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Authors
Barrett, Emily S
Padula, Amy M

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Joint Impact of Synthetic Chemical and Non-Chemical Stressors on Children's Health

Emily S. Barrett, PhD[1], **Amy M. Padula, PhD**[2]

[1]Department of Biostatistics and Epidemiology; Environmental and Occupational Health Sciences Institute; Rutgers School of Public Health, Piscataway, NJ

[2]Department of Obstetrics, Gynecology and Reproductive Sciences, University of California San Francisco, San Francisco, CA

Abstract

Purpose of review—Pregnant women are exposed to numerous synthetic chemicals (e.g. pesticides, phthalates, polychlorinated biphenyls) in their daily lives as well as a range of non-chemical stressors, including poverty, depression, discrimination, and stressful life events. Although many studies have examined individual exposures to chemical and non-chemical stressors in relation to child health outcomes, very few studies have considered these exposures together. Here, we review the recent epidemiologic literature on the joint impact of chemical and non-chemical stressors on child outcomes.

Recent findings—Considerable co-exposure to chemical and non-chemical stressors occurs in vulnerable populations. Non-chemical stressors may modify the impact of chemical exposures on children's health, typically exacerbating their negative impact, but associations differ considerably by the chemicals and populations of interest.

Summary—Additional research is urgently needed to better understand the cumulative risks of multiple stressors on children's health and the underlying physiological mechanisms.

Keywords

stress; chemical; pregnancy; perinatal

Corresponding author: Emily S. Barrett, PhD, Department of Epidemiology, Environmental and Occupational Health Sciences Institute, Rutgers University School of Public Health, 170 Frelinghuysen Road, Piscataway, NJ 08854, (848)445-0197 (phone), (732)445-0784 (fax), Emily.barrett@eohsi.rutgers.edu.

Conflict of Interest

The authors declare no conflict of interest.

Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Introduction

In addition to the thousands of synthetic chemicals we encounter in our environments daily, humans are exposed to a myriad of non-chemical stressors. These non-chemical stressors include facets of our built and social-structural environments that may contribute to our health including (but not limited to) socioeconomic disadvantage, violent crime, psychosocial stress and depression (**1). Starting in the 1980s with the rise of the environmental justice movement, there has been a demand for the joint consideration of chemical and non-chemical exposures in human populations. From an environmental justice perspective, this urgency comes from the recognition that environmental chemical burdens often disproportionately impact at-risk populations who may also face considerable non-chemical stressors such as poverty and psychosocial stress. It has been proposed, moreover, that the greater environmental hazards faced by disadvantaged communities, and more specifically the interaction of chemical and non-chemical stressors, may be a major contributor to health disparities in the United States (2, 3).

Despite this long history of concern about the health impacts of co-occurring chemical and non-chemical stressors and the continued dramatic rise in synthetic chemical production worldwide, very little epidemiological research has examined how these exposures may interact. Better understanding the “double jeopardy” of joint exposure to chemical and non-chemical stressors is particularly important in the context of pregnant women and children, who may be particularly vulnerable to these exposures (4). For example, individually, chemical and non-chemical stressors may each contribute to adverse pregnancy outcomes such as preterm birth and low birth weight (5, 6). By extension, combined exposure to these stressors, reflecting a more environmentally relevant scenario, may have an additive or multiplicative impact. Here we review the current epidemiological literature on how joint exposure to synthetic chemicals and non-chemical stressors in the perinatal period may shape pregnancy outcomes and children’s development. It is beyond the scope of this paper to review the extensive parallel literatures on the individual impacts of synthetic chemical (7) and non-chemical stressors (8); instead we review the emerging literature focused on their combined exposure, emphasizing recent publications (from 2015 to the present).

Exposure assessment and co-occurrence

Synthetic chemicals—The gold standard for assessing human exposure to synthetic chemicals is by collecting biospecimens such as urine or blood and then measuring concentrations of chemicals of interest and/or their metabolites. Using this approach, biomonitoring studies in the U.S. and Europe have demonstrated that the average pregnant woman has measurable levels of dozens of identifiable synthetic chemicals and their metabolites in her body (9, 10). These include organophosphate and organochlorine pesticides, polybrominated diphenyl ethers, perfluoroalkyl substances, phthalates, and phenols, among others. Most of these analytes (or their metabolites) are detectable in >90% of women sampled suggesting that exposure is nearly ubiquitous.

Non-chemical stressors—Exposure to non-chemical stressors is similarly widespread and can occur at multiple levels. Macro-level, social-structural stressors such as racism,

sexism and other forms of discrimination pervade daily life in the form of overt bias as well as micro-aggressions (11). Co-occurrence of these stressors is common (e.g. racism and sexism) and social-structural disadvantage may be further compounded by exposure to neighborhood and community-level stressors such as physical disorder, safety concerns, and poverty (12, 13). Demographic data (e.g. race, ethnicity, immigrant status, income, sexual orientation) is often used as a proxy for social-structural stress, but it can also be subjectively evaluated through questionnaires regarding experiences of discrimination (14). Similarly, neighborhood-level stressors may be quantified through objective geospatial measures (e.g. census tract level poverty) as well as subjective measures of neighborhood quality (e.g. cohesion, safety, violence) (15, 16). Importantly (from a public health perspective), chronic exposure to societal and neighborhood level stressors can become biologically embedded, resulting in long-lasting or permanent changes in physiology (sometimes called “weathering”) that may be measurable in altered neuroendocrine activity and metabolic function or increased inflammation (17, 18). Chronic and acute stressors can also occur at an individual level in the form of stressful life events, trauma, and mental health concerns, which can be assessed through objective measures (e.g. clinical diagnoses, stressful life events inventory, Adverse Childhood Experiences Scale) or subjective scales (e.g. Perceived Stress Scale, Penn State Worry Questionnaire). Essential to studying the impact of such stressors on children’s health is the concept that the experience of stress is translated into physiological changes such as alterations of hypothalamic-pituitary-adrenal (HPA) or sympathetic-adrenal-medullary (SAM) axis activity (19, 20). Immune, cardiometabolic, and other neuroendocrine pathways may play key roles as well (21).

Joint exposure to synthetic chemical and non-chemical stressors—Not surprisingly, exposures to synthetic chemicals and non-chemical stressors often go hand in hand, with exposure to non-chemical stressors often driving increased chemical exposure (4). For example, a 2018 review of the literature on endocrine disrupting chemicals (EDC) and metabolic disease observed that exposures to synthetic chemicals including polychlorinated biphenyls, phenols, and phthalates were consistently higher among low income individuals and racial minorities compared to higher income, white participants (22). As a result, the associated economic burden of EDC-related disease is estimated to be disproportionately high among African-American and Mexican-Americans, and plausibly among other disadvantaged populations as well (23).

There are numerous reasons why exposure to synthetic chemicals and non-chemical stressors may be increased among marginalized populations. For example, industrial sites and waste facilities, where chemicals are produced, used, and discarded, are more likely to be situated in low-income communities. One study examined residential proximity to unconventional gas development as a source of exposure to both chemical (e.g., air pollution and water contamination) and non-chemical stressors (e.g., noise, light pollution, noxious odors and psychosocial stressors), observing associations with preterm birth and fetal death (24). Additionally, lifestyle and consumer choices about personal care and cleaning products, building and furniture materials, and food may be important. For example, personal care products marketed to and disproportionately used by minority women (including skin lighteners, hair straighteners, and douching products) often contain high

levels of synthetic chemicals such as phthalates (28822238). Similarly, individuals with low food security are more likely to consume canned and processed foods, resulting in higher levels of Bisphenol A (BPA) and phthalate metabolites (25, 26). An organic food diet may lower exposure to certain organophosphate pesticide metabolites, but buying organic produce may not be economically feasible for disadvantaged populations (27, 28). There are some exceptions to this trend of higher chemical exposure among disadvantaged communities. For example, some studies have found higher concentrations of perfluoroalkyl substances (PFASs) and organochlorine pesticides among higher income women, possibly due to greater consumption of fish and produce, however these associations may be population-specific (25, 29).

Mechanistically, chemical and non-chemical stressors may act upon the same biological systems (Figure 1). For example, maternal exposures to psychosocial stress and endocrine disrupting chemicals (such as PBDEs and PFASs) have each individually been linked to altered cytokine profiles (8, 30, 31). Similarly, phthalates and psychosocial stressors may both act upon oxidative stress pathways (32, 33). Even when mechanisms are unknown or disparate, chemical and non-chemical stressors may influence the same outcomes. For example, prenatal exposures to psychosocial stress and pesticides have each individually been linked to adverse neurodevelopmental outcomes, though the hypothesized mechanisms may differ (34, 35). For these reasons, it is increasingly clear that chemical and non-chemical stressors need to be considered together. From a modelling standpoint, this co-exposure suggests a need to consider effect modification, whereby exposures to stressors may potentiate or exacerbate the impact of chemical exposures on health outcomes.

Air pollution-stress interaction example as a model

The majority of studies on early life environmental exposures, psychosocial stressors and child health outcomes have focused on air pollution due to the extensive exposure data available. Although the focus of this review is on synthetic chemicals, we briefly consider air pollution as a model of how psychosocial stressors, specifically on the individual and neighborhood/contextual level, have been incorporated into studies of early life environmental exposures and health outcomes.

Individual level psychological stressors examined in studies of air pollution have included income, education, health insurance type, perceived stress, discrimination and stressful life events (36–40). For example, maternal stress, as measured by the crisis in family systems (CRISYS) questionnaire assessing negative life events in 11 domains, has been demonstrated to modify the effects of particulate matter and risk of wheeze (41). A more recent study examined air pollution and maternal lifetime traumatic stressors in relation to mitochondrial DNA copy number (a measure of mitochondrial response and dysfunction) in cord blood and placental tissue at birth, and found that the combination of air pollution and lifetime trauma was associated with a higher number of mDNA copies, indicating greater mitochondrial dysfunction, among mothers carrying boys (42).

Examples of contextual variables that have been examined as stressors include neighborhood socioeconomic status (37, 43–52), greenspace, and built environment (53, 54). Neighborhood SES has been characterized by census tract/block or zip code-level

percentages of income, education, unemployment, households living below poverty, income from public assistance, crime rate, residential crowding or combinations of factors in various deprivation indices. Additional publicly available data on socio-demographics, land use and air pollution exposures have been accessed using the normalized difference vegetation index (NDVI), which includes data on neighborhood green space, proximity to recreational facilities, distance to coastal and freshwater and distance to major road, to assess multiple exposures from the social and physical environment and how they affect perinatal health (53, 54). In some cases, it is unclear whether the vulnerability was due to social disadvantage (e.g., lower neighborhood SES) or additional exposures to environmental insults (54). Most studies examining neighborhood disadvantage as a modifying factor show increased vulnerability to the adverse effects of air pollution on health outcomes, with few exceptions (48, 52). To date, upwards of 20 studies have examined the joint effects of early life exposures to air pollution and psychosocial stressors with the majority finding a greater impact on adverse health outcomes when exposed in combination (36–54).

These studies are relevant to studies of other synthetic chemicals because it is likely many of the same concerns of co-exposure and increased vulnerability apply to these additional chemicals beyond air pollution that are not as easily assessed across large populations. Most studies have considered nonchemical factors, such as socioeconomic status, as potential “effect modifiers”, e.g., air pollution is more strongly associated with adverse outcomes among lower compared to higher socioeconomic status groups. In other words, these chemical and non-chemical stressors in combination are detrimental. Both from a biological and social pathway, chemicals in our society and bodies may affect health, especially in our vulnerable populations such as pregnant women and children.

Review of recent literature on synthetic chemical-stress interactions

In contrast to the relatively large literature on how air pollution may interact with non-chemical stressors to impact children’s development, research on synthetic chemical and non-chemical stressors is extremely limited. Whereas air pollution is typically measured through monitoring systems, studies focused on synthetic chemical exposures usually require properly timed, prospective collection of maternal biospecimens (urine and/or blood) for exposure assessment making them more costly and challenging to implement. To evaluate the current literature in this field, we conducted a systematic scoping review with a structured search of synthetic chemical and non-chemical stressors, excluding air pollution and heavy metals, and including studies from references of the reviewed literature.

Methods

We performed a search in PubMed of keywords (Medical Subject Heading and title/abstract terms) to capture (**1) non-chemical stressors (depressive disorder, depression, stress, stressor, anxiety, life events, mental health, psychosocial, psychological, prenatal stress, social class, socioeconomic status, poverty, material deprivation, neighborhood deprivation, neighbourhood deprivation, residence characteristics, crime, social position), and (2) chemicals (environmental exposure, environmental pollutants, chemical, synthetic chemical, industrial chemical, endocrine disruptor, phthalate, phenol, paraben, polybrominated

diphenyl ethers, perfluorinated compound, perfluoroalkyl acid, polyfluoroalkyl substance, pesticide), and (3) pregnancy/childhood (prenatal, perinatal, antenatal, pregnancy, gravidity, gravidity, pregnant, parturition, birth, gestation, foetus, fetus, fetal, infant, newborn, neonate, child). The search was limited to English language journal articles of human studies in the last 5 years (4/13/2014–4/11/2019). We examined the titles and abstracts of 1242 articles and reviewed a subset of full text articles. Only those articles that assessed both synthetic and non-chemical exposures in the context of any perinatal or child health outcome were retained, including those that utilized composite exposure measures that included a synthetic chemical (e.g. pesticides). The authors discussed any articles that were unclear as to their inclusion/exclusion (e.g. stress as an outcome rather than an exposure) to come to a consensus. In addition, the authors reviewed references cited in the selected papers in order to identify any additional articles of interest, including any highly relevant older papers. Our search resulted in 12 included studies. We have displayed topics of resulting articles (Figure 2).

Results

Pesticides

To date, the largest literature on synthetic chemical-stress interactions has focused on co-exposure to stress and pesticides, both well-known developmental neurotoxins. By design, pesticides are engineered to interfere with neurotransmitter systems, inhibiting neural proliferation, migration, myelination, and synaptogenesis (55). Similarly, psychosocial stress disrupts neuroendocrine pathways, though the precise mechanisms are not well understood (56). Three studies have examined the joint impact of pesticides and non-chemical stressors on early childhood cognitive development. Two of these studies were based on CHAMACOS, a study of Latino farmworker families with elevated occupational pesticide exposures. Dialkyl phosphate metabolite concentrations (DAPs), biomarkers of organophosphate pesticide (OP) exposure, were measured in maternal urine during pregnancy while adversity and social support were measured at multiple time points from pregnancy through early childhood (57). Associations between maternal DAP concentrations and child full scale IQ at age 7 were strongest among children who also experienced greater adversity across childhood (including stressful life events, poverty, adverse learning environments, adverse home environments, and total adversity averaged across childhood) (n=329). This result was consistent across sexes, although the strongest stress-related modifier of the association between OP concentrations and IQ differed by sex. In boys, for example, learning environment was the strongest modifier such that a 10-fold increase in prenatal DAP concentrations was associated with a 13.3 point (95% CI: −19.9, −6.7) decrement in IQ in boys with a poor learning environment, but a non-significant 4.2 point increase (95% CI: −4.2, 12.5) in boys with a richer learning environment. In girls, poverty was a particularly important modifier, with a 10-fold increase in prenatal DAP concentrations being associated with a 8.5 point decrement (95% CI: −16/7. −0.4) in IQ in girls from households with greater economic adversity compared to a 4.7 decrement (95% CI: −12.8, 3.4) in IQ among girls from households with less economic adversity.

Subsequent work in this cohort at age 10 (n=501) used geospatial data from the California Pesticide Use Reporting (PUR) System to estimate residential proximity to OPs and carbamate pesticide use during pregnancy, and drew upon income and neighborhood (census tract) poverty data to model exposure to non-chemical stressors during childhood (58). Maternal pesticide exposure and neighborhood poverty were individually associated with 3–4 point and 2 point reductions in full-scale IQ scores (respectively) at age 10. Importantly, in stratified analyses, the impact of prenatal pesticide exposure on IQ was stronger among children raised in households at or below the poverty line compared to children raised in homes above the poverty line. For example, among children whose household was at or below the census tract poverty threshold, full-scale IQ scores were nearly four points lower (95% CI: −7.2, −0.5) in children in the highest quartile of pesticide exposure compared to the lowest quartile, whereas among children living above the poverty level, IQ scores in the highest and lowest quartiles of pesticide exposure did not differ significantly (β=−1.5, 95% CI: −6.6, 3.7). No effect modification by neighborhood poverty level was observed.

The Cincinnati-based HOME study also examined maternal OP metabolites during pregnancy in relation to child cognition at ages 1–5 and considered the role of maternal socioeconomic status (n=327) (59). In crude analyses, maternal concentrations of OP metabolites were positively associated with cognitive measures (Bayley Mental Development Index and Wechsler Preschool and Primary Scale of Intelligence scores), however adjustment for covariates including SES-related variables attenuated associations. Observing that OP metabolite concentrations were higher among well-educated, white, and married women, the authors suggested that in this cohort, OP bioburden was a marker of increased produce consumption and more generally a better diet and higher SES. One interpretation of these studies is that an adverse impact of prenatal pesticide exposure on neurodevelopment may be ameliorated by an enriched home or social environment, however more research is needed to understand these complex interactions in different populations.

Two additional studies have examined other child outcomes in relation to prenatal pesticide exposure. The South African VHEMBE study (n=674) observed that maternal concentrations of the organochlorine pesticide, dichlorodiphenyltrichloroethane (DDT), and its breakdown product dichlorodiphenyldichloroethylene (DDE) were associated with higher rates of childhood illness at age 2 (60). For example, a 10-fold increase in maternal p,p'-DDE concentrations was associated with a 1.21 times (95% CI: 1.01, 1.46) higher incidence rate ratio (IRR) for persistent childhood fevers (lasting 4 or more days). Importantly, these associations were much stronger among children from households with family incomes below the officially designated South African poverty line (IRR=1.31, 95% CI: 1.08, 1.59) compared to children from households above the poverty line (IRR= 0.93, 95% CI: 0.69, 1.25). Similarly, modification of the pesticide-fever association was observed in relation to insufficient maternal nutrient intake in pregnancy. In the absence of non-chemical stressors, no associations were observed, suggesting that only when maternal-child physiology was weakened by poverty or malnutrition did DDT/DDE have a measurable impact on the developing immune system. Given the pandemic poverty and malnutrition facing much of the developing world paired with the rampant production of synthetic chemicals, these interactions are especially important to consider. Importantly, although the preponderance of research on synthetic chemical exposures has focused on industrialized countries, these

findings suggest a need for additional work in the developing world. A final study, in 13,654 French mother-infant dyads, used administrative databases to examine concentrations of the herbicide atrazine in community drinking water across pregnancy, neighborhood "deprivation" (quantified using the European Deprivation Index), and preterm birth risk (61). No association between atrazine and preterm birth risk was observed even accounting for neighborhood deprivation. Given the lack of individual-level data on atrazine and non-chemical stressors, it remains unclear whether this represents a true null result or a case of exposure misclassification.

Phthalates

Phthalates are a class of endocrine disrupting chemicals that are widely found in consumer products including processed food, personal care products, and building materials (62). Given the sources of exposure, concentrations of phthalate metabolites are often higher among disadvantaged populations and minorities (63, 64). Although best known for their anti-androgenic properties, phthalates may also impact additional endocrine pathways (e.g. thyroid, estrogen) and activate inflammatory and oxidative stress mechanisms (65, 66). In animal models and humans, prenatal exposure to certain phthalates (such as diethylhexyl phthalate [DEHP] and dibutyl phthalate [DBP]) is associated with alterations in male reproductive development including reduced anogenital (AGD) distance (reviewed in (67)). AGD is best known as a marker of reproductive toxicity of chemical exposures in animal models, and in adult men, shorter AGD has been linked to lower semen quality, testosterone, and fertility (26846869). A 2009 rat study observed that prenatal exposure to dexamethasone, a synthetic glucocorticoid that readily crosses the placenta, exacerbated the adverse impacts of DBP on male reproductive development, suggesting a potential phthalate-stress interaction (68). A similar study in humans examined how psychosocial stress, as measured by maternal reported stressful life events during pregnancy (such as a death in the family, job loss, or financial strife), may modify phthalate-AGD relationships in mother-offspring dyads participating in the multi-center TIDES study (n=738) (69). In line with previous research, overall, mothers with higher concentrations of DEHP and DBP metabolites had sons with shorter anogenital distance. However, when analyses were stratified by whether mothers had reported any stressful life events during pregnancy, the inverse associations between phthalate exposure and AGD were limited to "lower stress" mothers who reported no stressful life events, and in many cases the phthalate-AGD relationship was positive in "higher stress" mothers. For example, first trimester maternal ΣDEHP concentrations were associated with shorter AGD in sons born to "lower stress" mothers (β=−1.78, 95% CI: −2.97, −0.59), but longer AGD in sons born to "higher stress" mothers (β=1.62, 95% CI: −1.09, 4.34). In contrast to some other studies, in which stress may heighten the impact of chemical stressors, these results suggest that in this case, stress may exert a protective effect against reproductive disruption by phthalate exposure, possibly by raising prenatal androgen levels. Similar results have been reported in a second, smaller U.S. cohort (n=105) (70).

A Charleston, SC area pregnancy cohort (n=380) further examined the impact of phthalates on child development with potential for modification by race, which is often used as a proxy for socioeconomic and/or psychosocial adversity (71). Consistent with some previous work,

for 6 out of 8 phthalate metabolites measured, African-American mothers had significantly higher concentrations than white women (72), and tended to be younger and less educated, with lower income and higher body mass index. When stratified by race (and adjusted for covariates including maternal age and education), associations between DEHP metabolites, such as MEHP, and one measure of sons' AGD, anopenile distance, was stronger among black participants (β=−2.07, 95% CI: −4.05, −0.08) than among white participants (β= −1.23, 95% CI: −3.18, 0.73). In fact, among white participants, concentrations of certain metabolites (including ΣDBP) were associated with significantly longer anoscrotal distance, a second measure of AGD (β=1.30, 95% CI: 0.03, 2.57). In the same cohort, racial differences in the relationship between maternal phthalate concentrations and fetal penile dimensions (as measured by ultrasound) were observed. For example, ΣDBP concentrations were associated with increased penile volume among white participants (β=3.84, 95%CI: −0.62, 8.29), but decreased volume among black participants (β=−1.71, 95%CI: −6.39, 2.96). Associations between prenatal phthalate exposure and birth outcomes (including preterm birth and low birth weight) in this cohort also showed some evidence of modification by maternal race, however variation by metabolite and outcome make it difficult to draw any firm conclusions, and additional measures that more accurately capture non-chemical stress were not reported (73). Importantly, this work also highlights the fact that pregnant women with higher exposure to synthetic chemicals like phthalates often have numerous additional risk factors for adverse outcomes (that may or may not be related to non-chemical stress) including minority race/ethnicity, young age, unmarried status, and low educational attainment and income.

Polychlorinated biphenyls

Polychlorinated biphenyls (PCBs) are synthetic chemicals that were used between the 1930s-1970s as insulation and flame retardants. Despite being banned in the U.S. in the 1970s and in the United Kingdom in the 1980s when adverse health effects were determined, they remain in the environment due to long biological half-lives and their bioaccumulation in the food chain. The Avon Longitudinal Study of Parents and Children (ALSPAC) is a birth cohort that has examined 14,541 pregnant women in Great Britain and their children. In a sample of 448 mother-daughter dyads, one study examined the association between 3 PCBs (PCB-118, PCB-153 and PCB-187) and fetal growth, after adjusting for parity, maternal age, pre-pregnancy BMI, educational status, tobacco use and gestational age of infant at sample collection (74). Mother's education status modified associations between prenatal serum PCB levels and birth weight, such that inverse associations were observed primarily among mothers with low educational attainment. Daughter's birth weight was −138.4 g lower (95% CI: −218.0, −58.9) for each 10 ng/g lipid increase in maternal serum PCB-118. Similarly, every 10 ng/g lipid increase in maternal serum PCB-153 was associated with a −41.9 g (95% CI: −71.6, −12.2) lower birth weight. Every 10 ng/g lipids increase in maternal serum PCB-187, was associated with a −170.4 g (95% CI: −306.1, −34.7) lower birth weight, among girls with mothers in the lowest education group.

Environmental Indices

Environmental indices including the Environmental Quality Index (EQI) and the Communities Environmental Health Screening Tool (also known as the CalEnviroScreen) were created to compare environmental exposures over wide geographies to compile data from multiple sources and identify areas of environmental justice. Studies have overlaid these cumulative exposure data with existing health records to identify risk factors examine combined effects of environmental and social stressors (75, 76). For example, pollution burden (a combination of air, water, pesticides, hazardous waste, traffic and other exposures in the CalEnviroScreen (77)) was associated with preterm birth in Fresno County, California (2009–2012), and associations were strongest among disadvantaged census tracts (as determined by neighborhood socioeconomic status) (75). Similarly, in a study of 24 million births across the U.S. (2000–2005), county level EQI was associated with preterm birth and domains that had the strongest associations included air and sociodemographic domains, which included data on housing, income, education and crime (76).

Conclusions

To date, the vast majority of studies have focused on the health impact of a single chemical exposure (or class of chemical exposures), however there is increasing recognition that chemical exposures co-occur with other types of non-chemical stressors, such as psychosocial stressors. We have presented recent examples of epidemiologic studies that have addressed combined effects of chemical and non-chemical stressors for several classes of chemicals, along with non-chemical stressors that include neighborhood- and individual-level stressors.

Cumulative risk assessment has been proposed to evaluate possible additive and synergistic effects of multiple chemical, physical and social stressors on human health, with the goal to inform policy and decision-making, and protect public health (21). The concept of the “public health exposome” has also been proposed to integrate environmental, individual, and population health measures, thereby expanding the definition of the exposome to include social-ecological factors operating over the life course (78). Given the relative infancy of the field and the need to integrate complex, variable data from multiple tools, sources, and disciplines, there is not yet a consensus as to the optimal quantitative approaches to assess combined effects of chemical and nonchemical exposures. Approaches depend on the specific research question being explored (e.g., whether chemical exposures are mediated by or modified by non-chemical stressors, or whether mixtures exposures jointly affect outcomes). A recent review discusses several statistical techniques used to evaluate cumulative impacts from chemical and non-chemical stressors (79), though this remains a topic of further discussion.

There is also a clear need for additional work to investigate the mechanisms by which chemical and nonchemical stressors may affect adverse health outcomes. For example, the many physiological sequelae of psychosocial stress (including effects on hormone pathways, immune function and inflammation, and oxidative stress) may prime the body to be more susceptible to the effects of downstream chemical exposures. Environmental toxicants and psychosocial stressors share many biological substrates and influence overlapping

physiological pathways and have been reviewed with regard to several neuroendocrine endpoints related to hypothalamic-pituitary-adrenal axis function, sex steroid levels, neurotransmitter circuits, and innate immune function (80). Better understanding the mechanisms may help to identify potential targets for intervention given the current challenges in reducing exposure to chemical and non-chemical stressors.

In addition, better understanding the timing of exposures will be important in future work and goes a step beyond traditional considerations about “critical periods” or “sensitive windows”. In studies integrating chemical and non-chemical stressors, we must not only consider the timing of exposures within the life course, but also the relative timing of the two exposures. For example, one conceptual model could suggest that chemical exposures only have an impact on development when physiology is suppressed or vulnerable due to non-chemical stressors. Alternatively, it is possible that the impact of prenatal chemical exposures on development is only unmasked when stressors emerge later in life. Questions about chronic versus acute stress are also important in this context and the extent to which disparate stressors (e.g. discrimination, depression, exposure to violence) may interact differently with chemical stressors is unknown. At present the literature is too sparse to compare these alternatives and additional well-designed longitudinal studies are clearly needed to evaluate these and other conceptual models.

There are an increasing number of studies and indices that have compiled geographic information systems data on environmental, social and built environment factors such as the Healthy Places Index, CalEnviroScreen and Environmental Quality Index. These indices provide an opportunity to observe joint associations across large geographic areas, though these ecologic measurements are subject to exposure misclassification. There is still a need for prospective cohorts with high quality exposure data that can ask more specific questions regarding the many stressors that affect our health and identify key combinations of chemical (e.g., product use) and non-chemical stressors (e.g., perceived stress). The National Institutes for Health (NIH)’s Environmental influences on Child Health Outcomes (ECHO) Program, established in 2015, is a consortium of cohorts representing up to 50,000 mother-child dyads from across the U.S. With its large sample size, extensive longitudinal data collection, and focus on environmental stressors, ECHO is well-poised to advance our understanding of how chemical and nonchemical stressors individually and jointly impact perinatal outcomes as well as asthma, obesity and neurodevelopment.

In summary, studies that have examined the joint effects of chemical and non-chemical stressors have generally found stronger associations with adverse health outcomes when combined compared to each stressor independently. Future studies should continue to explore joint effects to identify vulnerable populations and elucidate potential underlying mechanisms by which chemicals and non-chemical stressors may affect adverse health outcomes.

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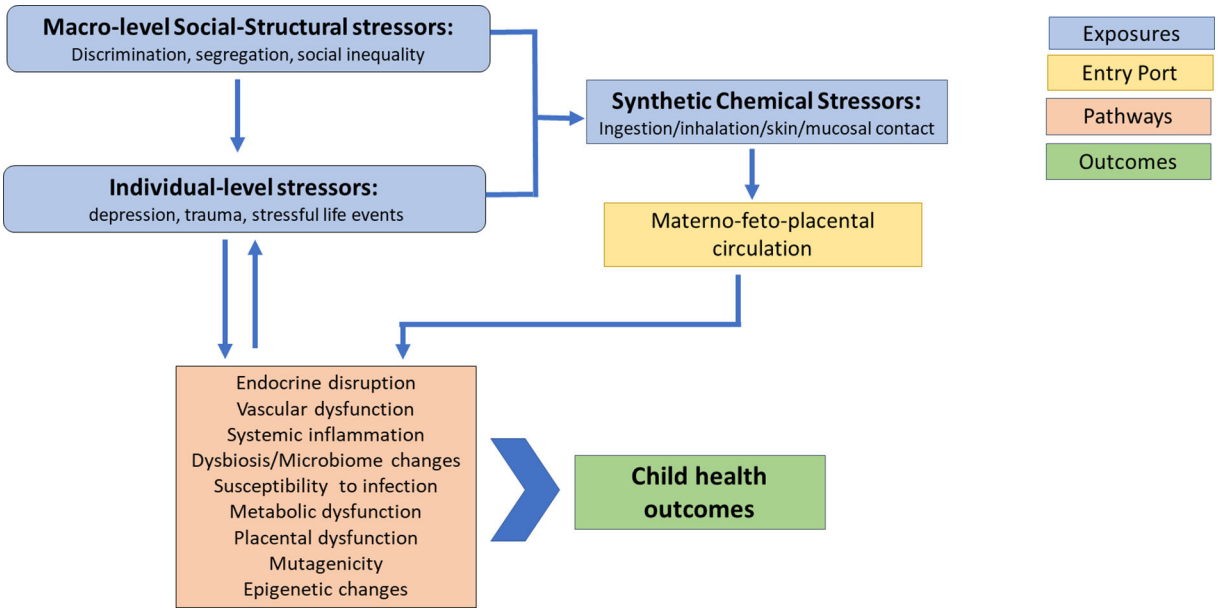

Figure 1:

Biological mechanisms by which synthetic chemical and non-chemical stressors may individually and jointly impact perinatal health. Adapted from Padula et al. (81)

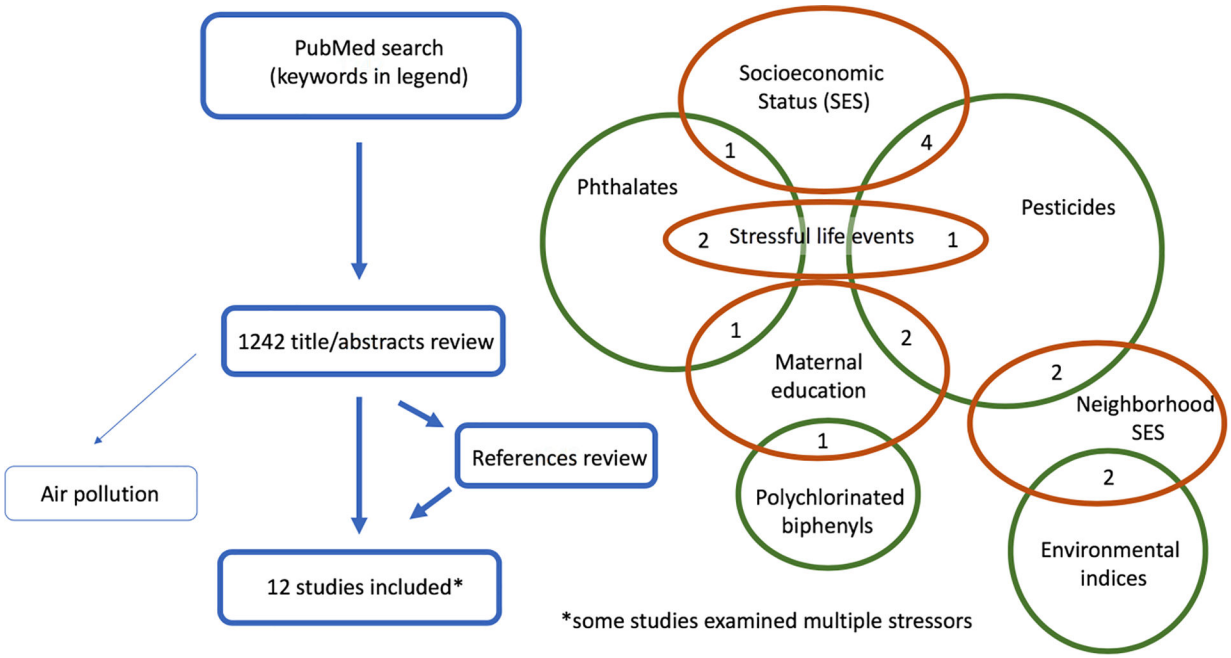

Figure 2:
Literature search methods and resulting studies that consider the joint impacts of chemical and non-chemical stressors on child health outcomes.