional study conducted with Korean adults, found a significant association between BPA and DM, especially in men, and between

Table 1. Results of the literature search

Authors	Year	Quality index	Title	Study type	Objectives	Results
(2020-2022)						
Oliviero *et al.*[20]	2022	IF = 5.6 Q1 66/285	Are BPA substitutes as obesogenic as BPA?	Review	Summarize recent data on the metabolic effects of BPA that suggest comparable effects with its analogs used as substitutes	Higher urinary concentrations of BPS have been linked to an elevated risk of T2DM; however, other studies have found no association between BPS or BPF and insulin resistance or hyperglycemia
Moon *et al.*[21]	2022	IF = 6.7 Q1 7/103	Exposure to bisphenol A, S, and F and its association with obesity and diabetes mellitus in general adults of Korea: KoNEHS 2015-2017	Cross-sectional study	Evaluate the associations between bisphenols and obesity and diabetes Adults aged 19 years or older (n = 3780) 49.7% are men, the rest women Self-administered questionnaires were used to indicate diabetes, and only 1/3 of the population had their blood HbA1c measured	A strong association was observed between BPA and diabetes, though after stratifying by gender, the association only exists in men A notable association was also observed between urinary BPS levels and the likelihood of developing diabetes, but only in patients above the LoD
Pérez-Bermejo *et al.*[22]	2021	IF = 4.757 Q2 121/297	The role of the bisphenol A in diabetes and obesity	Review	To examine the potential relationship between BPA and glucose metabolism and insulin resistance, with the aim of understanding its role in the development of diabetes and obesity	Urinary BPA levels were associated with an increased risk of hyperglycemia, obesity, insulin resistance, and higher levels of inflammation markers in humans. These alterations occurred even at low doses of BPA. Differences between sexes were observed in some studies
Farrugia *et al.*[23]	2021	IF = 4.614 Q1 45/182	Bisphenol A and type 2 diabetes mellitus: a review of epidemiologic, functional, and early life factors	Review (N = 27)	The key findings of epidemiological and functional studies on BPA and T2DM are summarized, compared, and analyzed	A positive correlation exists between increased BPA levels and insulin resistance, with a linear relationship observed between BPA exposure and the risk of T2DM. Some studies support a stronger correlation in women, while others show a greater association in men. In other studies, associations are observed but are not statistically significant. Three meta-analyses indicate a positive correlation between elevated BPA levels and insulin resistance and/or the risk of T2DM
Yang *et al.*[24]	2021	IF = 5.190 Q2 87/279	Serum Bisphenol A, glucose homeostasis, and gestational diabetes mellitus in Chinese pregnant women: a prospective study	Prospective study	To determine the associations between serum BPA levels and glucose homeostasis, a study was conducted with 535 pregnant women aged 20 to 40 years from Tangshan, China, between 2013 and 2014	A positive correlation was observed between serum BPA concentrations and elevated levels of fasting glucose, insulin, and HOMA-IR throughout pregnancy, suggesting an increasing trend in the risk of GDM
Lee *et al.*[25]	2021	IF = 13.352 Q1 16/279	Associations of urinary concentrations of phthalate metabolites, bisphenol A, and parabens with obesity and diabetes mellitus in a Korean adult population: KoNEHS 2015-2017	Cross-sectional study	To examine the associations between exposure to BPA and other EDs and the prevalence of obesity and DM using national biomonitoring data Participants: Adults aged 19 years or older (n = 3780). Korea, 2015-2017	Applying the CAS method, the fourth quartile of BPA was associated with a higher likelihood of DM compared to the first quartile
Taheri *et al.*[27]	2021	IF = 5.190 Q2 87/279	Bisphenol A exposure and abnormal glucose tolerance during pregnancy: systematic review and meta-analysis	Systematic review and meta-analysis (n = 7)	To investigate whether there is an association between exposure to BPA during pregnancy and the risk of GDM and IGT	The results did not show a significant relationship between BPA exposure and GDM. Similarly, no significant association was observed between BPA exposure and the risk of IGT. Subgroup analysis based on BMI did not alter the results. No heterogeneity was observed among the studies

Rotondo *et al.*[28]	2020	IF = 6.081 Q1 65/295	Endocrine-disrupting chemicals and insulin resistance in children	Review	Review the evidence linking background exposure to EDCs with insulin resistance in children	A meta-analysis of cross-sectional and prospective studies showed significant associations between BPA levels, along with other EDCs, and prevalent diabetes. Similar findings were also observed in a cross-sectional study
Predieri *et al.*[26]	2020	IF = 5.924 Q1 67/295	Endocrine disrupting chemicals and type 1 diabetes	Review (n = 65)	To summarize the existing evidence on the potential role of exposure to EDCs in the development of DM	In 2018, children (n = 50) with T1DM had higher mean urinary BPA concentrations compared to controls (n = 50), although the values were not statistically significant In adults from NHANES (n = 1455), increased urinary BPA concentrations were linked to higher fasting glucose and insulin levels, suggesting a potential link with T2DM
Filardi *et al.*[30]	2020	IF: 5.719 Q1 17/88	Bisphenol A and Phthalates in diet: an emerging link with pregnancy complications	Review	To gather the existing evidence linking BPA and phthalates with various complications in pregnancy, such as GDM, among others	Urinary BPA levels during pregnancy were positively associated with high post-load glucose levels. Additionally, BPA in urine measured during the first two trimesters of pregnant women with overweight and/or obesity was associated with high post-load glucose levels. However, a cohort study showed controversial results. A positive correlation exists between BPA, inflammation, and markers of oxidative stress during early pregnancy, which may contribute to the development of GDM and T2DM
(2017-2019)						
Song *et al.*[31]	2019	IF = 4.872 Q1 11/92	Serum concentrations of bisphenol A and its alternatives in elderly population living around e-waste recycling facilities in China: Associations with fasting blood glucose	Cohort study	Investigating the associations between fasting blood glucose levels and exposure to air pollution in three villages located in waste recycling areas (n = 119, including 46 men) compared to a reference village (n = 6 men), among adults in Qingyuan, China	Exposure to BPA is linked to abnormal fasting blood glucose levels in individuals residing in areas involved in electronic waste recycling. Specifically, BPA is linked to abnormal FBG levels but not with other BP. BPAF was associated with hypoglycemia in participants from recycling areas. No significant gender-related differences were observed. A negative correlation was found between serum BPAF concentration and fasting blood glucose levels
Wang *et al.*[32]	2019	IF = 7.518 Q1 10/143	Urinary bisphenol A concentration and glucose homeostasis in non-diabetic adults: a repeated-measures, longitudinal study	Cohort study	Investigating the relationship between BPA exposure and glucose homeostasis in non-diabetic individuals. Chinese population (n = 2336), middle-aged and elderly (average age of 60 years), predominantly women. Study duration from 2009 over 4 years. Urinary BPA levels were measured	Urinary BPA was strongly linked to fasting hyperglycemia, elevated FPG, and reduced HOMA-B in non-diabetic women, regardless of menopausal status. These associations were stronger in women who were obese or overweight. No significant associations were found in men. The associations remained robust in multiple sensitivity analyses
Rancière *et al.*[33]	2019	IF = 8.341 Q1 11/265	Exposure to Bisphenol A and Bisphenol S and Incident Type 2 Diabetes: A Case-Cohort Study in the French Cohort D.E.S.I.R.	Case-control study	To explore the potential association between exposure to BPA and BPS and the incidence of type 2 diabetes, two measurements were taken: at baseline and at year 3, in a cohort from the French DESIR study. The cohort consisted of 755 individuals, with 53% women and the remainder men, aged between 30 and 65 years. Participants were followed for 9 years. Urine samples were collected to measure BPA-G and BPS-G levels	No meaningful associations were observed between BPA-G and the incidence of diabetes at the beginning of the study; however, positive associations were observed at year 3. A positive correlation was observed between BPS-G and the onset of diabetes at year 3. The associations between BPS and diabetes were stronger in women, particularly those who were obese or overweight at the beginning, aged over 50 years, and with a family history of diabetes
Murphy *et al.*[34]	2019	IF = 3.056 Q2 99/265	Exposure to bisphenol A and diabetes risk in Mexican women	Case-control study	To assess the relationship between BPA exposure and diabetes, 70 diabetic women and 334 non-diabetic women from northern Mexico from 2007-2011	Urinary BPA concentrations were correlated with age. Therefore, after adjusting for age, urinary BPA was associated with diabetes

Zhang *et al.*[36]	2019	IF = 3.644 Q2 54/143	Exposure to bisphenol A substitutes and gestational diabetes mellitus: a prospective cohort study in China	Cohort study	To examine the relationship between urinary levels of BPA, BPS, BPF, and BPAF with the risk of GDM and glucose concentrations, a study was conducted with 1,841 pregnant women in Wuhan, China, in 2013 and 2015	Significant association between BPAF and increased risk of GDM in women of normal weight No significant associations between BPA, BPS, and BPF with GDM BPAF and BPS were associated with increased levels of FPG; for BPS, this association was significant only in women carrying female fetuses
Wang, *et al.*[37]	2018	IF = 4.991 Q1 3/157	Urinary bisphenol A concentration and gestational diabetes mellitus in chinese women	Cohort study	To examine the relationship between GDM and urinary BPA concentrations in pregnant women. 620 pregnant women from China, between 2012 and 2013	Only 12.7% of the mothers were diagnosed with GDM The probability of GDM decreased by 60% in mothers with higher concentrations of BPA. In other words, high concentrations of BPA are associated with a reduction in the likelihood of GDM
Duan *et al.*[35]	2018	IF = 5.714 Q1 25/251	Association of urinary concentrations of bisphenols with type 2 diabetes mellitus: a case-control study	Case-control study	To examine the relationship between urinary concentrations of bisphenols (BPA, BPS, BPF, and BPAF) and the risk of T2DM, using different statistical models. (*n* cases = 251, *n* controls = 251)	The concentrations of BPAF, BPS, and BPA in cases were significantly higher than in controls. There were no significant differences between cases and controls for BPF and BPA concentrations In categorical statistical models, a high probability of T2DM was observed in the second and third quartiles of BPA
Lee *et al.*[38]	2018	IF = 7.943 Q1 8/251	Bisphenol A exposure through receipt handling and its association with insulin resistance among female cashiers	Cross-sectional study	To assess the contribution of dermal exposure to BPA among female shop assistants who handle cash registers and examine the association between BPA exposure and clinical biomarkers linked to metabolic syndrome Adult women (*n* = 54) in Korea, from November to December 2016	After a shift without using gloves, urinary BPA levels were higher (almost double) compared to measurements taken before the shift. These levels increased significantly with longer shift durations. However, when gloves were used, the BPA concentrations before and after the shift were very similar. BPA levels showed a significant association with fasting insulin in adjusted models
Lind *et al.*[39]	2018	IF: 7.113 Q1. 12/145	Endocrine-disrupting chemicals and risk of diabetes: an evidence-based review	Review	To analyze the existing evidence on the relationship between exposure to environmental endocrine-disrupting chemicals, diabetes, and disruptions in glucose metabolism	Cross-sectional evidence was found for a significant relationship between prevalent diabetes and levels of dioxins, PCBs, organochlorine pesticides, and BPA
Kataria, *et al.*[29]	2017	IF = 3.123 Q1 16/124	Exposure to bisphenols and phthalates and association with oxidant stress, insulin resistance, and endothelial dysfunction in children	Cross-sectional study	To assess descriptive, univariable, and multivariable associations between urinary metabolites of bisphenols and phthalates with oxidative stress, insulin resistance, body mass, and endothelial dysfunction Healthy children (*n* = 41), aged 10-13 years, from the metropolitan area of New York	Only 8 children showed insulin resistance (HOMA-IR) There was no significant association between bisphenols and their association with body weight and insulin resistance. An increase of one logarithmic unit in BPA concentration was linked to higher levels of F2-isoprostane, a reliable indicator of oxidative stress A significant correlation was identified between BPS and the albumin-to-creatinine ratio

BPA: Bisphenol A; BPS: bisphenol S; BPF: bisphenol F; T2DM: type 2 diabetes mellitus; LoD: limit of detection; KoNEHS: Korean National Environmental Health Survey; HbA1c: hemoglobin A1c (glycated hemoglobin); HOMA-IR: homeostasis model assessment of insulin resistance; GDM: gestational diabetes mellitus; EDs: endocrine disruptors; DM: diabetes mellitus; CAS: chemical abstracts service; IGT: impaired glucose tolerance; BMI: body mass index; EDCs: endocrine-disrupting chemicals; T1DM: type 1 diabetes mellitus; NHANES: National Health and Nutrition Examination Survey; FBG: fasting blood glucose; BP: Bisphenol; BPAF: bisphenol AF; FPG: fasting plasma glucose; HOMA-B: homeostasis model assessment of beta-cell function; BPA-G: bisphenol A glucuronide; BPS-G: bisphenol S glucuronide; PCBs: polychlorinated biphenyls; GDM: gestational diabetes.

urinary BPS levels and DM in patients above the detection limit (LoD)[21]. Pérez-Bermejo *et al.* (2021), in reviewing the relationship between BPA and glucose

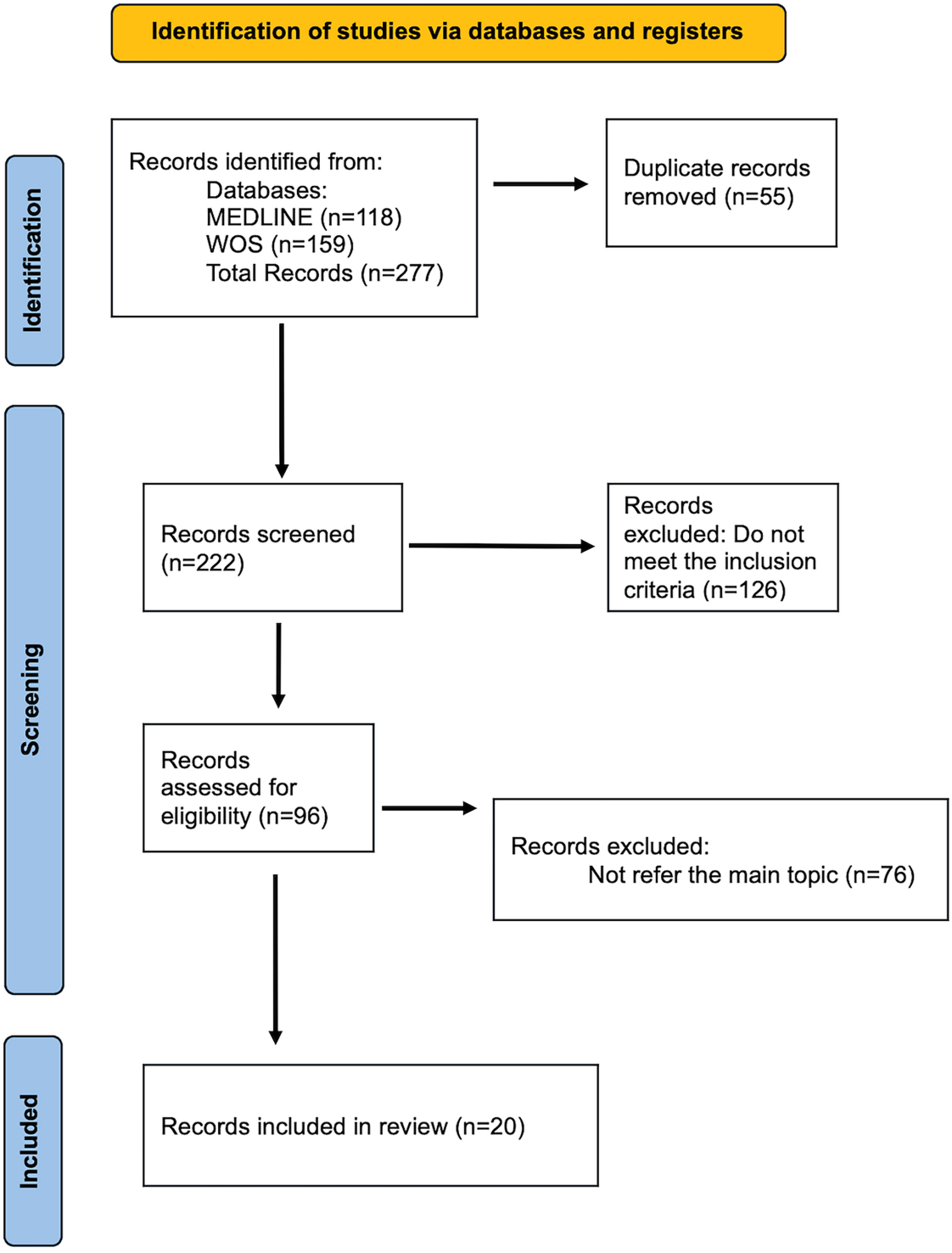

Figure 1. Study identification and selection.

metabolism, found that urinary BPA levels were associated with an increased risk of hyperglycemia, obesity, insulin resistance, and elevated inflammation markers, even at low BPA doses[22]. Meanwhile, Farrugia *et al.* (2021), after reviewing 27 studies, observed a positive correlation between elevated BPA levels and insulin resistance, emphasizing a linear relationship between BPA exposure and the risk of T2DM, although the associations differed based on the participants' sex[23].

Serum analysis

BPA. Studies examining BPA exposure in serum have provided important findings about its association with diabetes. In the prospective study by Yang *et al.* (2021) conducted with Chinese pregnant women, they found that serum BPA concentrations were associated with elevated fasting glucose and insulin levels throughout pregnancy, indicating a higher risk of gestational diabetes (GDM)[24]. Lee *et al.* (2021), in a cross-sectional study with Korean adults, found that the fourth quartile of BPA urinary concentration was associated with a higher likelihood of DM compared to the first quartile[25].

Inconclusive or negative studies

Some studies have not found clear associations between BPA exposure and diabetes. Predieri *et al.* (2020), in their review of EDs and type 1 diabetes (T1D), observed that children with T1D had higher mean urinary BPA concentrations than controls, but the values were not statistically significant. In adults, a relationship was found between elevated urinary BPA levels and fasting glucose and insulin[26]. Taheri *et al.* (2021), in a systematic review and meta-analysis, did not find a significant relationship between BPA exposure and GDM or impaired glucose tolerance (IGT), even when analyzing subgroups based on body mass index (BMI)[27].

Studies in children

Insulin resistance and oxidative stress

In the case of children, Rotondo *et al.* (2020) reviewed the evidence on ED exposure and insulin resistance in children and found that BPA levels, along with other EDs, were associated with prevalent diabetes and insulin resistance[28]. Kataria *et al.* (2017), in their cross-sectional study with children, did not find a significant association between BPs and body weight or insulin resistance, but observed a relationship between BPA and oxidative stress[29].

Studies in other demographic groups

Other studies have examined the relationship between BPA and diabetes in different demographic groups. Filardi *et al.* (2020) found that urinary BPA levels during pregnancy were associated with high post-load glucose levels, especially in women with overweight or obesity, suggesting a link to GDM and T2DM[30]. Song *et al.* (2019), in a cohort study conducted in China, found that BPA exposure was associated with abnormal fasting glucose in areas with electronic waste recycling, while BPAF was associated with hypoglycemia in those areas[31]. Wang *et al.* (2019), in a longitudinal study, found that urinary BPA was significantly associated with fasting hyperglycemia in non-diabetic women, especially those with overweight or obesity[32]. Rancière *et al.* (2019), in a case-control study, did not find significant associations between BPA glucuronide (BPA-G) and incident diabetes at the beginning of the study, but positive associations were found in the third year. Stronger associations were found between BPS and diabetes in women, especially those who were obese and over 50 years old at baseline with a family history of diabetes[33]. Murphy *et al.* (2019) found that after adjusting for age, urinary BPA concentrations were associated with diabetes in Mexican women[34]. Duan *et al.* (2018), in their case-control study, found that concentrations of BPAF, BPS, and BPA were significantly higher in cases of T2DM than in controls, with a high probability of T2DM in the highest quartiles of BPA[35].

Studies in pregnant women

Damages: GDM

In a prospective study conducted by Zhang *et al.* (2019) with 1,841 pregnant women in Wuhan, China, a significant association was found between BPAF and an increased risk of GDM in women with normal weight. However, no significant associations were found between BPA, BPS, or BPF and GDM. Additionally, BPAF and BPS were associated with higher fasting plasma glucose (FPG) levels, with this association being significant only in women carrying female fetuses[36]. On the other hand, Wang *et al.* (2018), in their study with 620 pregnant women in China, found that higher urinary concentrations of BPA were associated with a 60% decrease in the probability of developing GDM, suggesting an inverse relationship, where higher levels of BPA were associated with a lower likelihood of GDM[37].

Dermal exposure studies

Lee *et al.* (2018), in a study on dermal BPA exposure among Korean cashiers, found that BPA urinary levels were higher after a shift without gloves and showed a significant association with fasting insulin in adjusted models[38]. Lind *et al.* (2018), in their review, found a significant relationship between prevalent diabetes and BPA levels, as well as with other EDs[39].

DISCUSSION

Introduction to BPs and diabetes

A wide range of BPs, including BPA, BPS, BPF, and BPAF, have been associated with metabolic disorders, including diabetes. The goal of this review is to find out whether these BPs play a role in the epidemiology of DM. The reviewed material lays the groundwork for more detailed studies of the mechanisms whereby BPs may act to alter glucose metabolism, insulin resistance, and diabetes. It is suggested that these BP compounds act as EDs, which explains the relationships; however, this review seeks to explain how BPs affect metabolism more specifically. It is hoped that through high-caliber research, this work will clarify the issues of the effect of BP exposure on DM and point out the gaps in knowledge to be researched. A total of 7 reviews, one meta-analysis, 5 cohort studies, 3 case-control studies, and 4 cross-sectional studies were identified in the reviewed literature.

Association between bisphenol exposure and diabetes

As can be noted, the outcome measures generated appear to be quite heterogeneous. Overall association patterns linking diabetes and exposure to BPs using fasting hyperglycemia, insulin resistance, or increased risk of T2DM or GDM showed positive links in the majority of the studies reviewed (n = 20)[20-22]. On the contrary, some authors[27,36] claimed that BPA exposure and diabetes or metabolic outcomes were not significant. Several substantial reports, including those by others[29,34,35,37], suggest that while a link between bisphenol exposure and diabetes may exist, it appears weak in certain populations and may depend on the methods or biomarkers utilized. These findings are preliminary and modest at best, but they do point toward a possible positive link between the probability of diabetes and exposure to bisphenol, and therefore, more studies should be done to further explain and hopefully settle these associations. This association is biologically plausible, as DM involves disruptions in glucose metabolism and insulin homeostasis, and various studies have confirmed links between bisphenol exposure and metabolic alterations[40].

Specific population studies and findings

Several studies have reported positive associations between BPA exposure and DM in specific demographic subgroups, such as by age, sex, or other characteristics. For instance, a longitudinal cohort study[37] found that BPA exposure was associated with increased fasting hyperglycemia before the onset of diabetes and elevated FPG levels in adults, particularly older adults. Interestingly, these associations were only significant in women. This sex-specific finding could reflect biological or hormonal differences in how BPA is

metabolized, rather than being solely attributable to the higher proportion of women in the study (1,467 women versus 869 men). The study further noted that the associations were more pronounced among women classified as obese or overweight. In contrast, Rancière *et al.* (2009) examined a diverse sample with nearly equal numbers of women and men but did not observe any statistically significant interactions between BPs (BPA and BPS) and sex ($P > 0.05$)[33]. Thus, the evidence does not conclusively support stronger links between BPs and DM in women compared to men. Moreover, the limited number of recorded events in the study may affect the reliability of these results. Consistent with the findings of Wang *et al.* (2019), bisphenol exposure was linked to an increased risk of DM in specific subgroups[32]. Rancière *et al.* also highlighted that factors such as BMI, age, and family history of diabetes seemed to influence the relationship between BPS exposure and the onset of DM[33]. Notably, the risk of developing DM was higher among participants who were overweight or obese at the start of the study, those younger than 50 years, or those with a family history of diabetes. However, these interactions were not statistically significant ($P > 0.05$), so no firm conclusions can be drawn regarding stronger associations in obese or overweight individuals compared to those with normal weight. On the topic of sex differences, conflicting results have been reported. For example, Moon *et al.* (2022) found significant positive associations between BPA, BPS exposure, and DM, as well as obesity[21]. However, when analyzing by gender, they discovered that the positive associations between BPA and DM were present only in men. It has been suggested that these potential sex differences might stem from interactions between BPA and endogenous sex hormones, such as through estrogenic and androgenic signaling pathways. Nevertheless, the results remain inconsistent, with some studies indicating stronger associations in women, while others report them only in men. These inconsistencies highlight the need for further research to understand how sex differences influence the harmful effects of BPs, including exploring possible mechanisms related to hormone signaling pathways[41].

In summary, the variability in results across studies points to the importance of considering demographic characteristics such as sex, age, BMI, and family history when investigating the relationship between BPs and DM. Further research is necessary to clarify these associations and explore the underlying mechanisms, particularly those related to sex hormones.

The role of obesity and genetic factors

Therefore, it is inferred that it is not clear whether there are gender associations, and it is also suggested that age, genetic predisposition, overweight, and obesity are key factors to consider in the incidence of DM. Regarding the latter, in April 2022, a dose-response meta-analysis found robust results confirming that BPA exposure can increase the risk of obesity and overweight epidemics in children and adolescents[42]. Similarly, Wu *et al.* (2020), in a systematic review and meta-analysis, found a positive correlation between BPA levels and the risk of obesity[43]. Precisely, this obesogenic role of BP could have significant implications in the onset of diabetes, as obesity is a risk factor that can lead to T2DM[44].

Challenges in study design

One of the limitations found in the majority of studies is the method used to measure biomarkers of exposure to BP. Most studies use urinary BP measurements as a method to assess exposure, while others measure BP in serum to quantify exposure. It is important to note that using different exposure markers leads to a limited biological interpretation. It is not known with certainty whether exposure to BPA is detectable in serum concentrations of BPA[45], as oral exposure leads to rapid metabolism and subsequent elimination in the urine as conjugates, given that BPA is a lipophilic compound and its free form is insoluble in water[46].

It has been documented that transdermal and sublingual absorption of BPA can occur; thus, in these cases, the compound would not be completely metabolized[47,48]. However, it appears that free BPA levels are not detectable in the general population through serum measurements. According to Teeguarden *et al.* (2011), BPA undergoes nearly complete renal elimination, suggesting that urinary BPA measurement is a useful biomarker for assessing human exposure to BPA[49]. Most studies utilize urinary BPA measurements as a biomarker because they are easy to collect and have a lower risk of contamination. Nine studies found significant links between urinary BPA levels and metabolic risks, including hyperglycemia, obesity, insulin resistance, T2DM, or GDM[20-23,30,32,34,35,38], while two studies did not find any significant relationships[27,29]. In terms of serum BPA, two studies reported positive associations with insulin resistance and fasting glucose[24,38], while one study did not find consistent connections[31].

Limitations of study designs and sample sizes

One significant limitation found in the majority of studies is the lack of consideration for the time of day and the frequency of sample collection, which can lead to erroneous classification of BPA exposure levels, thus attenuating the association between BPA and the findings obtained. During the 9-year duration of the case-control study by Ranciére *et al.* (2019), urine and blood samples were collected only at 4 time points, corresponding to visits at baseline, the third year, sixth year, and ninth year, showing an association between BPA and BPS and incident DM at the 3-year mark[32]. However, this collection method may not accurately represent long-term exposure to these BPAs. Ye *et al.* (2011) collected 427 urine samples over 7 consecutive days from 8 individuals, considering factors such as food intake, beverages, and medications, among others, and observed significant interindividual and intraindividual variability in urinary BPA concentrations, both in samples collected on a single day and those collected over 7 days[50]. Therefore, due to the variability in absorption, metabolism, and elimination in individual participants, urinary concentrations of BPA can significantly fluctuate throughout the day. Hence, it is recommended to record the time of sample collection in biomonitoring studies and to consider other confounding factors such as previous dietary intake, the time of sample collection relative to meals, and the elapsed time since food consumption, among others[50,51].

Small sample sizes and limited generalizability

Several studies are limited by small sample sizes, which can lead to findings that are not representative of the general population. For example, in the study by Song *et al.* (2019), only 119 subjects living in villages near electronic waste recycling areas were included, of whom only 46 were males[31]. This study indicated a link between elevated BPA concentrations and abnormal fasting glucose levels, compared to only 6 male subjects from control areas distant from recycling sites. The small number of participants in the control group undermines the reliability and representativeness of the results. Similarly, Kataria *et al.* (2017) did not find associations between urinary BP concentrations and insulin resistance in 41 healthy children from the New York area, which contradicted expected outcomes, possibly due to the limited sample size as explained by the authors[29]. In contrast, Moon *et al.* (2022) demonstrated a link between BPA and BPS with diabetes and obesity in a large, representative sample of 3,780 adult Korean participants, where the gender proportion was equitable[21].

Specific population groups and limitations

There are also studies that have focused solely on specific population groups. For instance, Murphy *et al.* (2019) in a case-control study linked urinary BPA levels to a higher risk of DM in a group of Mexican women, making these findings not generalizable to the broader population[34]. This study also highlights a significant limitation regarding the method of DM diagnosis, as it relied on self-reported information from participants without initial diagnostic testing to confirm the presence of diabetes. While this approach reduces costs, participants may have made dietary or lifestyle changes after being diagnosed with DM,

potentially influencing BPA exposure and introducing errors in associations[33]. Additionally, there's a possibility that undiagnosed diabetic individuals were inadvertently included in the control group, leading to partially biased associations. This was noted by Jung *et al.*, who found that 35% of subjects were unaware of their diabetic status from 2016 to 2018[52].

Diverse study designs and findings

In a longitudinal study published by Wang *et al.* (2019), they explored the relationship between BPA exposure and disruptions in glucose homeostasis among 2,356 non-diabetic individuals[32]. By selecting a sample of healthy participants, potential biases related to lifestyle changes and treatment after diabetes diagnosis were indirectly mitigated. Moreover, this study provided new insights into BPA's impact on glucose homeostasis even within normal blood glucose ranges. Therefore, it is recommended to use diagnostic tests for DM to confirm diagnoses more reliably and avoid potential errors in study outcomes[31].

It appears that the studies reviewed encompass a variety of designs and age groups, providing a comprehensive look into the association between BPA and DM. Specifically, Rotondo *et al.* (2020) linked BPA exposure in healthy children to prevalent DM and insulin resistance[28]. Similarly, Predieri *et al.* (2020) found that children with type 1 diabetes mellitus (T1DM) exhibited higher concentrations of BPA compared to healthy children[26]. The review also includes other study designs, such as cross-sectional or prevalence studies, as well as observational studies like case-control studies - for example, Duan *et al.* (2018) demonstrated higher concentrations of total BP, BPS, and BPAF in cases compared to controls[35]. Furthermore, prospective studies, such as Zhang *et al.*'s (2019), found that BPS and BPAF were associated with increased fasting glucose levels in pregnant women, although statistically significant associations with GDM were not found for BPA, BPS, and BPF[36]. However, Yang *et al.* (2021) reported that serum BPA was associated with higher levels of fasting glucose, insulin, and HOMA-IR in pregnant women. These studies collectively highlight various aspects of BPA exposure and its potential links to different forms of diabetes across diverse populations and age groups, contributing to a broader understanding of the association between BPA exposure and DM[24].

Research gaps and the need for prospective studies

The research on BPs, particularly BPA, and their potential association with DM suggests significant hypotheses, yet does not establish causality due to the observational nature of most studies. The lack of prospective research linking BPs with DM limits definitive cause-and-effect conclusions. Prospective studies with large, diverse populations and extended durations are needed but face logistical challenges and costs. Intervention studies in humans are impractical and unethical, emphasizing reliance on observational data. Additionally, chronic exposure to a variety of EDs, including BPA and its analogs like BPS, BPF, and BPAF, may lead to cumulative effects beyond individual substance thresholds. Current regulatory frameworks often focus on BPA alone, neglecting other potentially harmful BPs. Establishing realistic and safe acceptable daily intakes (ADIs) for BPA and its analogs is crucial, considering both individual and combined effects in future research. Scientific evidence supports an association between BPA exposure and DM, with emerging links to other BPs, albeit requiring further robust study designs. Environmental factors, including ED exposure, are increasingly recognized as significant contributors to diabetes incidence, mortality, and associated costs. Addressing these factors collectively can potentially mitigate the diabetes epidemic and redirect resources toward societal needs. In conclusion, ongoing research should aim to clarify the relationships between BPs and chronic metabolic diseases like DM. This endeavor holds promise for reducing disease burden, improving quality of life, and optimizing resource allocation for broader societal benefit.

Strengths of the study

Comprehensive Review: The study conducts an exhaustive review that includes various study designs and age groups, providing a broad perspective on the association between BPs, especially BPA, and DM. Inclusion of Diverse Study Types: The review encompasses reviews, meta-analyses, cohort studies, case-control studies, and cross-sectional studies, enriching the understanding of how BPA exposure relates to different forms of diabetes in diverse populations. Studies in Young Populations: Specific studies highlighting associations between BPA exposure and DM in children, such as those by Rotondo *et al.* (2020) and Predieri *et al.* (2020), are emphasized, providing valuable insights into the effects of early BPA exposure[26,28].

Limitations of the study

Observational Nature of Studies: Most reviewed studies are observational, preventing the definitive establishment of causality between BP exposure and DM. The lack of prospective studies limits the ability to draw firm conclusions about cause-and-effect relationships. Limitations in Biomarker Measurement: There is variability in the methods used to measure BP exposure biomarkers across studies. Some use BPA measurements in urine while others use serum, which may introduce biases in exposure assessment and complicate direct comparisons between studies. Small Sample Sizes in Some Studies: The inclusion of small samples in certain studies limits the generalizability of findings to broader populations. This is evident in studies focused on specific demographic groups, such as the study by Murphy *et al.* (2019) on Mexican women, which may not adequately represent the general population's susceptibility to health impacts related to BPA. In addition, despite considering the possibility of conducting a meta-analysis, it was decided that a meta-analysis may not be necessary due to the diversity of the studies and their varied methodologies and objectives[34].

Conclusion

Exposure to various BPs, such as BPA, BPS, BPF, and BPAF, has been associated with metabolic disorders, including DM. The results of most of the studies reviewed suggest a positive relationship between exposure to these compounds and an increased risk of diabetes, although some associations are weak or inconsistent.

While some studies have reported stronger associations in women, others indicate that these links could depend on factors such as overweight, obesity, age, and genetic predisposition. However, it has not been conclusively confirmed whether sex significantly influences the relationship between BPs and diabetes.

Obesity is identified as an important factor that could amplify the adverse effects of bisphenol exposure on diabetes, as several studies suggest that obesity may increase the risk of T2DM associated with these compounds.

Current findings are preliminary, so further research with prospective designs, larger samples, and standardized methodologies is needed to better understand how BPs affect metabolism and diabetes. It is also important to investigate the interaction of BPs with other endocrine factors, such as sex hormones.

Urinary BPA biomarkers are generally more useful for assessing exposure as they allow for sample collection with a lower risk of contamination compared to serum measurements. However, interindividual and intraindividual variability in urinary BPA levels must be considered when interpreting the results.

Since exposure to BPs is associated with a higher incidence of diabetes and other metabolic disorders, it is essential for public policies to consider stricter regulation of products containing BPs and explore safer alternatives to reduce human exposure to these compounds.

In summary, while there are links between BPs and diabetes, the findings are inconsistent, and further research is required to fully understand the mechanisms involved and their implications for public health.

DECLARATIONS

Acknowledgments

This paper will be part of Alejandro Lopez-Moro's doctoral thesis, completed within the "Nutrition and Food Sciences Program" at the University of Granada, Spain.

Authors' contributions

Study design: Mariscal-Arcas, M.
Data collection and analysis: Mena, M. I.; Lopez-Moro, A.
Data interpretation and manuscript preparation: Lopez-Moro, A.; Mena, M. I.; Mariscal-Arcas, M.
All authors reviewed and approved the final manuscript.

Availability of data and materials

There are restrictions on the availability of data for this trial due to the signed consent agreements around data sharing, which only allow access to external researchers for studies following the project's purposes. Requestors wishing to access the trial data used in this study can make a request to corresponding author.

Financial support and sponsorship

This study was funded by the High Council for Sports (CSD), Spanish Ministry of Culture and Sport, through the NESA NETWORK "Spanish Network of Sports Care at Altitude" Ref. 19/UPB/23. This research was supported by an FPU grant from the Spanish University Ministry to Alejandro Lopez-Moro (FPU20/00210).

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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