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Exposure to obesogenic endocrine disrupting chemicals and obesity among youth of Latino or Hispanic origin in the U.S. and Latin America: a lifecourse perspective

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Abbreviations:

U.S.: United States; EDCs: endocrine disrupting chemicals; CHAMACOS: Center for the Health Assessment of Mothers and Children of Salinas; ELEMENT: Early Life Exposure in Mexico to Environmental Toxicants; POPs: persistent organic pollutants; PFAS: perfluoroalkyl substances; DDT: dichlorodiphenyltrichloroethane; DDE: dichlorodiphenyldichloroethylene; OPs: organophosphorous pesticides; PBDEs: polybrominated diphenyl ethers; BMI: body mass index; PFOA: perfluorooctanoate; PFNA: perfluorononanoate; PFHxS: perfluorohexane sulfonate; MCPP: mono-(3-carboxylpropyl) phthalate; DAP: dialkyl phosphate; PON1: paraoxonase 1; PFOS:

perfluorooctane sulfonate; DEP: diethyl phthalate; DBP: dibutyl phthalate; DEHP: di(2-ethylhexyl) phthalate; CCCEH: Columbia Center for Children's Environmental Health; MiBP: mono-isobutyl phthalate; MBP: mono-n-butyl phthalate: MBzP: monobenzyl phthalate; BPA: bisphenol A; MEP: monoethyl phthalate; MEHP: mono(2-ethylhexyl) phthalate; NHANES: National Health and Nutrition Examination Survey; DiBP: diisobutyl phthalate; BBzP: butylbenzyl phthalate; PAHO: Pan-American Health Organization.

ABSTRACT

Following a 2019 workshop led by the Center for Global Health Studies at the Fogarty International Center on the topic of childhood obesity prevention and research synergies transpiring from cross-border collaborations, we convened a group of experts in the U.S. and Latin America to conduct a narrative review of the epidemiological literature on the role of obesogenic endocrine disrupting chemicals (EDCs) in the etiology of childhood obesity among Latino youth in the U.S. and Latin America. In addition to summarizing and synthesizing results from research on this topic published within the last decade, we place the findings within a lifecourse biobehavioral framework to aid in identification of unique exposure-outcome relationships driven by both biological and behavioral research; identify inconsistencies and deficiencies in current literature; and discuss the role of policy regulations, all with the goal of identifying viable avenues for prevention of early life obesity in Latino/Hispanic populations.

1. INTRODUCTION

The World Health Organization estimates that obesity worldwide has tripled since the 1970s,[1] with 62% of adults categorized as overweight or obese in the Americas. The high prevalence of obesity has spared no age group, including young children.[2,3] Obesity during early life is concerning due to the short-term metabolic and psychosocial consequences of excess adiposity, as well as the lifelong implications for cardiometabolic disease risk.[4–6]

In the U.S., children and adolescents of Latino/Hispanic descent have approximately two-fold higher prevalence of obesity than their White counterparts.[7] While the root causes of this discrepancy are multifaceted, socioeconomic and ethnic inequities are key drivers. In Latin America, many countries are undergoing the epidemiological transition, related to a process of modernization and urbanization that coincides with increased life expectancy.[8] The industrial advancements occur in concomitance with reduced physical activity and higher intake of processed foods, foods high in calories, unhealthy fats and refined carbohydrates, and exposure to harmful chemicals used in food processing and wrapping[9] – a parallel process known as the nutrition transition.[10] Together, these shifting patterns result in rising rates of obesity and obesity-related chronic disease.[11] Beyond diet and other lifestyle factors, Latino/Hispanic populations have higher prevalence of some genetic polymorphisms that place them at greater risk of obesity-related disease – a topic reviewed in detail elsewhere.[12] Thus, in all populations but especially those in Latin America, it is important to identify risk factors and preventive strategies as early as possible.[13]

Nearly two decades ago, Baillie-Hamilton postulated the hypothesis that synthetic chemicals disrupt weight-control mechanisms and may be a cause of obesity.[14] These chemicals, known as obesogenic endocrine disrupting chemicals (EDCs) or "obesogens",[15,16] have been of increasing interest in recent years. Some EDCs are short-lived, with half-lives of days to months (e.g., bisphenol A and phthalates), while others are long-lived and can persist in the environment or *in vivo* for years (e.g., per- and polyfluoroalkyl subtances).[17] Although EDCs were initially developed for beneficial uses such as improvements in agricultural output (e.g., pesticides), enhanced safety of common household items (e.g., flame retardants in upholstery), and personal care (e.g., phthalates in soaps and shampoos), excessive exposure to these chemicals is a negative aspect of industrialization and globalization. Because of their endocrine-mimicking properties, EDCs can disrupt hormone biosynthesis, lipid metabolism and adipogenesis to promote weight gain and obesity[15,18,19] through numerous pathways, including but not limited to the following: activating peroxisome proliferator activated receptors;[20,21] disrupting the biosynthesis and function of sex steroid hormones;[22–24] altering thyroid function;[25,26] and impacting mechanisms that control appetite and satiety,[20,27,28] as summarized in **Supplemental Table 1**. Moreover, as shown in **Figure 1**, the impact of EDC exposure may be larger during vulnerable developmental life stages characterized by rapid growth and development, including the *in utero* period (exposure to the fetus via the mother's environment), infancy (exposure to the infant via the mother during breastfeeding, as well as the infant's own exposure via food/formula containers and household products), early

childhood (exposure to the child via diet and other aspects of the environment), and puberty (exposure to the child via diet and environmental exposure).[29]

The objectives of this narrative review are threefold. Our first goal is to review current evidence regarding the effects of early life EDCs exposure on obesity and body composition among youth in Latin America and U.S. youth of Latino/Hispanic descent. Our second goal is to place study findings within a lifecourse framework given the relevance of developmental stages vulnerable to environmental exposures. Our final goal is to discuss avenues for preventive efforts, with a specific focus on policy regulation given the potential for wide-ranging impact.

2. METHODS

This narrative review considers recent epidemiological studies examining the impact of exposure to EDCs on obesity and related measures of fat mass and distribution from birth through adolescence. We focused on original research studies published from January 1st, 2010 to January 31st, 2020 and restricted articles to human studies of EDC exposure in relation to obesity-related outcomes. We considered both cross-sectional and prospective study designs. Given our focus on Latino populations, we only included studies of youth in Latin American countries or those in the U.S. where Latino or Hispanic participants comprised ≥15% of the sample.

We conducted the literature search for this narrative review in duplicate. In the first step, two independent researchers identified available evidence using a search strategy comprised of separate keywords (i.e., substance AND outcome). The search was conducted using Pubmed/Medline and SCOPUS, given our interest in human health and the biomedical sciences, with the following keywords: "environmental obesogen," "endocrine disrupting compound," or "polychlorinated biphenyls (PCBs), dichlorodiphenyldichloroethylene (DDE), dichlorodiphenyltrichloroethane (DDT), hexachlorobenzene (HCB), hexachlorocyclohexane (HCH), perfluorooctanoic acid (PFOA), perfluorooctane sulfonate (PFOS), perfluoroalkyl substances (PFAS), perfluorinated compound (PFC), polybrominated diphenyl ethers (PBDE), polybrominated biphenyls (PBB), tributyltin (TBT), phthalate, bisphenol A (BPA), organophosphate pesticides (OP), dialkyl phosphate (DAP), diethyl phthalate (DEP), dimethyl phthalate

(DMP)" and "infant growth, weight gain, overweight, obesity, birthweight, adiposity, childhood obesity." We conducted the search in titles, abstract and full article text in Pubmed, and supplemented with additional studies identified through a review led by Liu and Peterson.[30] After compiling results of the search, we removed duplicates, followed by studies where outcomes were assessed in persons >18 years of age, those that focused on metals as the EDCs of interest given that metals operate through distinct mechanisms from those summarized above (specifically, heavy metals tend to accumulate in organs and disrupt organ function, as opposed to interfering with hormone function),[31] those that did not take place in the U.S. or Latin America, those where the outcomes were not obesity-related, and those where Latino or Hispanic participants comprised <15% of the sample. Abstracts and unpublished studies were not included. **Figure 2** shows the PRISMA flow diagram of the literature review pipeline. We organized results according to time-period of exposure (pre- and perinatal periods vs. childhood), followed by life stage of outcome assessment (birth vs. infancy through adolescence) within exposure period, followed by type of EDC within life stage of outcome assessment.

3. RESULTS

Using our search strategy, we identified 1731 unique studies. After removal of studies conducted in persons >18 years of age, where the EDCs of interest were metals, where the setting was not in the U.S. or Latin America, and where the outcomes were not obesity-related, we considered 57 studies. Of them, 24 met our criterion that the study population contains ≥15% Latino or Hispanic participants.

The study populations were in Mexico, Bolivia, and the U.S. The majority (n = 16) of studies comprised >90% Latino participants,[32–34] although we note that 10 studies used data from the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) study,[35–44] which includes mainly Mexican Americans living in the agricultural region of Salinas Valley in California; and three studies were based in the Early Life Exposure in Mexico to Environmental Toxicants (ELEMENT) Project,[45–47] a birth cohort based in Mexico City. Of the mixed-race studies, three comprised 50-70% Latino/Hispanic participants,[48–50] and five included 15%-30% Latino/Hispanic participants.[51–55] For cohorts with heterogeneous race/ethnic composition (i.e., where the study population is not entirely Latino or Hispanic), the results reported by investigators were not race- or ethnicity-specific.

Key EDCs of interest in this review included persistent organic pollutants (POPs) – namely, perfluoroalkyl substances (PFAS), dichlorodiphenyltrichloroethane (DDT), dichlorodiphenyldichloroethylene (DDE), polychlorinated biphenyls (PCB), and polybrominated diphenyl ethers (PBDEs), as well as short-lived chemicals – namely phthalates, organophosphorous pesticides (OPs), and phenols. **Box 1** includes information on major sources, routes and extent of human exposure for each EDC class, as well as key associations with obesity-related outcomes identified from this review.

The most commonly assessed obesity-related outcomes were birthweight (an established marker of the intrauterine environment, an indicator of neonatal adiposity, [56] and a bellwether for future obesity[57]), body mass index (BMI), and waist circumference.

Nine studies obtained direct measures of adiposity via bioelectrical impedance analysis (n = 7) or air displacement plethysmography (n = 2). Two studies followed participants through puberty (i.e., CHAMACOS and ELEMENT). Prenatal exposure to EDCs was primarily measured in maternal serum and urinary samples during pregnancy (the majority of which were collected during early and/or mid-pregnancy), and only one study used serum from cord blood (**Table 1**). In the sections below, we summarize findings regarding exposure to EDCs during each sensitive period of interest within the lifecourse in relation to obesity-related outcomes in Latino/Hispanic youth. EDCs and their sources, as well as metrics of obesity-related outcomes reviewed in this paper, are summarized in **Figure 1**.

3.1. EDC exposure during the pre- and perinatal periods

The majority of the studies focused on EDC exposure during the pre- and perinatal periods, with exposure assessment typically occurring during early or mid-pregnancy. While exposures around the time of conception and during pregnancy occur within the prenatal period, and those that occur immediately before or after birth take place within the perinatal period, we discuss findings for these two periods together given wide variability in the week of gestation at which EDC exposure was assessed, and the fact that assessments of exposure via maternal tissues in late pregnancy and at delivery may also reflect EDC exposure earlier in pregnancy.We summarize key findings below.

3.1.1. Pre- and perinatal exposure → adiposity at birth

We identified six studies that assessed pre- and perinatal EDC exposure in relation to outcomes at birth. Birthweight was the most widely-used indicator of adiposity, which

makes sense given the wealth of literature linking both low [58–61] and high birthweight[62] to obesity and obesity-related outcomes later in life.[30] Only one study (the Healthy Start Study) had data on directly measured body composition via air-displacement plethysmography.[51]

The majority of studies reported inverse associations of pre- and perinatal exposure to EDCs with neonatal adiposity, even after adjustment for key covariates like maternal age, pre-pregnancy weight status, glycemia during pregnancy (e.g., mid-pregnancy glucose levels, gestational diabetes status), smoking habits, gestational weight gain, gestational age at delivery, and infant sex. We discuss findings with respect to specific classes of EDCs, below.

PFAS

Among 628 mother-infant pairs in the Healthy Start Study, a Colorado-based pre-birth cohort comprising 23% Hispanic participants, Starling et al.[51] reported that concentrations of two PFAS, perfluorooctanoate (PFOA) and perfluorononanoate (PFNA), measured in maternal serum collected at median 27 weeks gestation were inversely related to birthweight (β for highest tertile [T3] vs. lowest tertile [T1] of PFOA = -92.4 [95% CI: -166.2, -18.5] g; β for above vs. below the median for PFNA = -92.1 [95% CI: -150.6, -33.6] g).[51] The authors noted similar associations for PFOA, PFNA, and perfluorohexane sulfonate (PFHxS) in relation to directly-measured % fat mass assessed (e.g., β for T3 vs. T1 of PFOA was -0.97 [95% CI: -1.74, -0.20] %). These findings suggest that some

perfluoroalkyl substances (e.g., PFOA) may influence fetal accrual of adiposity, while others affect overall size of the newborn (e.g., PFNA).

PDBEs

In 286 participants of the CHAMACOS study comprising Mexican-Americans living in the agricultural region of Salinas Valley in California, maternal serum levels of PDBEs assessed at 26 weeks gestation were inversely associated with birthweight. Each ten-fold increase in BDE-47 concentration corresponded to a 115 (95% CI: 2, 228) g decrement in birthweight, with similar findings for BDE-99 and BDE-100. However, the authors noted that after adjustment for gestational weight gain, the results were no longer statistically significant.[36]

DDT & DDT

We found one study that assessed pre- and perinatal exposure to DDT and DDE via cord blood. Among 200 mother-child pairs in the highly-exposed birth cohort located in Santa Cruz de la Sierra of Bolivia where metabolites of the persistent organic pollutants DDT were detected in more than 80% of cord blood samples, Arrebola et al. found that higher cord blood levels of *o,p'*-DDT corresponded with lower birthweight (-0.014 [95% CI: -0.028, -0.001] units log birthweight per 1 unit *o,p'*-DDT), whereas *p,p'*-DDE was related to higher birthweight (0.012 [95% CI: 0.003, 0.020 units log birthweight per 1 unit as *o,p'*-DDT) in mutually-adjusted models that also accounted for key covariates: maternal age, parity, smoking habits, gestational weight gain, BMI, and gestational age at delivery.[34] Interestingly, despite being associated with higher birthweight, *p,p'*-DDE was related to

shorter gestation length (-0.004 [95% CI: -0.008, -0.001] units of log gestational age per 1 unit *p,p'*-DDE),[34] suggesting that long-term DDT exposure may promote more rapid fetal growth at any given gestational age, and in spite of shorter gestation length.

In contrast, in an analysis of 253 mother-infant dyads in Morelos, Mexico, Garced et al. did not find any association of maternal serum DDE concentrations during any trimester of pregnancy with anthropometry at birth (weight, length, head circumference, arm and thigh length), or with growth from birth through one year of age.[33] The discrepancy in findings could be due to differences in the biospecimen type; Arrebola et al. analyzed cord blood whereas Garced et al. analyzed maternal serum, the latter of which may not represent true fetal exposure due to protective functions of the placenta. Other possible reasons for differences in findings include differences in level of exposure (though difficult to assess directly given the different biospecimen types), variability in covariate adjustment (Garced et al. included a number of lifestyle characteristics, like maternal diet during pregnancy, that were not accounted for by Arrebola et al.), and or other differences in the study populations (Bolivian vs. Mexican participants).

POPs mixtures

In addition to the above-mentioned studies that document inverse associations of pre- and perinatal POPs exposure on neonatal adiposity, one study reported null findings. In the National Institute of Child and Human Development Fetal Growth Studies, a large cohort of 2,106 healthy mother-infant dyads recruited from 12 sites across the U.S. of which over 25% are of Latino/Hispanic origin, Buck Louis et al. explored associations of

76 POPs in maternal serum during the first trimester of pregnancy, including PDBEs, polybrominated biphenyls, and PFAS with neonatal anthropometry.[53] The authors found no relationship between these chemicals and neonatal adiposity, although they noted inverse associations of PFAS with arm and thigh length. These findings suggest that bone length at birth may be a sensitive marker of early intrauterine EDC exposure, which is relevant to obesity and its sequelae given that shorter stature later in life has been linked to an adverse metabolic profile.[63]

Phthalates

A few studies have examined associations with respect to short-lived EDCs. A study of 350 participants in the Lifecodes pregnancy cohort in Boston, of which 15% of participants are Latino/Hispanic, found that average concentrations of mono-(3-carboxylpropyl) phthalate (MCPP) across gestation was associated with higher birthweight among mother-child pairs for which the mother had post-50-g glucose challenge test glucose level was ≥140 mg/dL),[54] suggesting a potential synergistic interaction between some phthalates and maternal hyperglycemia.

Organophosphate pesticides

Following a study in CHAMACOS showing generally null associations of organophosphate pesticide exposure with birth size,[64] Harley et al. led a gene x environment study among 470 mother-infant dyads to explore effect modification to the relationship between organophosphate pesticide exposure as measured by non-specific dialkyl phosphate (DAP) metabolites in maternal urine, and birth outcomes by paraoxonase

1 (*PON1)*, a gene that regulates expression of the paraoxonase enzyme involved in detoxification of organophosphorus pesticides.[35] The authors found that higher maternal urinary DAP concentrations were associated with shorter gestation length, particularly among those with the susceptible *PON1* genotype. They also noted that maternal urinary levels of DAP metabolites were positively associated to birthweight, but only among infants with the non-susceptible *PON1* genotype. Such findings are unexpected, but may be due to the fact that in non-susceptible women, high urinary DAP concentrations may be an indicator of more rapid metabolism and detoxification of organophosphorus pesticides, as opposed to high exposure.

3.1.2. Pre- and perinatal exposure→ adiposity from infancy through adolescence

Due to the relatively small literature on pre-/perinatal EDC exposure and adiposity beyond birth, we summarize the evidence on obesity outcomes from infancy through adolescence together. We identified three studies for which outcomes were assessed during infancy (<2 years of age). [32,33,52] The other 15 studies involved participants across a wide range of age: most studies (n = 8) focused on early and middle childhood from 2 to approximately 9 years of age, [37–40,44,48–50] some (n = 4) eclipsed the peripubertal transition from late childhood into adolescence age 5 through 18 years, [42,46,47,55] and three studies spanned 2 years through 12-14 years [41,43,45] (*nota bene*, Yang et al. assessed associations of EDCs with longitudinal growth for individual children from 2 through 14 years of age, as opposed to children of differing age groups).

Common anthropometric indicators of adiposity include age- and sex-standardized weight and length based indices (weight-for-age, weight-for-length, BMI-for-age), waist circumference, and skinfold thicknesses. Additionally, at older ages (i.e., middle childhood onward), some cohorts collected data on body composition via air displacement plethysmography and bioimpedance analysis.

PFAS

In the previous section, we reported findings of Starling et al.[51] of an inverse relationship between maternal serum PFAS and offspring birthweight. In a follow-up study comprising 415 mother-infant pairs,[52] the investigators found that several PFAS were related to higher adiposity at 5 months, as well as with rapid weight gain from birth to 5 months in a sex-specific fashion. Among male infants, maternal serum PFOA and PFNA were positively associated with higher % fat mass at 5 months, ranging 1.5–1.7% per 1-unit natural-log (ln)-transformed ug/mL of a given chemical. Among females babies, maternal serum levels of perfluorooctane sulfonate (PFOS) and PFHxS were associated with lower weight-for-age z-score at 5 months (PFOS: $\beta = -0.26$ [95% CI −0.43, −0.10] SD per ln-ng/mL; PFHxS: $\beta = -0.17$ [95% CI: −0.33, −0.01] SD per ln-ng/mL PFHxS). In analyses pooled by sex, 2-(*N*-methyl-perfluorooctane sulfonamido) acetate above vs. below the limit of detection was associated with greater odds of rapid adiposity gain, as indicated by change in weight-for-age or weight-for-length equivalent to ≥0.67 z-scores between birth and 5 months of age (odds ratio [OR] = 2.2 [95% CI 1.1, 4.3] for weight-for-age; OR = 3.3 [95% CI 1.8, 6.2] for weight-for-length).[52] Such findings indicate that while PFAS are

inversely related to birthweight which includes both fat and fat-free mass, these chemicals may be associated with greater fat accrual during early infancy in a sex-specific manner.

PDBEs

In 224 CHAMACOS participants, Erkin-Cakmack et al. found that maternal serum PBDEs concentrations during late pregnancy (~27 weeks) and delivery were associated with higher BMI z-score among boys (β = 0.26 [95% CI: –0.19, 0.72]) and lower BMI z-score among girls (β = –0.41 [95% CI: –0.87, –0.05]) at 7 years of age after controlling for maternal age, education, pre-pregnancy BMI, gestational weight gain, years of residence in the U.S., poverty during pregnancy, offspring gestational age at delivery, duration of breastfeeding, and child's fast food and soda consumption.[40]

DDT & DDE

Heggeseth et al.[39] characterized four distinct BMI growth trajectory classes for 249 participants from the CHAMACOS cohort, then examined sex-specific associations of DDT and DDE with odds of membership in each trajectory class. The investigators found that higher maternal serum concentrations of DDT and DDE during pregnancy were associated with a BMI gain pattern characterized by a stable increase from 2 to 5 years, followed by a rapid increase in BMI gain from 5 to 9 years of age in boys.[39] In girls, higher prenatal DDT exposure was associated with stable growth from 2 to 9 years of age.[39] Moreover, while DDT and DDE exposure was not related to obesity status at 7 years of age in this cohort,[37] investigators noted a sex-specific effect of these chemicals on adiposity at later ages among boys only. Specifically, starting at age 9 years, the odds of being

overweight or obese doubled per 10-fold increase in prenatal concentrations of DDT and DDE in boys.[38] By 12 years of age, prenatal exposure to DDT and DDE was not only associated with overweight/obesity, but also with continuous BMI z-score and waist circumference in boys, even after accounting for pubertal status.[41] On the other hand, in a highly-exposed population in Chiapas, Mexico, Cupul-Uicab et al. found no association of DDE exposure with BMI growth patterns from birth through 18 months in 789 children.[32] These null findings could be due to the fact that health effects of toxicants may not become apparent until mid- to late-childhood.

Phthalates

Of the different classes of toxicants reviewed herein, prenatal exposure to phthalates received the most attention, although the evidence across study populations is inconsistent. These discrepancies in findings with respect to phthalates and phenols across individual studies may arise from differences in nativity of the study populations, as well as challenges of assessing exposure to short-lived chemicals.

In CHAMACOS, a study of 345 participants found that maternal urinary concentrations of the low-molecular weight phthalates diethyl phthalate (DEP) and dibutyl phthalate (DBP), and the high-molecular weight di(2-ethylhexyl) phthalate (DEHP) during pregnancy, were positively associated with BMI z -score, waist circumference z -score, and percent body fat during childhood, with particularly strong associations with overweight/obesity status at 12 years of age (OR = 1.3 [95% CI: 1.1, 1.5] per two-fold increase in DEP; OR = 1.2 [95% CI: 1.0, 1.4] per two-fold increase in DBP; and OR = 1.3

[95% CI:1.0, 1.6] per two-fold increase in DEHP),[42] as well as with continuous BMI z-score through 14 years of age.[43] We note that in these analyses, the investigators did not adjust for pubertal status as it could be on the causal pathway between EDC exposure and weight status or growth.

In contrast to findings in CHAMACOS, a study of 326 mother-child pairs from the Columbia Center for Children's Environmental Health (CCCEH) Obesity Project (67% of participants are Dominican) found inverse associations of maternal phthalate exposure and offspring adiposity. Higher levels of maternal urinary mono-isobutyl phthalate (MiBP), mono-*n*-butyl phthalate (MBP), monobenzyl phthalate (MBzP), monoethyl phthalate (MEP), and MCPP operationalized as a single latent variable (via principal components analysis) was associated with lower BMI z-score (β = –0.30 [95% CI: –0.54, –0.06]), and % body fat (β = –1.62 [95% CI: –2.91, –0.34]), and smaller waist circumference (β = –2.02 [95% CI: –3.71, –0.32] in boys.[48]

Among 249 participants from the ELEMENT Project, Yang et al.[46] reported that maternal urinary concentration of MBzP during the third trimester was inversely associated with BMI z-score at age 8-14 years (β = -0.21 [95% CI: -0.41, -0.02]). In a subsequent study that involved 223 of 249 participants in Yang et al.'s analysis, Bowman et al.[47] explored potential mediation of the effects of trimester-specific phthalate exposure on adiposity trajectories from 8-14 years to 9-17 years of age and found both trimester- and sex-specific associations. In girls, exposure during the first trimester appeared to be more important than later in pregnancy. Specifically, maternal urinary MBP and MiBP

concentrations during the first trimester were positively associated with BMI z-score across the two time-points (β = 0.25 [95% CI: 0.03, 0.46] per 1 unit natural log-transformed MBP; β = 0.28 [95% CI: 0.12, 0.45] per 1 unit natural log-transformed MiBP). On the other hand, mid-pregnancy exposure appeared to be most relevant for boys; i.e., higher maternal urinary MBzP concentrations in the second trimester were associated with higher BMI z-score (β = 0.25 [95%CI: 0.01, 0.49] per 1 unit ln-MBzP) and waist circumference (β = 2.11 [95% CI: 0.27, 3.95] cm per 1 unit ln-MBzP).[47]

In an analysis of 180 participants from the Mount Sinai Children's Environmental Health Study (52.8% Latino/Hispanic participants), prenatal exposure to phthalates was not associated with adiposity at 4-9 years of age, with the exception of an inverse relation of tertiles of maternal urinary concentrations of the sum of DEHP metabolites (∑DEHP) with % fat mass measured by bioimpedance analysis at 4-9 years of age (β for T3 vs. T1 of ∑DEHP = -3.06% [95% CI: –5.99%, –0.09%] for both boys and girls).[49]

Phenols

In another study of participants (*n* = 173) from the Mount Sinai Children's Environmental Health Study, concentrations of benzophenone-3 (a naturally-occuring phenol occurring in flowering plants, but used in lotions and cosmetics for its ultra-violet ray absorbing properties [65]) in maternal urine during pregnancy were negatively associated with % body fat in 4-to-9-year old girls (β = −1.51 [95% CI: −3.06, 0.01], but not in boys.[50] In a similar vein, a study of 311 children from the CHAMACOS study observed that average urinary bisphenol A (BPA) concentrations across two measurements in pregnancy

were negatively associated with BMI z-score and % body fat in female offspring only at 9 years of age (BMI z-score: β = -0.47, 95% CI: -0.87, -0.07]; % fat mass: β = -4.36% [95%CI: -8.37%, -0.34%] for T3 vs. T1 of maternal urinary BPA concentrations).[44] On the other hand, among 249 youth from the ELEMENT Project, no associations were found between prenatal BPA concentrations and offspring BMI z-score during mid- to late-childhood,[46] or with respect to BMI trajectories across the peripubertal transition.[45]

3.2. EDC exposure during childhood

We identified four studies from three cohorts that characterized exposure to EDCs during childhood and/or adolescence (roughly defined as age 3 through 15 years), and related EDC exposure to adiposity outcomes. All four of these studies focused on BPA and phthalate exposure.

The first study was a longitudinal investigation of girls in The Breast Cancer and Environment Research Program. In this study, Deierlein et al. measured urinary concentrations of nine phthalate metabolites of 1,017 girls aged 6-8 years at enrollment. The authors assessed associations of the phthalates at baseline (categorized as low, medium, and high) with change in BMI, height, and waist circumference during 7 years of follow-up. The primary finding was that girls with the highest molar sum of the low-molecular-weight phthalates MEP, MBP, and MiBP (referred to as ΣDBP) exhibited a greater increase in BMI and waist circumference than those with the lowest concentrations of ΣDBP.[55]

The second study, among 311 CHAMACOS participants, found that urinary concentrations of BPA at 5 years of age was not related to adiposity at 5 or 9 years of age.[44] However, at 9 years of age, higher concurrent BPA exposure, dichotomized as above the median vs. below the level of detection, was associated with higher BMI z-score (β = 0.55 [95% CI: 0.15, 0.95]), waist circumference (β = 5.89 cm [95% CI: 1.19, 10.59]) and % fat mass [β = 4.62% [95% CI: 0.26%, 8.98%]). In this cohort, data were also available for four PBDEs measured at age 7 years in 224 participants, the sum of which (Σ4PBDE) exhibited a negative association with concurrent BMI z-score (β= -0.44 [95% CI: -0.83, -0.06] per 1-unit increment in Σ4PBDE) and waist circumference z-score (β= -0.35 [95% CI: -0.66, -0.04] per 1-unit increment in Σ4PBDE).[40]

Finally, one cross-sectional analysis in the ELEMENT Project linked urinary concentrations of BPA and phthalates to adiposity indicators at 8-14 years of age. Yang et al. found that higher urinary BPA was associated with higher skinfold sum among 117 girls (β = 3.47 mm [95%CI: 0.05, 6.40] per 1-unit ln-BPA).[46] In boys (*n* = 132), the authors detected an inverse relationship between mono(2-ethylhexyl) phthalate (MEHP) and skinfold thicknesses (β = -2.95 [95%CI: -5.08, -0.82] per 1-unit ln-MEHP). Subsequently, Bowman et al. led a follow-up study that included a repeat assessment of adiposity measures 3 years later in 223 participants and found an inverse association of MBzP with average skinfold thickness (β =−2.43, 95% CI: −4.69,−0.17) and waist circumference (β = −1.91 cm, 95% CI: −3.64,−0.19) among boys (*n* = 109), but no associations in girls (*n* = 114).[47]

4. DISCUSSION

4.1 Summary of findings

Here, we build upon existing reviews [11,66] that summarize the influence of environmental and behavioral factors to obesity in Latino/Hispanic youth by honing in on the specific contributions of EDCs to obesity-related outcomes in this vulnerable population. This is a topic of great importance given that identification of key chemicals that are consistently associated with excess adiposity in Latino/Hispanic youth across research publications and study populations may inform preventive action.

Our review identified 24 published studies in the last decade that examined associations of early life exposure to EDCs with obesity-related outcomes in Latino/Hispanic youth in the U.S. or Latin America. Over half (n = 13) of these studies were based on two cohorts of Mexican/Mexican-Americans (CHAMACOS in the Salinas Valley of California with >90% Latino participants, and ELEMENT in Mexico City with 100% Latino participants). In addition to studies based on these two cohorts, on study in Cruz de la Sierra in Bolivia,[34] and two additional studies in Mexico (Chiapas[32] and Morelos[33]) had 100% Latin American participants. The remainder of the studies (n = 8) comprised mixed race populations, with 15-70% Latino/Hispanic participants, though the investigators did not report race/ethnicity-specific estimates, making it difficult to directly compare estimates across studies. Regardless, we noted some general trends with respect to EDC exposure, adiposity outcomes, and research findings.

The current literature focuses largely on EDC exposure during the pre- and perinatal periods, which is likely related to numerous animal models indicating the importance of this timeframe as a sensitive period for environmental exposures.[18,67,68] We also noted that DDT/DDE, organophosphate pesticides, and phthalates have received quite a bit of attention, which makes sense given the increased use of these chemicals in industrializing and agricultural countries such as those in Latin America.[69] During the childhood and adolescent life stages, the majority of studies focused on exposure during the pre- and perinatal periods. The chemical of greatest interest were non-persistent chemicals like BPA and phthalates, which may become more relevant in older children who regularly consume packaged snacks and beverages which are major sources of BPA and phthalates. Older children also use personal care products that are fraught with such chemicals (e.g., deodorants, cosmetics, hair products).

With respect to health outcomes, most studies focused on weight- and length/height-based metrics as proxies for excess adiposity, which are widely-used given the low cost and ease of weight and height measurement, especially in younger children. Several cohorts also measured waist circumferences and skinfold thicknesses, which are highly correlated with fat mass in children.[70] One cohort directly measured adiposity via air displacement plethysmograhy (the Healthy Start Study) and four cohorts assessed body composition via bioimpedance analysis (The Mount Sinai Children's Environmental Health Study, ELEMENT, CHAMACOS and CCCEH).

Despite variability in the types of EDCs assessed, biospecimens used, and method of adiposity assessment, we noted a few consistent trends in the findings. With respect to EDC exposure during the pre- and perinatal periods, exposure to POPs (e.g., PFAS, PDBE, DDT, and DDE) was associated with lower birthweight and lower % neonatal fat mass, even after accounting for known determinants of neonatal adiposity. Potential mechanisms include an effect of POPs on shorter gestation length (though many studies accounted for gestational age at delivery as a covariate), and physiological consequences of oxidative stress on fetal growth.[71] On the other hand, *in utero* exposure to short-lived chemicals – namely, DAPs and phthalates – was generally unrelated to birthweight, although there was suggestive evidence that certain phthalates (e.g., MCPP) were associated with higher birthweight in the presence of maternal hyperglycemia.[54] Similarly, one study reported that *in utero* organophosphate pesticide exposure (via maternal urinary DAP concentrations) was related to higher birthweight, but only among infants of mothers who had a specific genotype,[35] pointing toward relevant biological interactions to test in future studies.

When considering the associations of pre- and perinatal EDC exposure on obesity beyond infancy, sex-specific associations began to emerge. We noticed a consistent pattern that prenatal POPs exposure corresponded with higher adiposity in boys but not girls. Exposure to short-lived chemicals, like phenols and phthalates, also was associated with adiposity in a sex-specific fashion, although findings are inconsistent. The lack of consistency in findings could be attributed to the various ways in which *in utero* exposure was handled in the statistical analyses (e.g., average across pregnancy vs. trimester-specific,

assessment of individual chemicals vs. summary scores or latent variables), and the extent to which assessment of short-lived chemicals in these studies is an accurate representation of true exposure.

Finally, when considering the relatively small body of literature on EDC exposure and obesity-related outcomes during childhood and/or adolescence, we noted that despite differences in study design, chemicals of interest, and whether or not sex-specific associations were considered, exposure to short-lived chemicals used as plasticizers and in personal care products (i.e., BPA and phthalates) was associated with higher adiposity in girls and lower adiposity in boys. Such discrepancies between males and females are likely driven, in part, by differences in the endocrine regulation system and fat deposition in pre- and peripubertal youth.[72,73]

Limitations of literature reviewed herein include the fact that only two Latin American countries were represented, and that studies of mixed race/ethnic groups did not report race/ethnicity-specific estimates (thereby hindering inference to Latino/Hispanic youth). Additionally, none of the studies distinguished between indigenous vs. non-indigenous segments of Latino/Hispanic populations – a topic of relevance given that indigenous persons have distinct exposure profiles and obesity-related disparities that warrant special attention.[17] We also noted a general lack of biomonitoring of human exposure in Latino/Hispanic populations. Finally, because this review was narrative (as opposed to a systematic review) and focused on the most recent biomedical evidence (i.e.,

within the last decade) archived on PubMed/Medline, there may be other relevant studies that were not included. .

4.2. Gaps in knowledge, future directions, and research priorities

4.2.1. Gaps in knowledge

As noted earlier, the life stage during which EDC exposure has received the most attention is the pre- and perinatal periods in relation to birthweight and gestation length. This focus is likely related to greater phenotypic plasticity during this timeframe (likely due to the lability of the fetal epigenome[74]), and thus, greater potential for behaviors and environmental factors to impact long-term health.[75,76] While continued research on EDC exposure during the pre- and perinatal periods will undoubtedly be beneficial, the prenatal period is but one sensitive period during early life (**Figure 1**). Therefore, studies that consider independent and joint effects of EDC exposure across multiple sensitive periods of development will aid in identifying the most relevant life stages within which interventions may have the largest impact on the reduction of obesity-related disease. This is particularly important among youth of Latino/Hispanic origin given evidence of race/ethnic differences in timing and tempo of puberty.[77] Moreover, we found that evidence surrounding EDC exposure during childhood and adolescence in relation to obesity-related health was scant, and not all studies considered sex-specific (in addition to race/ethnicity-specific) associations which are likely to emerge and diverge from childhood onward. A better understanding of specific culprits of excess adiposity and metabolic risk will unveil the most effective and timely actions for preventive efforts.

Many studies assessing exposure to EDCs during the pre- and perinatal periods used a single maternal biospecimen to represent the entire pregnancy, thereby precluding the ability to disentangle trimester-specific effects. Additionally, it is unclear whether EDC levels measured in maternal biospecimens reflect maternal exposure specifically during pregnancy or the woman's lifetime exposure. This issue is particularly relevant for long-lived and lipophilic EDCs that may be retained in maternal tissues,[28] which may result in continued fetal exposure in the absence of acute exposure. This concept has important implications for a potential biological interaction between maternal peripartum weight status and EDC exposure on offspring health, as well as for similar interactions between a child's own weight status and EDC exposure.

4.2.2. The role of policy regulation

The U.S. and Canada are ecological examples of the effectiveness of policy regulations to reduce EDC exposure.[78] In the U.S., policies to reduce or prohibit use of EDCs in consumer products have reduced exposure. For example, DEHP, DBP and benzyl butyl phthalate use have been targets of regulation since 2008.[78] Accordingly, data from the National Health and Nutrition Examination Survey (NHANES) showed that U.S. concentrations of EDC metabolites in blood, serum, and urine decreased in the last decade.[79] Despite implementation of such policies, U.S. Latino/Hispanic populations still incur disproportionate exposures to air pollutants, pesticides, and toxic industrial chemicals.[80,81] Reasons for this disparity are complex.[82] Additional surveillance and research is warranted to better understand sociocultural determinants of environmental

health of Latino and Hispanic youth in the U.S., and to develop the appropriate intervention efforts and initiatives.

Though it is challenging to make inference on the effectiveness of policy to regulate EDC exposure in Latin America due to a lack of surveillance in these settings (**Supplemental Table 2**), cross-country comparisons allow us to extrapolate. In the ELEMENT Project, Lewis et al. found that pregnant women in Mexico City have up to three-fold higher concentrations of MBP (~65 ng/mL during the 3rd trimester) and MEHP (~6.9 ng/mL during the 3rd trimester) than adult women (MBP: 17.0–21.6 ng/mL, MEHP: 2.2–4.2 ng/mL) in U.S. NHANES 1999-2004.[79] Similar trends are observed for Mexican children and adolescents.[79,83] A recent study conducted among pregnant women in Mexico reported no declines in phthalate metabolite concentrations over time.[84] In fact, urinary concentrations of diisobutyl phthalate (DiBP) and butylbenzyl phthalate (BBzP) metabolites were higher among women enrolled in a cohort study from 2008 to 2010 than to those enrolled in 2007. Similarly, concentrations of DBP, DiBP, and BBzP metabolites assessed among women enrolled from 2007 to 2011 were higher than those reported for a similar population of women studied from 1997-2005.[84]

Such findings point toward a need to monitor and regulate use of EDCs in foods,[85,86] food containers,[87] personal care products, and common household items. In the Pan-American Health Organization (PAHO)'s five-year Plan of Action to stem childhood obesity (2014–2019), current environmental conditions were identified as a cause of overweight and obesity, with dietary preferences and access, as well as trade and

agriculture policies being the main determinants of the quality of food supplies. PAHO's recommendations include fiscal policies and other incentives for production and consumption of healthy foods; regulation of marketing of unhealthy foods; better labelling of processed food and drink products; and improvement of school food and increased physical activity among schoolchildren.[88] We suggest similar recommendations and policies targeting the use of EDCs in food and food products, especially among pregnant women, infants, children, and adolescents. However, such policies will only have measurable impacts on obesity reduction if they are backed up by relevant actions, including population education, enforcement, and program implementation.

4.2.3. Research priorities

Key research priorities include detailed biomonitoring of EDC exposure levels in Latin American countries and communities of predominantly Latino/Hispanic populations. Following implementation of policies to regulate use of EDCs in agriculture, personal care items, and household products (an effort for which assessment of feasibility is beyond the scope of this review), there will be need to assess the efficacy of such policies to reduce exposure to chemicals and any subsequent impacts on obesity-related health.

5. Conclusions

The evidence reviewed herein implicates early life EDC exposure in the etiology of childhood obesity. Despite the relatively large body of literature on this topic, EDCs are not typically included as points of intervention in obesity prevention frameworks, possibly reflecting a need for additional research yielding consistent and reproducible findings

across study populations, age groups, and settings. Regardless, pregnant women, infants, and young children are populations of special concern. Therefore, promoting education, awareness, and vigilance of EDC exposure in these populations is especially important when considering EDCs as an actionable target for childhood obesity prevention programs. Such efforts are especially salient for Latin American countries where industrialization is increasing EDC exposure, as well as in regions of the U.S. comprising large Latino/Hispanic populations and/or where agricultural work or other jobs with a high burden of chemical exposure (e.g., firefighting, textile and paper manufacturing) represent a large proportion of the economic output.

Ultimately, policy regulations are needed to reduce the production and release of EDCs into the environment. Such systems-level regulations may have wider-ranging impacts than recommendations that put the onus on individuals to change behaviors and lifestyle, although in all likelihood both "top-down" and "bottom-up" activities will be needed to produce a measurable impact on obesity and other aspects of human health (e.g., smoking cessation and tobacco control in the U.S. resulting from top-down efforts like policies to control smoking indoors and tobacco taxes, as well as bottom-up efforts comprising disseminations of health information and education). Given that public policy draws insight from research findings, effective communication and engagement among scientists and stakeholders (business leaders, regulators, and politicians) will be instrumental to achieve the shared ultimate goal of improving health.

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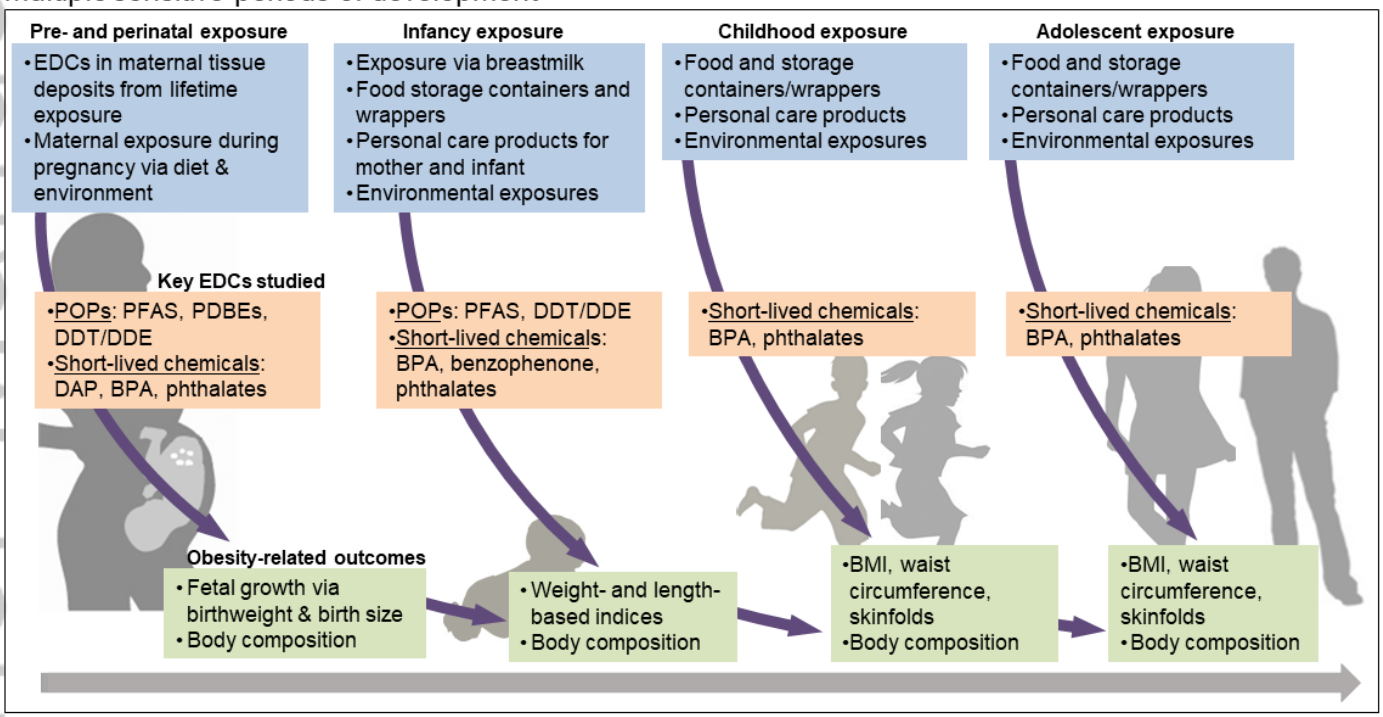
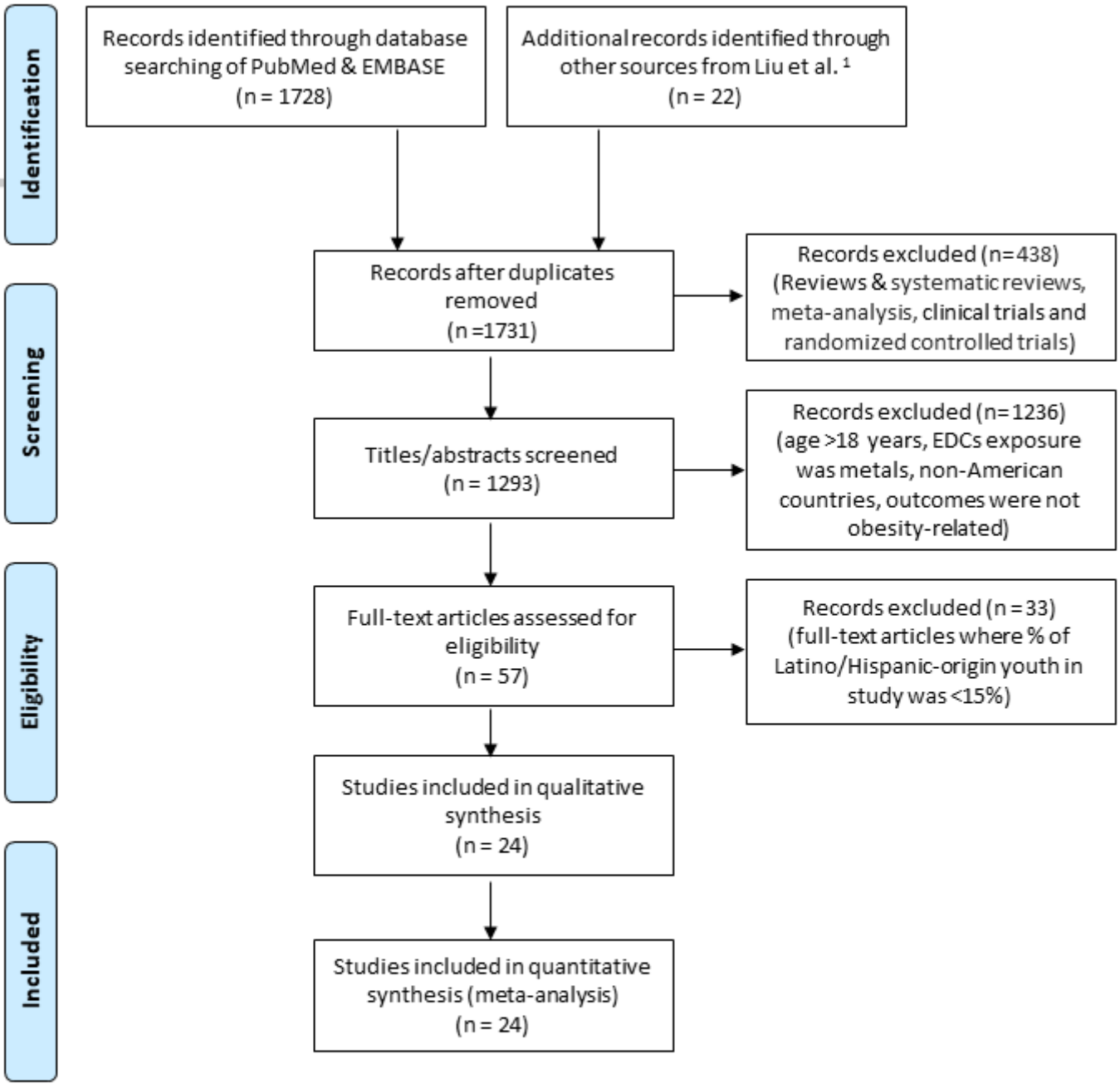
Figure 1 Exposure to obesogenic endocrine disrupting chemicals (EDCs) and childhood obesity across multiple sensitive periods of development



OBR_13245_EDCs.Cross Border.Figure1.Final.tif

Figure 2 PRISMA 2009 Flow Diagram



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OBR_13245_EDCs.Cross Border.Figure2.Final.tif