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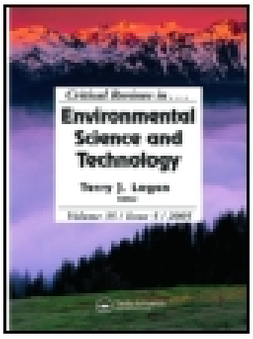

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Systematic review of pregnancy and neonatal health outcomes associated with exposure to e-waste disposal

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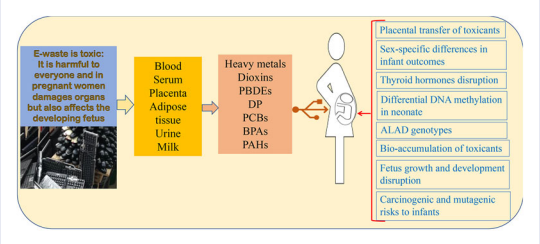
ABSTRACT



Electronic waste (e-waste), the world's fastest-growing category of hazardous solid waste, poses a serious health risk for recyclers, scavenger workers, and residents of communities near waste disposal sites in many countries with developing economies and those in transition. The toxic components of e-waste have been linked to various adverse health outcomes. The objective of this study was to assess the effects of e-waste exposures on pregnancy outcomes and neonate's health. We systematically searched original full-length articles in three electronic databases namely Web of Science, ProQuest health and medical databases, and Google Scholar for publications related to e-waste and pregnancy outcomes and neonate's health. Outcomes from most study showed possible association between exposure to e-waste and pregnancy and adverse neonatal health outcomes including sex-specific differences in infants' growth, placental transfer of toxicants, thyroid hormones disruption, DNA methylation and oxidative damage, ALAD genotypes, carcinogenic risks, and sex hormones disruption in pregnant women and developing fetus. The results support evidence that e-waste exposure is associated with negative effects on pregnancy and neonatal health outcomes. However, improvements in the design of epidemiological investigations, and more investigations from South Asia, Africa, and Latin America are needed to confirm these associations.

KEYWORDS E-waste; human health; prenatal women and neonate

1. Introduction

E-waste exposure has been associated with a wide range of negative health outcomes and the risk of e-waste exposure is a global concern, especially in

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developing countries where informal recycling often through dismantling, "cooking", desoldering and other open burning activities, as well as acid washing of electronic components that release both marketable and toxic substances. These recycling activities are often carried out by the women, and sometimes the children are also involved, resulting in chemicals from combustion (e.g. dioxins and furans, polyaromatic hydrocarbons) which higher levels were associated with negative neonatal outcomes. (Bakhiyi et al., 2018; Balde et al., 2017; Holgate, 2018). In many countries, e-waste is recognized as hazardous waste and international exportation is strictly prohibited. Therefore, there is a high level of interest in discovering methods for responsible recycling within the country of origin (BAN, 2019a; Ogunseitan, 2013). However, despite strict regulations, illegal export of e-waste from developed countries to developing countries continues, a situation that puts vulnerable populations at risk of exposure to hazardous chemicals, heavy metals, and rare earth elements (Henríquez-Hernández et al., 2017). The reasons for this have been attributed to due to the high cost of formal e-waste disposal and recycling, permissive regulations and lower labor costs that provide important economic opportunities for impoverished workers and communities (BAN, 2019b; PACE, 2019). As a result of the increasing generation and global flow of e-waste, towns in countries such as Ghana, Nigeria, India, Vietnam, Pakistan, and China, are recognized among the most polluted places on earth (Blacksmith-Institute, 2013; Chen et al., 2018; Heacock et al., 2018; Gangwar et al., 2019).

Pollutants released during e-waste recycling have been linked to adverse health consequences that include general injuries, respiratory diseases from inhalation, growth retardation, skin disease, immune weakness, neurodevelopmental effects, risks of cancer, increases in spontaneous abortions, and premature births (Grant et al., 2013; Song & Li, 2014; WHO, 2013). Despite these outcomes, there is a lack of generalizable knowledge and understanding of the associated epidemiological and social-ecological variables, especially regarding prenatal women and neonate outcomes. An early systematic review conducted concluded that there were no well-designed epidemiological investigations that can confirm that exposure to e-waste is harmful to pregnant women and infants (Grant et al., 2013); whereas another subsequent review identified several publications showing evidence of negative health effects of e-waste exposure on prenatal women and children, although the authors did not perform a detailed assessment of pregnant women outcomes, citing inconsistent reporting of results and over-estimation of actual exposure levels across studies (Song & Li, 2015).

Scientific literature on a broad spectrum of health risks and adverse pregnancy outcomes associated with exposure to e-waste for populations in or near e-waste recycling sites is increasing in geographic scope and in the

variety of methods used (Huang et al., 2016; Heacock et al., 2016; Leung, 2019; Zeng et al., 2016). The published information needs to be assessed comprehensively to refine the putative association of e-waste hazards with adverse health outcomes. Known developmental neurotoxicants present in e-waste including lead (Pb), cadmium (Cd), chromium (Cr), polybrominated diphenyl ether (PBDEs), polychlorinated biphenyl compounds (PCBs), and polycyclic aromatic hydrocarbons (PAHs) have been shown to also be present in higher than normal concentrations in prenatal women and neonates, but the potential mechanisms of the adverse effect on women and neonates was not verified because of insufficient data (Chen et al., 2011). Overall, since the initial hint of potential problems, numerous articles have been published on exposure to e-waste in relation to human health outcomes, but these results have not yet been systematically reviewed.

Therefore, linking the current status of information on the negative impacts of e-waste exposure to policy-making and international regulation has been challenging (Ogunseitan, 2013; Ogunseitan et al., 2009). A binding international agreement on targeting toxic substances in the electronic industry is lacking (PACE, 2019; The-UN, 2018), and the inclusion of e-waste in the Basel Convention on the Transboundary Movement of Hazardous Waste and their Disposal remains challenging because the Convention is yet to be ratified by some countries generating large amounts of e-waste (UNTC, 2019). There have been few studies on exposure to e-waste on pregnant women and neonates or other adverse human epidemiological outcomes from any country except China (Grant et al., 2013). Before proceeding with recommendations for policymakers or imposing international regulations on the electronic industry and e-waste management programs, it is important to improve the understanding of the population health circumstances. Here, we contribute to this improvement by systematically reviewing information on the consequences of e-waste toxicity on prenatal women and neonatal health outcomes.

2. Methods

In accordance with PRISMA-2015 guidelines (Moher et al., 2015), we conducted a systematic review of all relevant full-length original articles published in all languages that we identified through three major electronic databases namely Web of Science (WOS, CSCD, KJD, MEDLINE, RSCI, and SCIELO), ProQuest health and medical databases (consumer health database information, health & medical collection information, healthcare administration database information, Medline, nursing & allied health database information, psychology database information and public health

database information) and Google Scholar. We focused on publications assessing the association between exposure to e-waste and pregnancy and infant's health outcomes from January 2000 to September 2019. We followed the search strategies suggested for systematic reviews and also used the cited references lists within the selected articles (Grant et al., 2013). To ensure that all articles evaluating the effects of e-waste exposures on pregnancy outcomes and neonate's health are included, articles published in languages other than the English language were translated. Electronic databases were searched comprehensively by Boolean search methods ("or" and "and") using terms: ("electronic waste" OR "e-waste" OR "WEEE" (Waste Electric and Electronic Equipment)) AND ("health" OR "Women" OR "pregnant women" OR "pregnancy outcomes" OR "neonate" OR "exposure" OR "toxicity" OR "development" OR "environment" OR "breast milk" OR "gestation period"). We used a wide range of search terms to ensure that articles were not omitted.

2.1. Selection criteria

Publications were included if they described epidemiological studies meeting the following inclusion criteria: (1) assessment of the effects of e-waste on outcomes related to pregnancy and neonatal health; (2) publication in peer-reviewed journal; (3) reported original data; (4) examination of outcomes in prenatal women and neonates; Analysis if blood, urine, adipose tissue, placenta, and breast milk samples. We excluded reports of research conducted in non-human organisms, and research that did not report an outcome related to exposure to e-waste. Publications were also excluded when a comparison between the exposed and control group was not clearly identified and outcomes of interest were not reported. A total of 2,424 publications were retrieved, among which 27 satisfied the selection criteria.

2.2. Data extraction

After preliminary identification of relevant articles, we prepared a data extraction sheet to collect key indicators and then relevant studies were retrieved for assessment (details are attached in Supplementary Information (SI)). The key indicators were study characteristic including the details about authorship, time period of sampling, location of the study, sample size and design of the study, use of a comparison or control group, measurement of exposure and outcomes, study methodology, confounding factors (age, education, smoking habits, alcohol consumption, BMI, demographics, socioeconomic and other lifestyle factors), and study outcome. Eligibility was assessed independently by all the authors; differences

were fixed by consensus for selected studies and all possible reported key indicators were included. Based on the key indicators such as types of methodology, sample representation of the population, study design (ecological or prospective, retrospective), sampling bias of exposure to e-waste, assessment of health outcome and methods to control confounding we assessed the risks of bias.

3. Results

We included 27 articles on research conducted in China (n = 23), Ghana (n = 2) and Vietnam (n = 2) that described the association between exposure to e-waste and pregnancy and neonatal health outcomes (Figure 1). The studies varied on several important aspects, including population sample sizes ranging from 10 to 939 pairs of mother-infants per a study, study design (ecological and case-control studies), the timing of exposure measurements, outcome assessment, and statistical methods. However, the confounding factors were similar among the selected articles. The 27 selected studies included 8 on general health risks on neonates (Asamoah et al., 2018; Chan et al., 2007; Kim et al., 2019; Li et al., 2018; Man et al., 2017; Nguyen Minh et al., 2014; Wu et al., 2012; Zeng et al., 2019), 6 on placental transfer of toxicants (Ben et al., 2013; Li et al., 2011; Xu et al., 2015; Zhang et al., 2011; Zhao et al., 2013; Zheng et al., 2017), 3 on bio-accumulation of chemicals (Ben et al., 2014; Li et al., 2017; Tue et al., 2010), 2 on sex-specific differences in infant outcomes (Wang et al., 2019; Zhang et al., 2018), 2 on fetal growth and development (Xu et al., 2013, 2015), 2 on DNA methylation and oxidative damage in neonate (Huo et al., 2019; Ni et al., 2014), 1 on thyroid hormones levels (Lv et al., 2015), 1 on ALAD genotypes in infants (Huo et al., 2014), 1 on carcinogenic and mutagenic risks to infants (Asamoah et al., 2019), and 1 on sexual hormones disruption in prenatal women and developing fetus (Zhou et al., 2013). Detail information on the selected studies is presented in Table 1.

The selected articles were published between 2007 and 2019 and were based on research conducted between 2004 and 2017. The number of human participants in each research varied widely within the range of 10 participants in a study of neonate health outcomes to 939 participants in a study of DNA methylation and oxidative damage. Twenty-six studies were case-control studies and used comparison groups while one was a case study design.

3.1. Sex specific differences in infant outcomes

Results of two studies supported the association between exposure to e-waste and sex-specific differences in birth outcomes (Wang et al., 2019;

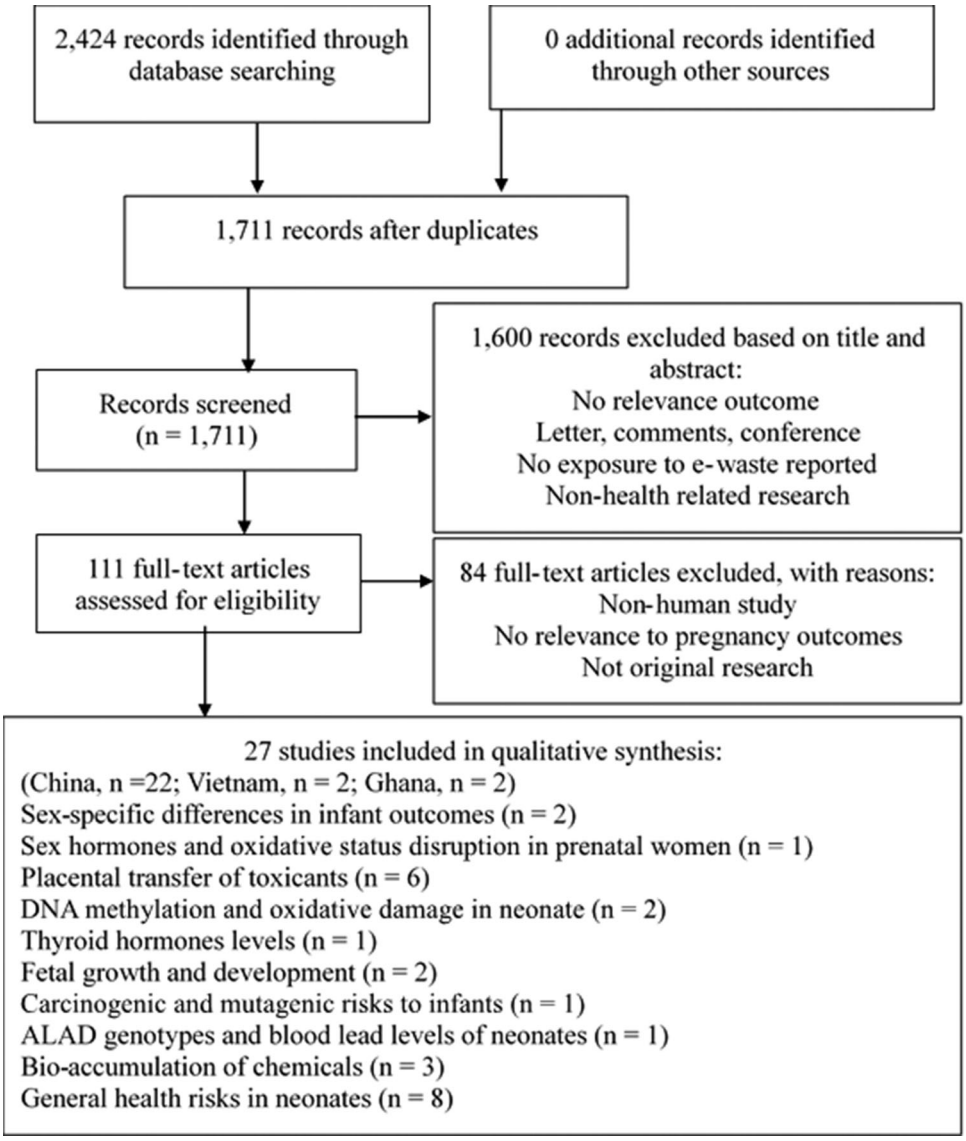

Figure 1. Flow of study selection through review (Note: adopted from PRISMA guidelines).

Zhang et al., 2018). Wang et al. (2019) investigated the impacts of dioxin on sexual dimorphism in the growth of infants from their mothers who were residing in the e-waste recycling site and compared with those who were not residing in the e-waste town. The researchers collected the data and samples from mothers and infants at the age of 6 months and 3 years old preschoolers. The study results show that the concentration of total dioxin-related chemicals in breast milk was significantly higher among the mothers residing in e-waste dismantling town than those residing in a control town. Observational data showed a link between dioxin exposure and

Table 1. Reported key outcomes, countries, sample types and time, methods, confounding factors, exposure setting and population and toxicants effects.

Author	Country	Study time period	Samples type and time	Chemical component	Detection method	Confounding factors	Exposure setting	Exposed Population	Effect
Sex-specific differences in infant outcomes									
(Wang et al., 2019)	China-Taizhou	2015-2017	Breast milk	Dioxin	HRGC and MS; JMP-9 software package	Age, education, smoking habits, alcohol consumption, health and body mass index (BMI)	Ecological: exposed area vs control area	Mother-infant pairs (n = 100) (50 vs 50)	Concentrations of TCDDs-TEQ: 12.9 vs 4.3 pg/g lipid; $p < 0.0001$) Male- PCDDs-TWQ ($\beta = -0.454$, $p = 0.046$), Female - PCDDs-TEQ ($\beta = 0.759$, $p = 0.005$)
(Zhang et al., 2018)	China-Guiyu	Sep 2011 - Jun 2012	Urine	Cd	Graphite furnace atomic absorption spectrophotometry (GFAAS), Misaki neonate scale; SPSS-19	Age, education, occupation, household income, health background, family history, and BMI	Ecological: exposed area vs control area	Mother-infant (n = 449) (237 vs 212)	Mother with female vs male neonate: 1.59 vs. 1.38 μg/g, creatinine, $p < 0.05$.
Sex hormones and oxidative status disruption in prenatal women									
(Zhou et al., 2013)	China- Guiyu	Dec.2005- Jul 2006	Blood and umbilical cord blood (UCB)	E2, PROG, and TESTO hormone levels	Radioimmunoassay (RIA kit), real-time-PCR, revert aid first-strand cDNA synthesis kit, triazole Reagent; Statistical analysis-SPSS 12.0	Age, education, occupation, household income, health background, family history, and BMI	Ecological: exposed area vs control area	Parturient women (n= 90) (46 vs 44)	Concentration of E2 in serum: 2137.52 vs 1549.74 pg/ml; P, 0.05). E2 in umbilical cord blood (UCB): (2757.91 vs 2211.29 pg/ml; P, 0.01). PROG in serum: 100.10 vs 61.61 ng/ml; P, 0.05; PROG in UCB: 156.52 vs 145.87 ng/ml; P, 0.05.
Placental transfer of toxicants									
(Ben et al., 2014)	China-Wenling	Jul 2010 and Jul 2011	Blood	Dechlorane plus (DP)	GC/MS; SPSS 13.0	Age, education, occupation, household income, health background, family history, and BMI	Ecological: exposed area vs control area	Mother-infant (n= 72) (48 vs 24)	∑DP in serum: 13.5 vs 3.68 ng/g lipid weight (lw), Placental tissue: 4.27 vs 1.25 ng/g lw, UCB: 4.02 vs 2.03 ng/g lw.
(Zhao et al., 2013)	China-Taizhou	Oct2009- May 2011	Blood and Umbilical cord blood	PBDEs	GC–MS; SPSS 16.0	Age, education, occupation, household income, health background, family history, and BMI	Case study: aborted fetuses (n = 65), placentas (n = 65), and maternal blood samples (n = 31)	Mother-infant (n = 161)	∑PBDE fetuses: 4.46 ng/g lw, placentas 7.90 ng/g lw, and blood 15.7 ng/g lw.
(Li et al., 2011)	China-Guiyu	2005 to 2007	Blood and placenta	Cd	GFAAS; SPSS 13.0	Age, education, occupation, household income, health background, family history, and BMI	Ecological: exposed area vs control area	Pregnant women (n = 423) (289 vs 134)	Placental Cd level in neonates: 3.61 vs. 1.25 mu g/L, $p \leq 0.01$.
(Zhang et al., 2011)	China-Guiyu	Oct 2008 and Jun 2009	Placental	Cd and Pb	GFAAS; SPSS 13.0	Age, education, occupation, household income, health background, family history, and BMI	Ecological: exposed area vs control area	Pregnant women (n = 105) (55 vs 50)	Placental Cd: 83.99 vs. 51.59 ng/g, $p < 0.001$). Placental Pb: 521.01 vs. 273.24 ng/g, $p = 0.299$
(Xu et al., 2015)	China-Guiyu	Sep 2010 to Sep 2011	Blood and placenta	Cd, BPA and PCBs	GFAAS, GC/MS; SPSS 13.0	Age, education, occupation, household income, health background, family history, and BMI.	Ecological: exposed area vs control area	Pregnant women (n= 262) (192 vs 70)	Placental Cd: 96.6 vs 20.9 ng/g; BPA: 6.369 vs. 2.824 μg/L; PCBs: 76.13 vs. 33.23 ng/g. KISS1 expression: 0.495 vs. 0.178; mRNA: $p < 0.05$.

(*continued*)

Table 1. Continued.

Author	Country	Study time period	Samples type and time	Chemical component	Detection method	Confounding factors	Exposure setting	Exposed Population	Effect
(Zheng et al., 2017)	China- Wenling	Jun 2011-Dec 2011	Blood and placenta	PBDEs	GC/MS; SPSS 22.0	Age, education, occupation, household income, health background, family history, and BMI	Ecological: exposed area vs control area	Pregnant women (n= 72) (48 vs 24)	∑ PBDEs–serum: 19.3 vs 8.13 ng g − 1 lw; UCB: 6.84 vs 4.47 ng g − 1 lw; Placental tissue: 2.20 vs 1.06 ng g − 1 lw.
DNA methylation and oxidative damage									
(Zeng et al., 2019)	China-Guiyu	Jun 2011-Sep 2012	Umbilical cord blood	Heavy metals (Pb)	GFAAS; SPSS 20.0	Age, education, occupation, household income, health background, family history, and BMI	Ecological: exposed area vs control area	Mother-infant (n= 939) (593 vs 346)	UCB–Pb: 7.34 vs 3.07 μg/dL, $p <$ 0.001. Methylation level: 8 % vs 7 %; $p < 0.05$. CTNNA2: 62% vs. 64 %, $p < 0.05$.
(Ni et al., 2014)	China-Guiyu	Mar 2012-Jan 2013	Umbilical cord blood	Pb, Cd, Cr, and Ni	GFAAS; SPSS 19.0	Age, education, occupation, household income, health background, family history, and BMI	Ecological: exposed area vs control area	Mother-infant (n= 201) (126 vs 76)	Pb–serum: 110.45 vs. 5731 ng/mL; Cd: 2.50 vs. 0.33 ng/mL, $p < 0.001$. Cd: 2.50 vs. 0.33 ng/mL, $p < 0.001$, and Ni 9.09 vs 8.63 ng/mL
Thyroid hormones levels									
(Lv et al., 2015)	China-Wenling	Jun 2011-Dec 2011	Serum and adipose tissue	PCBs/PBDEs	GC/MS; SPSS 13.0	Age, education, occupation, household income, health background, family history, and BMI	Ecological: exposed area vs control area	Pregnant women (n= 64) (54 vs 10)	∑PCBs –serum: 63.3 vs 3.33 ng g-1 lw ∑PBDEs: 6.67 vs 4.32 ng g-1 lw. Associated found between maternal exposure and thyroid-stimulating hormone (TSH) level, $p < 0.001$.
Fetal growth and development									
(Xu et al., 2015)	China-Guiyu	Mar 2012 – Aug 2012	Placenta	PBDEs	GC/MS; SPSS 13.0	Age, education, occupation, household income, health background, family history, and BMI	Ecological: exposed area vs control area	Pregnant women (n= 155) (69 vs 86)	∑PBDE: 32.25 vs 5.13 ng/g lw.
(Xu et al., 2013)	China-Guiyu	Sep 2014 and July 2016	Umbilical cord blood (UCB) and placentas	PAHs and PBDEs	GC/MS; SPSS 13.0	Age, education, occupation, household income, health background, family history, and BMI	Ecological: exposed area vs control area	Pregnant women (n= 154) (101 vs 53)	16-PAHs: 14.43 vs 10.05 ppb, $p < 0.00$; PBDEs: 57.55 vs. 8.23 ng/g lipid, $p < 0.001$
Carcinogenic and mutagenic risks to infants									
(Asamoah et al., 2019)	Ghana- Agbogbloshie	2014 and 2016	Breast milk	PAHs	GC–MS/MS; R software (3.4.0.).	Age, education, occupation, household income, health background, family history, and BMI	Ecological: exposed area vs control area	Mother-infant; (n = 128) (105 vs 23)	∑PAHs: 1304.16 vs 199.27 ng/g lw.
ALAD genotypes and blood lead levels of neonates									
(Huo et al., 2014)	China-Guiyu	2005 – 2006	Blood	Pb	GFAAS; PCR-RFLP; SPSS 19.0	Age, education, occupation, household income, health background, family history, and BMI	Ecological: exposed area vs control area	Mother-infant (n = 273) (189 vs 84)	Blood-Pb: 10.50 vs. 7.79 ng/mL in 2004/2005 and 9.41 vs. 5.49 ng/mL in 2006.
Bio-accumulation of e-waste toxicants									
(Ben et al., 2013)	China-Wenlin	Jul 2010 to Mar 2011	Blood and milk	DP	GC–MS/MS; SPSS 13.0	Age, education, occupation, household income, health background, family history, and BMI	Ecological: exposed area vs control area	Mother-infant (n= 49) (33 vs 16)	DP –milk: 37.7 vs 2.67 ng/g, lipid; Serum: 71.5 vs 4.84 ng/g, lipid.

(Li et al., 2017)	China-Wenling	2012 to 2013	Breast milk	PBDEs	GC–MS/MS; SPSS 13.0	Age, education, occupation, household income, health background, family history, and BMI	Ecological: exposed area vs control area	Mother-infant (n = 46) (25 vs 21)	∑PBDE: 19.5 vs 3.88 ng/g lw, $p < 0.05$.
(Tue et al., 2010)	Vietnamese	August 2007	Breast milk	PCBs, PBDEs and HBCDs	GC–MS/MS-Agilent 7890 series; R version 2.9.0	Age, education, occupation, household income, health background, family history, and BMI	Ecological: exposed area vs control area	Mother-infant (n = 27) (20 vs 7)	∑PCBs–milk: 34 vs 1.6 ng/g lw; ΣPBDEs: 84 vs 3.2 ng/g lw; HBCDs: 2.0 vs 0.36 ng/g lw.
General health risks in neonates									
(Asamoah et al., 2018)	Ghana-Agbogbloshie	September 2014 and July 2016	Breast milk	PCBs	GC–MS/MS; R version 3.4.0	Age, education, occupation, household income, health background, family history, and BMI	Ecological: exposed area vs control area	Mother-infant (n= 128) (105 vs 23)	PCBs: 4.43 vs 0.03 ng/g lw.
(Huo et al., 2019)	China-Guiyu	September 2011 and June 2012	Urine	PAHs	HPLC; SPSS 19.0; Stata 12.0	Age, education, occupation, household income, health background, family history, and BMI	Ecological: exposed area vs control area	Mother-infant (n= 257) (155 vs 102)	∑OH-PAH: 6.87 vs 3.90 mu g/g); PAH metabolites: 6.87 vs 3.90 μg/g creatinine, $p < 0.01$.
(Li et al., 2018)	China-Guiyu	Mar 2012-Aug 2012	Umbilical cord tissue	PBDEs	GC/MS; LC-MS/MS; HPLC; SPSS version 20.0	Age, education, occupation, household income, health background, family history, and BMI	Ecological: exposed area vs control area	Pregnant women (n= 300) (150 vs 150)	∑PBDE: 71.92 vs. 15.52 ng/g lipid, $p < 0.01$).
(Kim et al., 2019)	China-Guiyu	Sep 2011-Aug 2012	Blood and urine	Pb, Cd, and Cr	GFAAS; SAS 9.4	Age, education, occupation, household income, health background, family history, and BMI	Ecological: exposed area vs control area	Pregnant women (n = 634) (314 vs 320)	Blood-Pb: 6.66 vs 3.81 μg/dL, blood-Cd: 1.72 vs 1.43 μg/dL, blood-Cr: 4.02 vs 3.52 μg/dL; urine-Cd: 1.06 vs 0.54 μg/dL, urine-Cr: 1.66 vs 0.97 μg/dL.
(Man et al., 2017)	China-Taizhou	Aug 2005 and Dec 2005	Breast milk, placenta and hair	PCBs	GC/MS; SPSS 16.0	Age, education, occupation, household income, health background, family history, and BMI	Ecological: exposed area vs control area	Mother-infant (n = 25)	∑PCBs–milk: 363 vs ng/g lipid, placental–PCBs: 224 vs ng/g lipid and hair–PCBs: 386 vs ng/g dry wt.
(Nguyen Minh et al., 2014)	Vietnamese	September 2008	Breast milk	Dioxin-related compounds (DRCs)	GC/MS	Age, education, occupation, household income, health background, family history, and BMI	Ecological: exposed area vs control area	Mother-infant (n = 25) (19 vs 6)	DRCs: 2.3-10 vs 0.60-5.7 pg CALUX-TEQ/g lipid. PCDFs: 13-15 vs 2.3-8.8 pg/g lipid and PBDFs: 1.1-1.5 vs <1.1 pg/g lipid.
(Chan et al., 2007)	China-Zhejiang	Aug2005 and Dec 2005	Breast milk, placenta, and hair	Dioxin	GC/MS; SPSS 11.0	Age, education, occupation, household income, health background, family history, and BMI	Ecological: exposed area vs control area	Mother-infant (n = 10)	Milk-TEQ: 21.02 vs 9.35 pg/g fat, $p > 0.05$); Placenta-TEQ: 31.15 vs 11.91 pg/g fat; hair-TEQ: 33.82 vs 5.59 pg/g dry wt, $p < 0.05$.
(Wu et al., 2012)	China-Guiyu	May 2007 and Jul 2007	Serum	Perfluorooctanoic acid (PFOA)	HPLC–MS/MS; SPSS v13.0	Age, education, occupation, household income, health background, family history, and BMI	Ecological: exposed area vs control area	Pregnant women (n = 167) (108 vs 59)	PFOA–serum: 16.95 vs 4.4 ng/mL; $p < 0.001$.

adverse health outcomes in infants. The higher concentration of dioxin in mothers' milk was associated with the slower growth in male infants; whereas growth in female children was greater at the age of 3 years. Statistical analysis was used to reveal inverse association between height and polychlorinated dibenzo-p-dioxins-Toxic equivalency (PCDDs-TEQ) in male neonates while in female neonate it was positive ($\beta = -0.454$ vs 0.759; $p = .046$ vs 0.005). However, at the age of 6 months, both male and female infants showed no significant responses to dioxin concentration with respect to growth development. Another study conducted by Zhang et al. (2018), examined the concentration of Cd in pregnant women and its impacts on sex-specific birth outcomes from an e-waste exposed town, Guiyu, China, and another town that served as control location, Haojian, China. The results showed significantly higher concentration among mothers in exposed town than control town and surprisingly, the cases with female fetuses had higher levels of urine-Cd than those with male fetuses. Statistical analysis showed significant inverse associations between the levels of urine-Cd and birth anthropometric measurements (birth weight, birth length, head circumference and Apgarscores with 1 min and 5 mins) in female infants but with the male infants, no significant associations were observed except the Apgar Score, which is a composite measure on a scale of zero − 10 based on five assessments (Appearance, Pulse, Grimace, Activity, and Respiration). The study noted that exposure to e-waste was significantly associated with the absorption and metabolism of toxicants in the fetus based on the fetal sex in pregnant women, which were associated with adverse birth outcomes.

3.2. Sex hormones and oxidative status disruption in prenatal women

Findings of research by Zhou et al. (2013) showed the association between exposure to e-waste and disruption in the levels of sex hormones and homeostasis in pregnant women residing in the e-waste recycling sites in China. Prior to enrollment both the cases and controls confounding factors were alike except for the education level, which was significantly higher in the control group. Results of the study showed that sex hormones levels and oxidative homeostasis in women residing in the e-waste site were significantly different from those of women at the control site. The levels of estradiol and progesterone were expressively higher in the exposed group than those of control. Further, the study found the inverse association between the levels of estrogen receptor and progesterone receptor in the exposed group ($p < 0{\cdot}05$). Similarly, the study shows an elevated growth in malondialdehyde and suppression of the activities of superoxide dismutase and glutathione peroxidase. These elevated levels of hormones in maternal serum and placentas were significantly associated with those in umbilical

cords. The obtained findings showed that the e-waste exposed group had significantly disrupted sex hormones and oxidative stress levels than those of women in the control town.

3.3. Placental transfer of toxicants

Six studies have examined the effects of exposure to e-waste on the placental transfer of toxicants. Ben et al. (2014) examined the concentration of dechlorane plus (DP) and its placental transfer from e-waste-exposed mother to the fetus. Results show the high concentration of DP and its related compounds in cord sera of e-waste-exposed town that clearly exhibited placental transfer of chemicals to the fetus. The results also showed the significant differences in thyroid-stimulating hormone (TSH) levels ($p = .046$) in the maternal serum between the mother and the neonate but found no differences in the free thyroxine (FT4) levels ($p > .05$). These changes were only observed in people residing in the local e-waste exposed environment; no relationship with other confounding factors to pregnancy and total DP contamination was observed in the control town. Therefore, the presence of DP and related compounds in the exposed population proved that the toxicants could translocate from e-waste exposed mothers to fetuses. Other findings from Zhao et al. (2013) show the concentrations of various PBDE congeners can be translocated from mother to the fetus in the first trimester. The study found a significant correlation between the total PBDEs concentrations in the fetus tissues and PBDEs levels of mothers' blood samples in the e-waste exposed town.

In the case of toxic metals, Li et al. (2011) studied Cd exposure in neonates through their mothers in Guiyu, China, a notorious e-waste management site. The outcomes in Guiyu were compared with outcomes in pairs of mother-neonate in Chaonan, a control site also in China. The researchers found that the association between Cd levels in the polluted environments and in exposed neonates were significantly correlated. The expression of metallothionein (MT) in the placenta was positive in 67% among mothers living in the polluted area, compared with 32.7% among mothers in the control location, Chaonan. Statistical analysis showed a positive association between the expression of MT and Cd levels in neonates. Zhang et al. (2011) examined the levels of Cd and Pb in pregnant women and its association with the downregulation of placental calcium-binding protein S100P, in Guiyu and compared with residents of control town, Shantou, China. The findings showed that the levels of heavy metals in the exposed group were significantly higher than those of the control town. The mRNA expression of S100P and integrated optical density (IOD) value for MT were significantly lower in the e-waste exposed group (0.175 vs. 1.462, $p < .001$ and 0.026 vs.

0.032, $p = .045$); however, IOD value for MT showed opposite findings (0.051 vs. 0.035, $p = .003$). The higher concentration of Cd in pregnant women showed a negative association with the level of S100P protein while with MT protein level it showed a positive association. In the case of Pb concentration, it showed no association with S100P or MT level. Association between S100P and the levels of protein and mRNA showed an opposite link with the time (Parents lived at recycling area) and gestational age, but the level of MT protein was positively linked with time, gestational age and Apgar score. The changes in S100P expression due to elevated Cd level in the exposed group confirmed that S100P might be a potential biological indicator of heavy metal transfer from mother to infant.

Similarly, Xu et al. (2015) examined the exposure of mixed toxicants including heavy metal Cd and organic toxicants BPA and PCBs to the fetus in utero with placental gene expression. The results show a significantly higher level of placental Cd (96.6 vs 20.9 ng/g), BPA (6.369 vs. 2.824 µg/L), and PCBs (76.13 vs. 33.23 ng/g) in e-waste exposed town than that in control town. Likewise, the median KISS1 expression and the levels of mRNA in utero were significantly higher in exposed infants than those in the control group. Overall, the levels of Cd, BPA, and PCB concentration showed a positive correlation with KISS1 gene expression. The levels of mRNA and anthropometry of neonates showed a positive association though, the Cd and PCB levels and anthropometry of neonates showed a negative association. The study concluded that infants born in the e-waste recycling sites have adverse health effects due to elevated toxicants transfer from exposed mother to fetus and its association with high KISS1 gene expression. Zheng et al. (2017), findings show the effect of placental partitioning due to PBDEs exposure from mother to fetus. The results show the total PBDEs in the serum (19.3 vs 8.13 ng g^{-1} lipid wt), umbilical cord serum (6.84 vs 4.47 ng g^{-1} lipid wt), and placental tissue (2.20 vs 1.06 ng g^{-1} lipid wt) were significantly higher in the exposed group than that of control. The levels of BDE-7,153 and Total Thyroxine (TT4), a principal hormone secreted by the thyroid gland, were significantly correlated. The study concluded that the PBDEs might be partially responsible for the partitioning but, the study further showed that the concentration of PBDEs was also associated with the TT4 levels in the serum.

3.4. DNA methylation and oxidative damage

Two studies showed the association between exposure to e-waste and differential DNA methylation and oxidative damage in neonates. Zeng et al. (2019) examined the effects of heavy metals on differential DNA methylation in neonates from their e-waste exposed mothers who were residing in e-waste recycling town and compared it with the control group, non-

e-waste residents in china. The results showed that CpGs of *BAI1* and *CTNNA2*, which are mostly responsible for neuron differentiation and development, were significantly involved in brain neuronal development in infants and had shown a close association with the elevated maternal Pb levels in the exposed group. Besides, an increased gestational age, differences in neonatal birth BMI, and almost 10 times higher umbilical cord blood (UCB) Pb levels were found in the exposed group than the control group. Other selected heavy metals did not show much difference between the two groups. The second study by Ni et al. (2014) found a significantly higher level of UCB Pb in the e-waste exposed group than that of the control group (110.45 compared to 57.31 ng/mL; $p < .001$). However, UCB plasma 8-hydroxy-2′-deoxyguanosine (8-OHdG) levels showed no difference between the two groups. But, this UCB plasma 8-OHdG concentrations in the fetus were positively associated with other heavy metals such as Cd, Cr, and Ni. These observations confirmed that exposure to e-waste metals and their association with the elevated 8-OHdG concentrations influenced the neonates' DNA oxidative damage.

3.5. Thyroid hormones levels

A study showed the effects of e-waste toxicants on the disruption of thyroid hormones (THs) in pregnant women. Lv et al. (2015) investigated the concentrations of PCBs and PBDEs in the adipose tissue and matched serum of pregnant women residing in the e-waste recycling town and a control town in China. The results show the significant associations between the concentration of blood PCBs levels and THs levels in the exposed mothers, confirmed adverse health impacts on mothers and fetus development. However, the concentration of blood PBDEs and THs levels showed no association except with BDE-209, which may pose potential health hazards to the mother and fetus development.

3.6. Fetal growth and development

Two studies examined the association between exposure to e-waste and fetal growth and development. Xu et al. (2015) studied the effect of PBDEs exposure on the developing fetus in pregnant women residing in the e-waste recycling location in the township of Guiyu, and a residential study control area in China. The results show that PBDE levels were higher among the mothers in Guiyu compared to the control site. The presence of dominated BDE 183, 209 and other lower-level brominated compounds in the placenta showed that they might have been readily passed through the placenta and eventually effects the fetus development. Infants outcomes

showed reduced head circumference in the exposed group and had been adversely correlated with BDE-47. The study concluded that with the concern for neonatal neurodevelopment and pregnancy exposure to BDE 47 and 183 in the e-waste area. A similar study was conducted by Xu et al. (2013), who found significant associations between exposure to PAHs and PBDEs, and gene expression in the developing fetus. The results show that 16 PAHs and total PBDEs were identified in the UCB samples and significantly higher levels of toxicants were found in the exposed group than that of control. The study concluded that exposure to PBDEs and PAHs could be a potential health hazard for the fetus development but, the authors could not explain the exact mechanism of their effects on placental gene expression.

3.7. Carcinogenic and mutagenic risks to infants

The findings of one study showed the association between exposure to e-waste and carcinogenic effects on infants. Asamoah et al. (2019) examined the PAHs level in the breast milk and carcinogenic effects on the infants living in an e-waste recycling site, Agbogbloshie and a residential control area, Kwabenya in Ghana. The results show the PAHs levels were significantly higher in the breast milk samples of exposed town compared to that in the control area (1304.17 vs 199.27 ng/g lipid wt). The most common cocarcinogenic high molecular weight PAHs (chrysene, benzo[a]pyrene, benzo[k]fluoranthene and benzo [g, h, i] perylene) were found in the exposed group while were absent in the control group. However, the outcome of carcinogenicity and mutagenicity assessment of PAHs in both groups, e-waste recycling sites and reference sites had a negligible risk.

3.8. ALAD genotypes and blood lead levels of neonates

Huo et al. (2014), showed the associations between delta-aminolevulinate acid dehydratase (ALAD) genotypes and concentrations of lead (Pb) in the blood of infants residing in an e-waste recycling site in China. Studies have shown that ALAD genotype influences the distribution and accumulation of lead in the blood and cause organ failure (Zhao et al., 2007). A total of 273 infants from Guiyu, an e-waste exposed town, and Cheonan, a reference town, were selected for the study. The results show that the concentration of blood-Pb levels was slightly higher in the neonates of the exposed group than the reference group (10.50 vs. 7.79 ng/mL). However, the levels of blood-Pb and ALAD-1/ALAD-1,2 showed no significant differences in neonates. However, ALAD-2 allele's distribution rate in the exposed infants showed a lower concentration than that of control group,

and overall distribution of ALAD gene did not influence the blood Pb levels of neonates, which confirmed that the elevated blood Pb in the infants were possibly influenced by the exposure of e-waste, but not from ALAD genotypes.

3.9. Bio-accumulation of toxicants

Two studies showed the association between exposure to e-waste and bio-accumulation of e-waste toxicants. The first study by Ben et al. (2013) found that DP and its mono-dechlorinated analog toxicants from an e-waste recycling site can bio-accumulate in the maternal serum and eventually expose to the infant through breast milk. The study showed that the concentrations of syn-DP or anti-DP in the serum and milk (on a lipid-adjusted basis) were moderately consistent and presented a stable partitioning relationship. The study found that the main factor behind the elevated DP levels was e-waste recycling activities. However, the study did not analyze the health hazards of DP in pregnant women and infants residing in the e-waste recycling town. The second study by Li et al. (2017) showed the $\sum$PBDE concentrations in the women residing in e-waste recycling were significantly higher than those in the controlled group (19.5 vs 3.88 ng/g lipid wt, $p < .05$). Among all the identified PBDEs congeners, BDE-153 and BDE-209 were the most predominant, accounting more than 60% of total PBDE concentrations. In Vietnam, Tue et al. (2010) found a significant accumulation of PBDEs and PCB in the breast milk of women living in two Vietnamese e-waste dismantling sites and were sufficiently high to be considered unsafe for breastfeeding infants but according to Vietnamese standard, they were within the safe limit of daily intake. These studies showed that the potential sources of the elevated PBDEs levels are be e-waste recycling activities.

3.10. General health risks in neonates

The findings of eight studies showed the association between exposure to e-waste and health risks in neonates. Asamoah et al. (2018) studied the association between PCBs concentration in breast milk and exposure risk to infants from mothers residing in an e-waste exposed and non-exposed area in Ghana. The results show that almost all the samples from the exposed group were detected positive to PCB-28, PCB-18, PCB-52, PCB-101, PCB-138, and PCB-153, while only one sample out of 23 samples from non-exposed area tested positive to PCB-28. According to the Canadian health guidelines for maximum tolerable limit for total PCBs in a day (1 µg/kg bw/day), the infants were within the safe limit of daily intake.

However, when considering the minimal risk value of 0.03 μg/kg bw/day, the exposed infants were out of the safe limit of daily intake. Huo et al. (2019) studied the exposure of PAHs and risks in birth outcomes from an e-waste recycling site in China. The outcomes revealed that the exposed group from Guiyu had the lower head circumference, Apgar 1 score and BMI than that of the reference group from Haojiang ($p < .01$). Besides, the gestational age and length of the neonates were also increased in the exposed group. All PAH metabolites in the exposed group were higher than those in the control group ($p < .01$). Spearman correlation analysis showed that all PAH metabolites from the exposed group were closely related to each other and were responsible for a significantly elevated 1-OHPyr ($\beta = 0.069$; 95% CI: 0.053, 0.326). These findings of elevated PAH levels showed a potential health risk for neonates.

Li et al. (2018) examined the protein's expression evaluation of human UBC tissue exposed to PBDEs. They found that the concentration of $\sum$14PBDEs in the e-waste exposed group's umbilical cord samples was significantly higher than in the reference group (71.92 vs 15.52 ng/g lipid wt). Approximately 697 differentially-expressed proteins were identified through proteomic analysis. Most of the identified proteins such as catalase, glutathione S-transferase omega-1 and cytochrome c were related to antioxidant activity and apoptosis. Confounding factors and infant's anthropometry were positively correlated ($p < .01$). However, the concentration of PBDEs and infant's anthropometry showed negative correlation. Besides, the authors also mentioned that the study has some limitations such as lack of sampling and identification of the toxicants from a complicated e-waste exposure in Guiyu. Kim et al. (2019), studied the associations between the levels of heavy metals in pregnant women and neonate outcomes from an e-waste exposed area in China. The results show that the concentration of maternal heavy metals (B-Pb-6.66 vs 3.81 μg/dL; B-Cd-1.72 vs 1.43 μg/L; B-Cr-13.78 vs 8.90 μg/L) was significantly higher in the exposed group than that of in reference group. Similarly, the maternal urinary metal concentrations were also significantly higher in the exposed group. Another study was done by Man et al. (2017), found that breast milk from the e-waste recycling sites contained high levels of PCBs (363 vs 116 ng/g lipid) than the reference group in China. According to the WHO guidelines for maximum tolerable limit (3 pg WHO-PCDD/F-TEQ/g lipid), these results had exceeded the recommended tolerable level for raw milk, the infants were out of the safe limit of daily intake.

Chan et al. (2007) studied the concentration of dioxin levels and effects on neonate's development from the e-waste recycling sites in China. The results show that the total TEQ value of human milk (21.02 pg compared with 9.35 pg WHO-TEQ/g fat); placenta (31.15 compared with 11.91 pg WHO-TEQ/g fat) and hair (33.82 pg compared with 5.59 pg WHO-TEQ/g

dry wt) were higher in the exposed group than that of the reference group. The concentration of dioxins in human milk, placenta, and hair samples showed significant positive correlations with each other in the exposed group, whereas in the reference group, dioxins showed a positive association between the milk and placenta. In the case of neonate's health assessment outcomes, both the groups had exceeded the WHO tolerable daily intake. Nguyen Minh et al. (2014) studied the dioxin-related compounds in breast milk and effects on infant development from the e-waste recycling sites and reference area in Vietnam. The concentrations of total PBDEs levels in the breast milk samples of the exposed group were significantly higher than that of the reference group (11–19 ng/g lipid vs 0.2–2.8 ng/g lipid). The study found that e-waste recycling activities were likely to be the main cause of elevated dioxin levels in the milk. Among PBDFs analysis, only TeBDF was detected in the samples, but further examination indicated that the samples from the exposed area may have contained unidentified compounds similar to dioxin. According to the Vietnamese health guidelines for maximum tolerable limit found in human milk of this study remained within the safe limit of daily intake. However, the calculated intake doses for infants in the exposed group were higher than the WHO (1–4 pg/kg/d) tolerable dose. Wu et al. (2012), investigated the association between maternal exposure to perfluorooctanoic acid and neonatal health outcomes in China. The results show that the concentrations of perfluorooctanoic acid (PFOA) in the serum of the pregnant women residing in Guiyu had a higher level than that of the control town (16.95 vs 4.4–30.0 ng mL^{-1}; $p < .001$). Besides, the husband's involvement, job-related to e-waste recycling and the house being a family workshop were showed a significant factor contributing to maternal Perfluorooctanoic acid (PFOA) exposure. Statistical analysis showed that the elevated serum concentration of PFOA was associated with a decrease in mean gestational age, a decrease in mean birth weight, a decrease in mean birth length and a decrease in mean Apgar score.

4. Discussion

In this systematic review, we identified and evaluated 27 research studies that investigated a plausible association between exposure to e-waste and adverse pregnancy and neonatal health outcomes. These outcomes are of concern, particularly given recent evidence suggesting that exposure to e-waste is prevalent in vulnerable populations, especially among pregnant women and children (Heacock et al., 2016). We followed the Austin Bradford Hill framework to assess evidence for the association between exposure to e-waste and adverse pregnancy outcomes by focusing on temporality, strength and consistency of the associations, dose-response

relationship, biological plausibility, and the consideration of alternative explanations (Hill, 1965). In this regard, we advanced previous work that evaluated the evidence of causality between exposure to e-waste and various outcomes (Grant et al., 2013).

The temporality of the association was assessed to be positive with the adverse outcomes in sex-specific differences in the infant's growth by comparisons at 3 years intervals. The relevant studies found that the higher concentration of dioxin in mothers' milk caused the deteriorated growth in male neonates while enhancing the growth in female neonates after the 3 years interval; whereas at the age of 6 months both male and female neonates showed no significant correlation with exposure (Wang et al., 2019). We noted evidence of significant associations between e-waste exposure and disruption of thyroid hormone function, adverse neonatal outcomes, bio-accumulation of PBDEs, PCBs and DP in tissues, deterioration of fetal growth and development, DNA methylation and oxidative damage, and sexual hormones disruption in pregnant women. These adverse effects of e-waste exposure remained when confounding variables were considered. All the studies show the consistent difference between the e-waste-exposed and control populations (details are attached in Supplementary Information (SI) Table S1). However, we note that a large majority of research studies are limited by geographic scope and the characteristics of impacted populations concerning social determinants of occupation and health. Almost 90% of the studies were conducted in southern China, particularly in and around the township of Guiyu, which was notorious for rudimentary e-waste management (Li et al., 2018, 2019; Wong et al., 2007). The environment surrounding the town was severely polluted as a result of informal e-waste recycling and other industrial activities, which have impacted the food chain (Song & Li, 2015).

Consistency of associations was difficult to assess and similar concerns have been reported previously (Grant et al., 2013). The wide range of metallic and organic chemicals found in e-waste and the complex outcomes of exposure accounts for the difficulty of demonstrating consistency in the linkage of exposure to disease. However, in this review, we found a consistent association in studies assessing the effects of e-waste exposure on sex-specific differences in infant growth, placental transfer of toxicants, bio-accumulation of chemicals, deteriorated fetal growth and development, DNA methylation and oxidative damage in neonates. Throughout the studies, investigators reported higher levels of toxicants in all e-waste-exposed populations than in control populations, and their findings show consistency across all the studies (details are attached in Supplementary Information (SI) Table S2).

Exposure-response relationship for exposure to e-waste was difficult to establish because of the complex mixture of the chemical pollutants released from e-waste processing, and the lack of available databases related to e-waste exposure routes (Tue et al., 2019; WHO, 2013). The identification of the e-waste pollutants and their causal effects on humans have not been extensively studied. This information gap turns out to be wider and more complicated in regions where different kinds of industrial wastes are already present in the environment, especially in Guiyu, China. Chemical components of e-waste include a mixture of metals and persistent organic pollutant compounds (Bakhiyi et al., 2018), but there are many unknown substances, which may also be created as part of the e-waste management processes, including burning. One of the research studies that we reviewed reported that some human milk samples from the exposed area may have contained unidentified compounds similar to dioxin (Nguyen Minh et al., 2014). In this study, we found that the key toxicants including PAH, DRCs, DP, PBDEs PCBs, HBCD, BPA, PFOA, Cd, Pb, Cr, and Ni were associated with the adverse pregnancy and neonatal health outcomes.

Through the current review, we established that most studies of e-waste health effects are based on the ecological study design, which produces results that are subject to fallacious attribution of exposure to health outcomes. However, we cannot ignore the observation that the populations exposed to e-waste generally had a higher frequency of adverse health effects among both pregnant women and neonates (Grant et al., 2013; Song & Li, 2014; WHO, 2013). Another weakness of the strength of association among selected studies is the reliance on pooled samples in exposed and control populations. This practice renders the findings prone to information bias and possible overreporting of disease in exposed groups, especially when childhood outcomes were recorded through parental reports. Nevertheless, the studies that investigated adverse birth outcomes in neonates with concentrations of blood and serum, chemical compounds did find significant associations and higher chemical levels in the e-waste exposed population (Figure 2). Besides, it is also important to mention that the limitation of the study that didn't include studies which were focused on toxicants, similar to the e-waste, such as PAHs and negative neonate outcomes in the America, Europe and other regions (Cabrera-Rodríguez et al., 2019; Choi et al., 2006, 2008).

In conclusion, limited sources of observational data, positive associations, mostly consistent results in selected studies, and limited understanding of exposure-response and biological mechanisms make it difficult to conclude a causal relationship between exposure to e-waste and pregnancy and neonatal health outcomes. However, based on the significant consistency and associations, the increasing volume and distribution of the primary risk

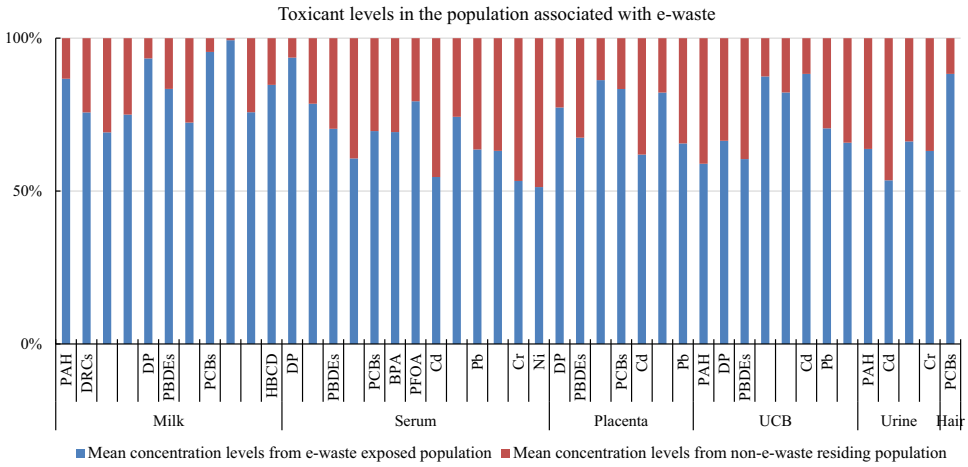

Figure 2. Toxicant levels in milk, serum, placenta, umbilical cord blood, urine, and hair of the population associated with e-waste activities or living near to the recycling area. (UCB- umbilical cord blood, PAH- polycyclic aromatic hydrocarbon, DRCs- Dioxin-related compounds, DP- dechlorane plus, PBDEs- polybrominated diphenyl ethers, PCBs- polychlorinated biphenyl compounds, HBCD- Hexabromocyclododecane, BPA- bisphenol A, PFOA- perfluorooctanoic acid, Cd-cadmium, Pb- lead, Cr- chromium, and Ni-nickel.

factors (e-waste) coupled with the expanding contact between laborers in developing countries, support the conclusion that regulatory policies are developed to prevent exposures at this time.

Although the findings confirmed that the association between exposure to e-waste and negative effects on pregnancy and neonatal health outcomes, almost 90% of studies were conducted in China, specifically in the township of Guiyu, where there is a long history of e-waste recycling and documented environmental pollution. The findings from China, Vietnam, and Ghana shows that proximity to e-waste-associated pollutants is associated with higher levels of toxic chemicals in the serum of exposed population than in the serum of people at reference sites but, unlike the findings in China, studies in Vietnam and Ghana show that exposed neonates remain within the safe limit of daily intake of toxic chemicals through their exposed mother's milk. Therefore, improvements in the design of epidemiological investigations from other countries hosting informal e-waste management operations are needed to confirm these associations.

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Contributors

NS, OAO, and YT initiated the work. NS collected the data and did the initial search. NS and YT independently reviewed the publications. NS wrote the first draft, and OAO wrote the final draft. YT supervised the study, and all authors independently reviewed and approved the final draft manuscript.

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