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Early life risk and resiliency factors and their influences on developmental outcomes and disease pathways: a rapid evidence review of systematic reviews and meta-analyses

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Review

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Abstract

The Developmental Origins of Health and Disease (DOHaD) framework aims to understand how environmental exposures in early life shape lifecycle health. Our understanding and the ability to prevent poor health outcomes and enrich for resiliency remain limited, in part, because exposure–outcome relationships are complex and poorly defined. We, therefore, aimed to determine the major DOHaD risk and resilience factors. A systematic approach with a 3-level screening process was used to conduct our Rapid Evidence Review following the established guidelines. Scientific databases using DOHaD-related keywords were searched to capture articles between January 1, 2009 and April 19, 2019. A final total of 56 systematic reviews/meta-analyses were obtained. Studies were categorized into domains based on primary exposures and outcomes investigated. Primary summary statistics and extracted data from the studies are presented in Graphical Overview for Evidence Reviews diagrams. There was substantial heterogeneity within and between studies. While global trends showed an increase in DOHaD publications over the last decade, the majority of data reported were from high-income countries. Articles were categorized under six exposure domains: Early Life Nutrition, Maternal/Paternal Health, Maternal/Paternal Psychological Exposure, Toxicants/Environment, Social Determinants, and Others. Studies examining social determinants of health and paternal influences were underrepresented. Only 23% of the articles explored resiliency factors. We synthesized major evidence on relationships between early life exposures and developmental and health outcomes, identifying risk and resiliency factors that influence later life health. Our findings provide insight into important trends and gaps in knowledge within many exposures and outcome domains.

Introduction

Over 30 years ago, David Barker observed that maternal nutrition during pregnancy and birth weight were related to adult health including rates of ischemic heart disease[1,2]. Those observations led him to suggest that poor fetal nutrition could "increase the susceptibility to the effects of an affluent diet" which could then increase the risk of cardiovascular disease in later life[3]. Thus, he hypothesized that suboptimal environments during pregnancy could affect development, influencing the risk of adult chronic diseases[1–4].

Barker's hypothesis inspired an onslaught of studies eventually leading to the emergence of the field now known as the Developmental Origins of Health and Disease (DOHaD). DOHaD has grown into the dominant theoretical framework that is used to investigate how environmental exposures during embryonic, fetal, neonatal, child, and adolescent life can shape the development and occurrence of chronic diseases and disorders[5–8]. Specifically, DOHaD research has inspired a series of large-scale longitudinal cohort studies that start early during development to investigate these exposure–outcome relationships[9–13].

Despite important advances in DOHaD knowledge, our understanding of the role that early life exposures have on poor health outcomes and our ability to prevent these outcomes and enrich for resiliency remain limited. These limitations are due in part to the highly complex

nature of exposure–outcome relationships and the tendency of most studies to focus on single variables, often through a biomedical lens, when most outcomes have multivariable origins. Therefore, a comprehensive list of exposures, or their interactions, associated with health trajectories is difficult to generate, which limits our ability to predict risk or resiliency. Further, the dissemination of information to individuals, caregivers, and policy-makers has also been limited.

We conducted a Rapid Evidence Review (RER) to better understand the complex relationships between early life exposures and their contributions to later health outcomes and asked the following question: what are the major risk and resiliency factors in early life that are associated with adult-onset disease pathways that could be used to predict health and disease trajectories? There is a strong need to integrate and consolidate available information on the social, environmental, and biomedical determinants of health[14] into the DOHaD framework. We aimed to identify geographical trends and socioeconomic and cultural groups that are captured by DOHaD studies. These findings may have implications for policy, public health, education, and well-being[15].

Methods

We conducted an RER following guidelines provided by the National Collaborating Centre for Methods and Tools[16]. Additionally, our study adhered to a modified version of the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) checklist[17] (Supplementary Table S1).

Information sources and search terms

A literature search was conducted between May 6 and May 10, 2019, using the search engines CINAHL, PubMed, ProQuest, and Web of Science. The following search string was used: (Maternal* OR Paternal*) AND (weight OR obes* OR nutrition OR diet* OR stress OR social support) AND (child OR infant) AND (Programming AND Development); Mother–child relation* AND Programming; Child* AND development AND Programming AND (stress OR depression OR anxiety OR sensitivity OR temperament) AND mental health; Parent–child relation* AND Programming; Programming AND *natal; Development* AND Origins AND Programming; Development* Origins of Health and Disease; (Maternal* OR Paternal*) AND (gene* OR immune* OR metabol* OR inflam* OR brain OR neuro* OR cardio* respiratory) AND (development OR growth OR Programming) AND (child OR infant). The search was limited to articles published within the last 10 years, between January 1, 2009 and April 19, 2019. This search yielded 2380 articles in the English language (Fig. 1), in which 2030 articles were retained after deduplication. EndNote Basic was used as a reference manager application.

Inclusion criteria

Due to a large volume of results initially captured ($n = 2380$), we narrowed our search to include only systematic reviews and meta-analyses. Further inclusion criteria included: (1) human studies, (2) studies that looked at health and disease origins with exposures during the preconception, prenatal, or postpartum periods and outcomes during birth or after birth, (3) studies that looked at health and disease origins with exposures applicable to the mother, father, or offspring and outcomes affecting the offspring, (4) studies that involved assessing risk or resilience outcomes, and (5) access to full text. Studies of drug effects on adult-onset disease pathways were excluded.

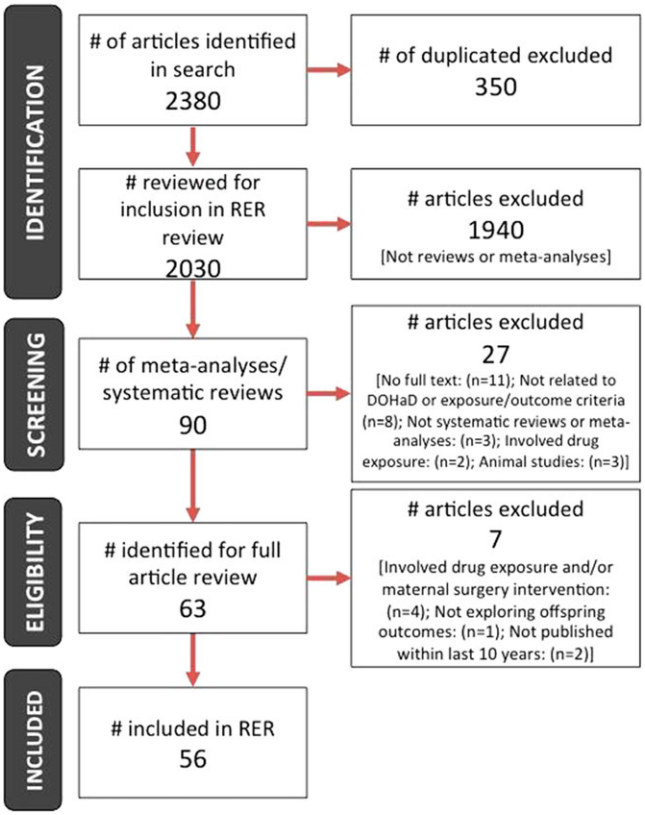

Fig. 1. Flow diagram of the review of citations identified by the search the initial capture resulted in 2380 articles using identified search terms. After deduplication, abstracts and title of records underwent level 1 screening to identify which were systematic reviews or meta-analysis, where 1940 articles were excluded, resulting in 90 articles. At level 2, full text of articles was reviewed to assess for the outlined inclusion criteria, after which 26 were excluded, resulting in 64 articles. At level 3, an additional 8 studies were deemed to not fit the outlined inclusion criteria, and a final total of 56 studies were obtained.

Creation of exposure and outcome domains

Studies were categorized into discrete domains based on the main exposures and outcomes investigated (Tables 1 and 2). This is an approach that has been used in the DREAM BIG consortium[18] and builds on approaches used by ALSPAC and GENERATION-R cohorts[19,20]. The exposure domains were developed after consideration of the developmental era during which the exposure was experienced (preconception, prenatal, or postpartum), biological risks and exposures, and exposures applicable to the mother, father, or offspring. The most frequently studied fields of exposures were identified through a preliminary search of DOHaD literature and expert consensus. Outcomes present at any developmental era after birth were considered. Studies that involved multiple exposures or outcomes were included in multiple domains, as appropriate.

Article screening and data extraction

A 3-level screening process (Fig. 1) was performed by three independent reviewers. In the case where there was disagreement, the issue was resolved by discussion. At level 1, articles evaluated based on title and abstract were screened out if they were not a systematic review or meta-analysis. References for 90 articles were obtained

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Table 1. Classifications for exposure domains

Domain	Definition
Toxicants Environment	Involving environmental risks such as air pollution, contaminated food and water, and/or exposure to environmental toxic substances.
Early Life Nutrition	Involving maternal, paternal, or infant (post-weaning) nutrition, diet, supplement intake or lack of, breastfeeding (BF) behaviors (e.g. ever/never, exclusive BF, duration of BF), or breast milk composition.
Maternal/Paternal Physiologic Health	Involving exposure from metabolic and physiologic health status of mother or father (e.g. maternal/paternal obesity, underweight, diabetes, gestational weight gain, infectious or immune diseases, etc.).
Maternal/Paternal Psychological	Involving exposures such as stress, depression, anxiety, and/or other psychological features from the mother or father ascertained in the preconception, prenatal, and/or postpartum period.
Social Determinants	Involving social determinant exposures such as poverty, occupation, education, and/or discrimination as well as environment enrichment factors (e.g. home environment).
Other	Does not fall into any of the domains above. This involves things such as infant birth size and advanced maternal age.

Table 2. Classification for outcome domains

Domain	Definition
Neurological	Involving brain development, cognitive capacity and abilities (such as memory and intelligence), and/or learning disabilities
Behavior	Involving temperament, behavior, and personality influences.
Physiologic Programming	Involving metabolic programming such as stress reactivity, effects of lipids, protein hormones, receptors, and metabolic and physiological disorders such as obesity, diabetes, cancer, cardiovascular, age-related disease, immune diseases/disorders, and respiratory disorders (Asthma, wheeze, etc.)
Development/Growth	Involving growth in height, weight, body composition, muscle and bone, as well as birth measures such as anthropometric measures, preterm birth, birth weight, small for gestational age, large for gestational age, etc.
Psychological	Involving stress management, depression, anxiety, and/or other psychological features.
Genetics	Involving structure, function, evolution, and mapping of genomes.

for full-text review in level 2. Articles were excluded if there was no full-text access ($n = 11$), were not related to DOHaD or discussed exposure or outcome criteria on offspring ($n = 8$), were not systematic reviews/meta-analyses ($n = 3$), assessed drug exposure ($n = 2$), or contained animal studies ($n = 3$), leaving 63 articles for review and data extraction. At the third-level screening, articles were further excluded for examining drug exposure and maternal surgery intervention, which were not specified exposures in inclusion parameters ($n = 4$), primarily focused on maternal outcomes and not offspring ($n = 1$), and were not within the search date range ($n = 2$). For the third screening stage, extracted data for $n = 56$ included PECO data (patient/population, exposure [time period and specific type of exposure], comparison group(s), outcome [specific type of outcome)] descriptions), follow-up times (categorized into discrete developmental periods of 0–4 years, 5–10 years, 11–14 years, 15–19 years, 20 years+), themes (domains) for exposures, and themes (domains) for outcomes. The 56 included systematic reviews/meta-analyses were reviewed to determine if some of the same studies were included in multiple reviews/meta-analyses. There was no overlap of studies within the 56 systematic reviews/meta-analyses included in this RER.

To determine the magnitude of effect of the various exposures on outcomes of interest within each of the 56 studies, pooled summary statistics for the most significant or primary findings, as reported in the full text of the studies, were extracted. Summary statistics were either reported as an Odds Ratio (OR), Risk Ratio (RR), Relative Index of Inequality (RII), Pearson's correlation, mean difference (weighted or standard), Cohen's d, range, or a beta value. For summary statistics that could be converted to OR, a point estimate for the odds ratio is provided in the figure legend. In the case where the studies reported inconclusive main findings or summary statistics, no value was retained.

Data synthesis

Graphical Overview for Evidence Reviews (GOfER) diagrams (21) were created to visualize exposure–outcome relationships and present key data collected from reviews such as size, design, follow-up, participant characteristics, and outcomes used[21]. We grouped studies within a GOfER diagram based on exposure domains identified in Table 1 and displayed the value and type of pooled summary statistics extracted from each study as applicable. Other data visualizations were created using RStudio software (version 0.97.551 for heatmaps, stacked area graphs) or RAWGraphs[22] (for Alluvial diagrams).

Study quality appraisal

Study quality was determined based on the quality assessments reported in the 56 reviews and categorized on a scale consisting of low-, moderate-, and high-quality categories. Reviews containing either a majority of low- or a majority of high-quality studies were categorized as low or high, respectively. Other studies that included a mixture of low- and high-quality evidence were categorized as moderate. Due to the heterogeneity of the studies within and between the 56 reviews, it was not possible to conduct an independent formal quality assessment of the methodology and evidence.

Results

Assessing global trends

We first evaluated global trends in the 56 captured studies[23–78] by identifying countries where studies took place or where study populations or cohorts originated. Studies included within the reviews assessed in the RER were from a diverse range of countries (Fig. 2). However, the majority of cohorts or study populations originated from high-income countries, predominantly the United States, followed by the United Kingdom and Australia (Fig. 2). Fewer studies were from South American, African, and

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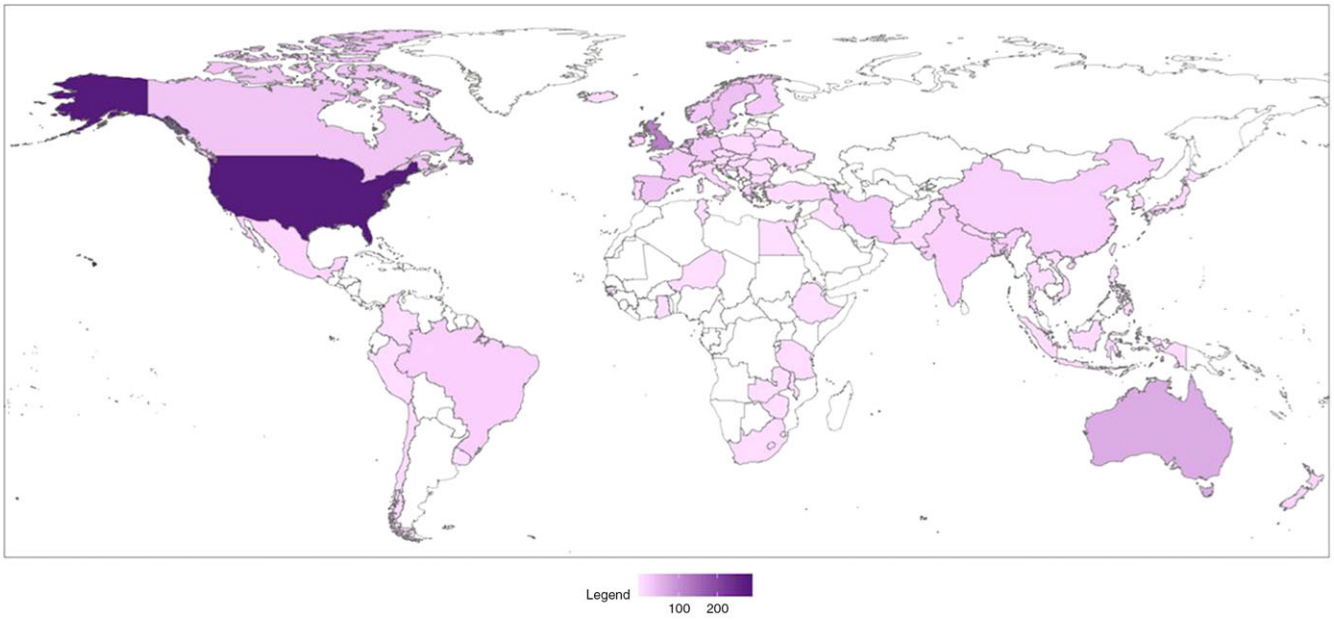

Fig. 2. Heatmap of distribution of each study contained within the systematic reviews/meta-analyses by country where the study took place or where cohort or study population were based. Data values of the country count are represented as colors where the darker to lighter gradient represents higher study counts to lower study counts of countries where studies were based. Data are shown for 50 studies.

South East Asian countries, suggesting that the effects of early life exposures on lifecourse health outcomes may not be as extensively documented in these regions.

Domain distributions

To understand trends between early life exposure variables and health outcomes, we evaluated the frequency of exposures being represented in the literature over time (Fig. 3). Within the exposure domains, 19 articles fell under "Early Life Nutrition"; 12 under "Maternal/Paternal Physiologic Health"; 9 under "Maternal/Paternal Psychological Health"; 12 under "Toxicants/Environment"; 5 under "Social Determinants"; and 3 under "Other". More studies are published at a later date indicating that research in the DOHaD field is increasing within these exposure domains (Fig. 3). Within the outcome domains, 23 articles were related to "Development/Growth"; 24 were related to "Physiological Programming"; 20 were related to "Neurological/Cognitive"; 5 were related to "Genetics"; 5 were related to "Psychological"; and 7 articles were related to "Behavior".

We also aimed to identify where evidence for DOHaD relationships may be greatest or lacking. Studies that involved "Early Life Nutrition", which was the most studied exposure domain, explored mostly development/growth, physiological programming, and neurological/cognitive outcomes (Fig. 4). The second (Maternal/Paternal Health) and third (Maternal/Paternal Physiological) most commonly studied exposure domains explored outcomes across all categories.

Associations between early life exposures and health outcomes

The 56 systematic reviews/meta-analyses included in the RER were grouped according to exposures studied and organized into GOfER diagrams to visualize exposure and outcome relationships and trends within the six domains (Fig. 5–9).

Articles investigating exposures related to parental and/or infant diet and nutrition were categorized under the domain early life nutrition (Fig. 5). Out of the 19 articles grouped in this domain, 14 found moderate to significant associations with summary statistics obtained for 11 studies. According to one meta-analysis, studies investigating maternal nutrition during pregnancy found that maternal probiotics and fish oil supplements are associated with decreased risk of eczema and allergies in the offspring[38]. Meta-analytic evidence also showed that moderate fish intake during pregnancy was also found to be associated with lower risk of preterm birth and increased birth weight[52]. Resiliency factors in this domain include lifestyle interventions (i.e. diet and physical activity) during pregnancy adopted by women who have obesity that were associated with reduced measures of obesity in infants[31]. Another study exploring breastfeeding behaviors found human milk to be protective of physiological programming and neurological/cognitive outcomes (i.e. late-onset sepsis, severe premature retinopathy, and severe necrotizing colitis)[58]. Furthermore, meta-analyses revealed that vitamin D supplementation was found to be positively associated with increased birth weight, decreased risk of small for gestational age at birth, and reduced risk of wheeze in children, while low vitamin D status was associated with infant adiposity and risk of childhood eczema[63,65,74]. Another nutritional exposure, long-chain polyunsaturated fatty acid supplementation during pregnancy, was associated with improvement in child crystallized intelligence[69] and reduction of allergic disease[42] as shown through a meta-analysis. Only physiological programming, development/growth, and neurological/cognitive outcome domains were studied in this exposure domain. No studies investigated associations between early life nutrition exposures and psychological, behavioral, and/or genetics outcomes.

Studies investigating exposures related to parental physiologic or metabolic health were grouped under the domain maternal/paternal physiologic health (Fig. 6). A total of 12 articles fell under this domain, with 10 reporting moderate to significant findings.

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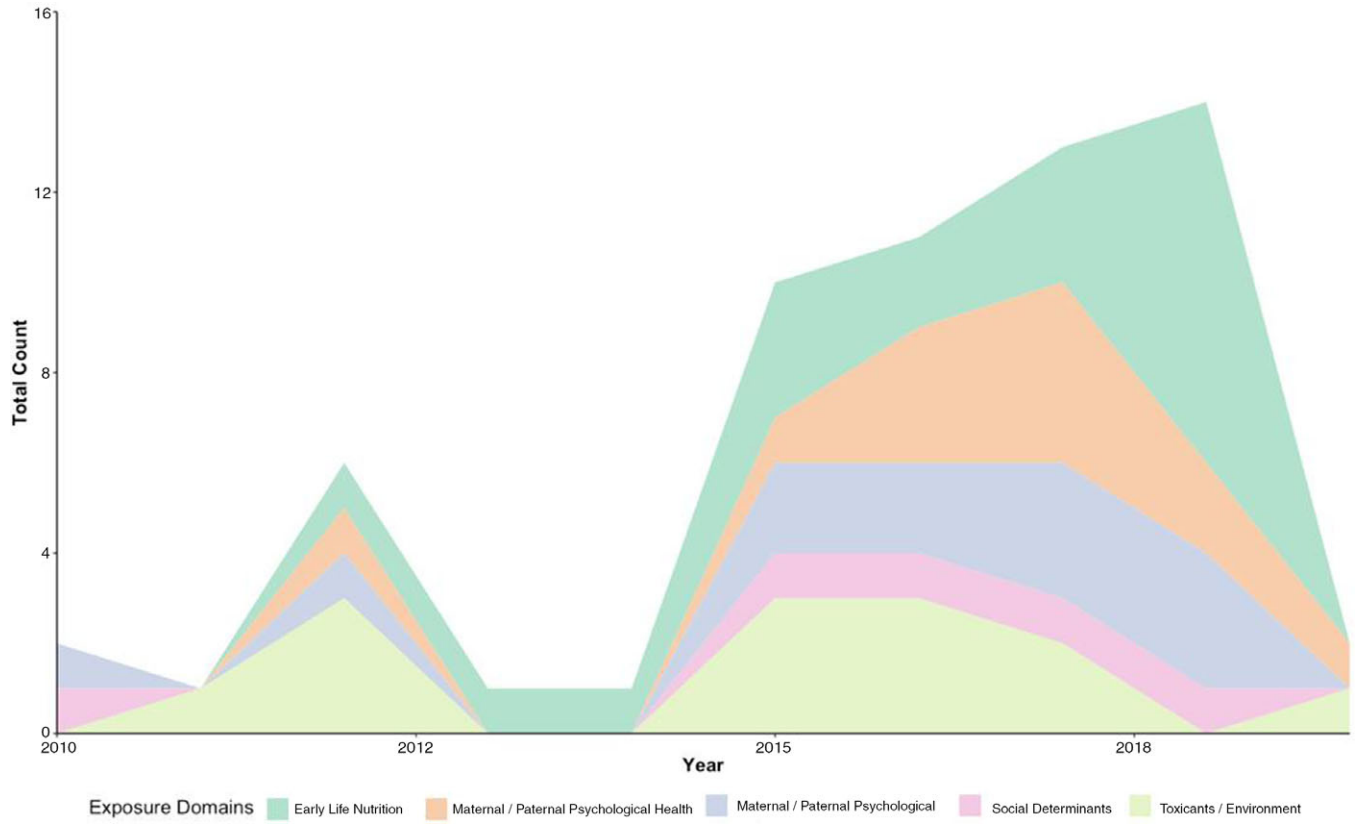

Fig. 3. Stacked area graph displaying the total number of studies published within each exposure domain over time, pulled from studies included in the 56 systematic reviews/meta-analyses. Each stack as coded by color in the figure legend represents a total count of that particular exposure domain within the included systematic reviews/meta-analyses over the last 9 years. Higher stacks at a particular year indicate a greater total count of the exposure domain for that time point.

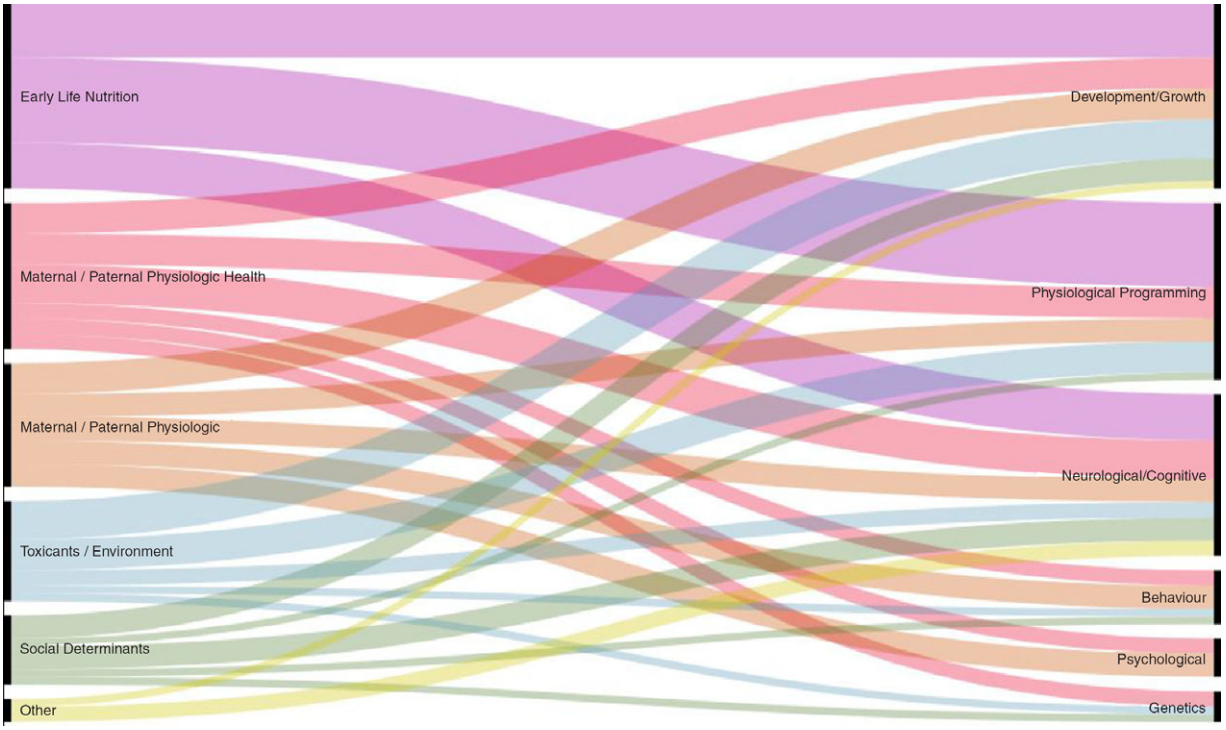

Fig. 4. Alluvial diagram of exposure and outcome domains showing the flow of weighted links between exposure and outcome domains indicating the number of studies included in the RER that explore that particular exposure–outcome relationship.

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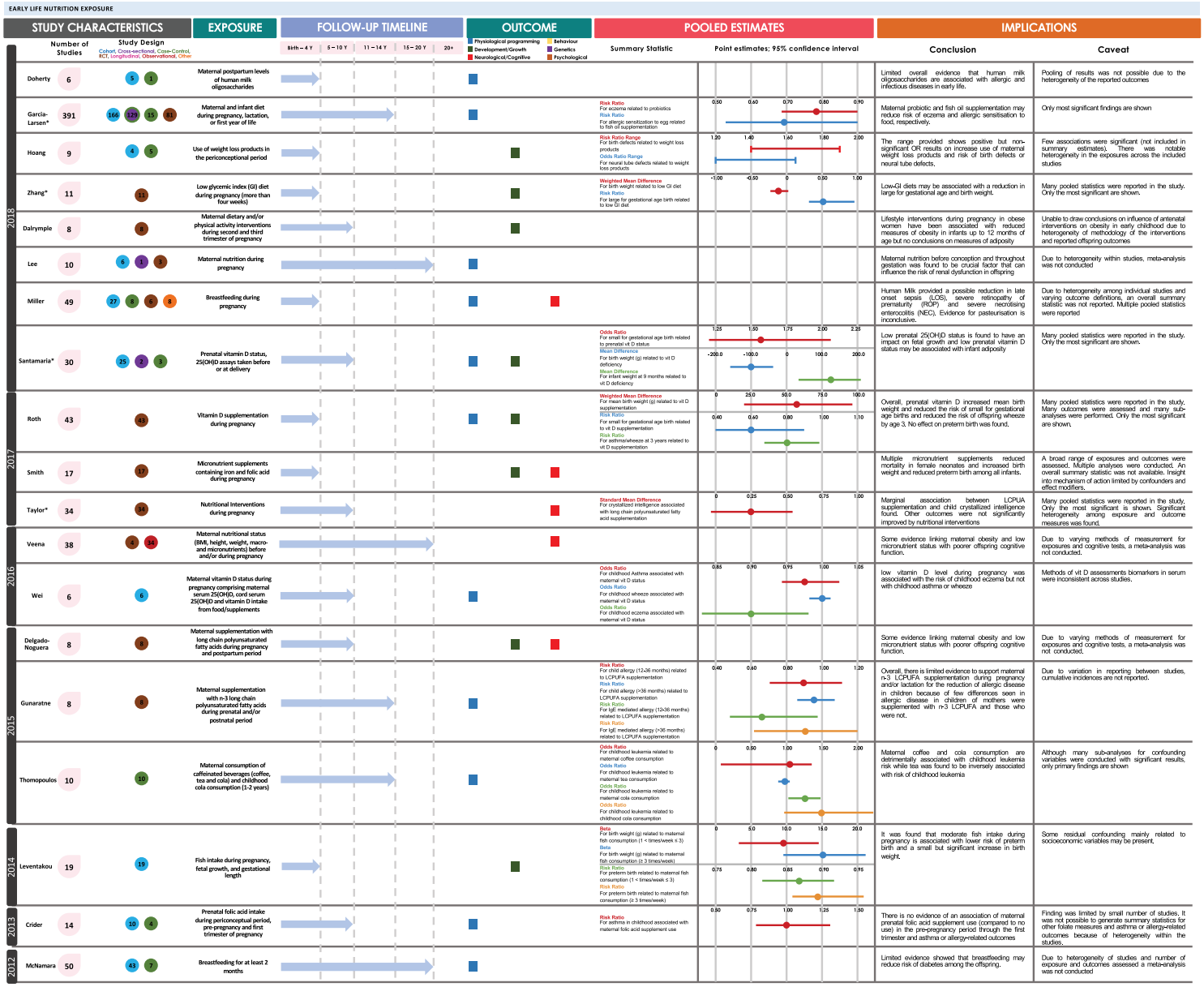

Fig. 5. Summary of studies within the early life nutrition exposure domain. Study characteristics, specific exposures, and outcomes explored within each study, major findings, and implications are summarized. Follow-up timelines include the range of ages during which results were ascertained. The outcome column identifies the domains of outcome which were tested for association with the corresponding exposure. For studies that reported 1–4 primary/significant summary statistics or ranges, pooled estimates are presented. Studies that did not conduct a meta-analysis, did not report a summary statistic, or reported 5 or more primary/significant statistics are identified under "caveat" in the implications column. * Only the most significant pooled estimates, as identified by the systematic review/meta-analysis, are reported for these studies; refer to Supplementary Table S2 for more information.

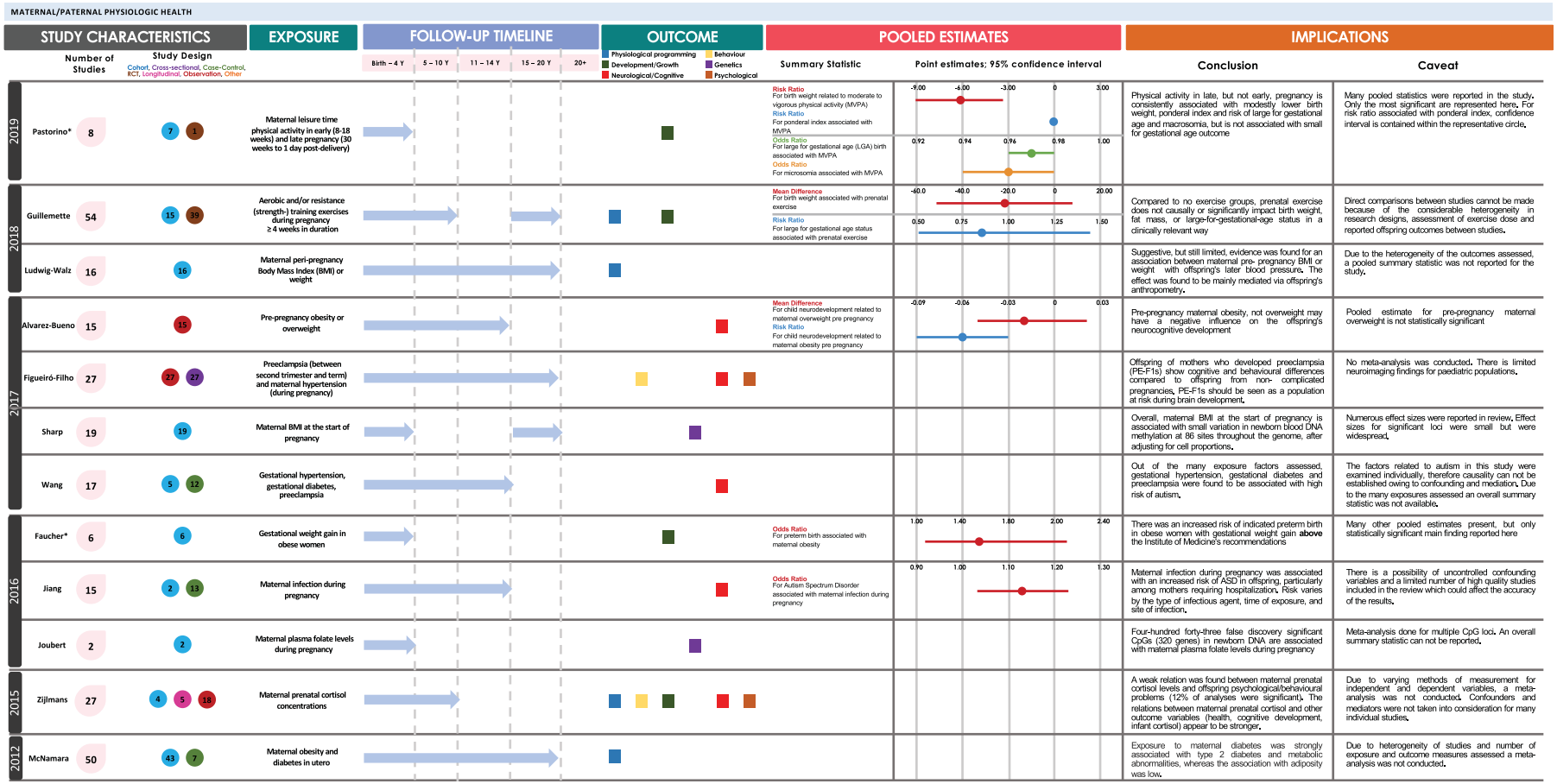

Fig. 6. Summary of studies within maternal/paternal health exposure domain. Study characteristics, specific exposures, and outcomes explored within each study, major findings, and implications are summarized. Follow-up timelines include the range of ages during which results were ascertained. The outcome column identifies the domains of outcome which were tested for association with the corresponding exposure. For studies that reported 1–4 primary/significant summary statistics or ranges, pooled estimates are presented. Studies that did not conduct a meta-analysis, did not report a summary statistic, or reported 5 or more primary/significant statistics are identified under "caveat" in the implications column. * Only the most significant pooled estimates, as identified by the systematic review/meta-analysis, are reported for these studies; refer to Supplementary Table S2 for more information.

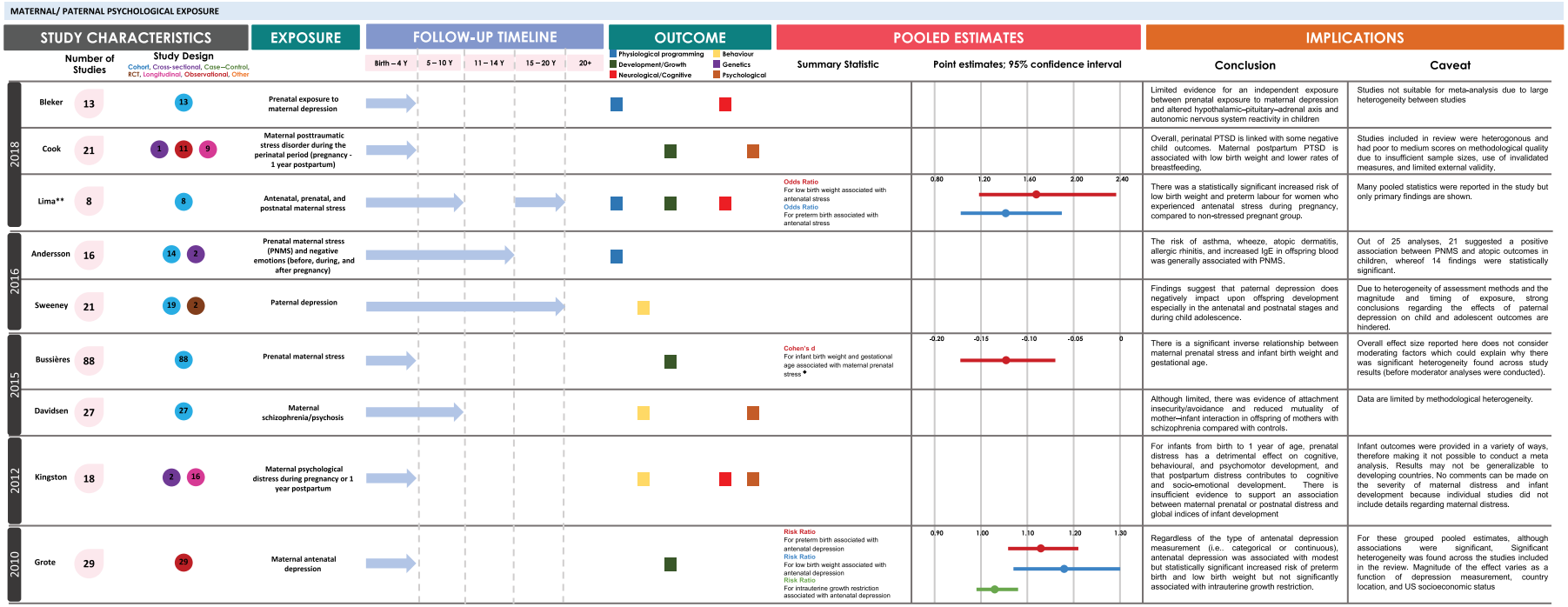

Fig. 7. Summary of studies within maternal/paternal psychological exposure domain. Study characteristics, specific exposures, and outcomes explored within each study, major findings, and implications are summarized. Follow-up timelines include the range of ages during which results were ascertained. The outcome column identifies the domains of outcome which were tested for association with the corresponding exposure. For studies that reported 1–4 primary/significant summary statistics or ranges, pooled estimates are presented. Studies that did not conduct a meta-analysis, did not report a summary statistic, or reported 5 or more primary/significant statistics are identified under "caveat" in the implications column. ** Only primary pooled estimates, as identified by the systematic review/meta-analysis, are reported for these studies; refer to Supplementary Table S2 for more information. ◆ Odds Ratio = 0.804.

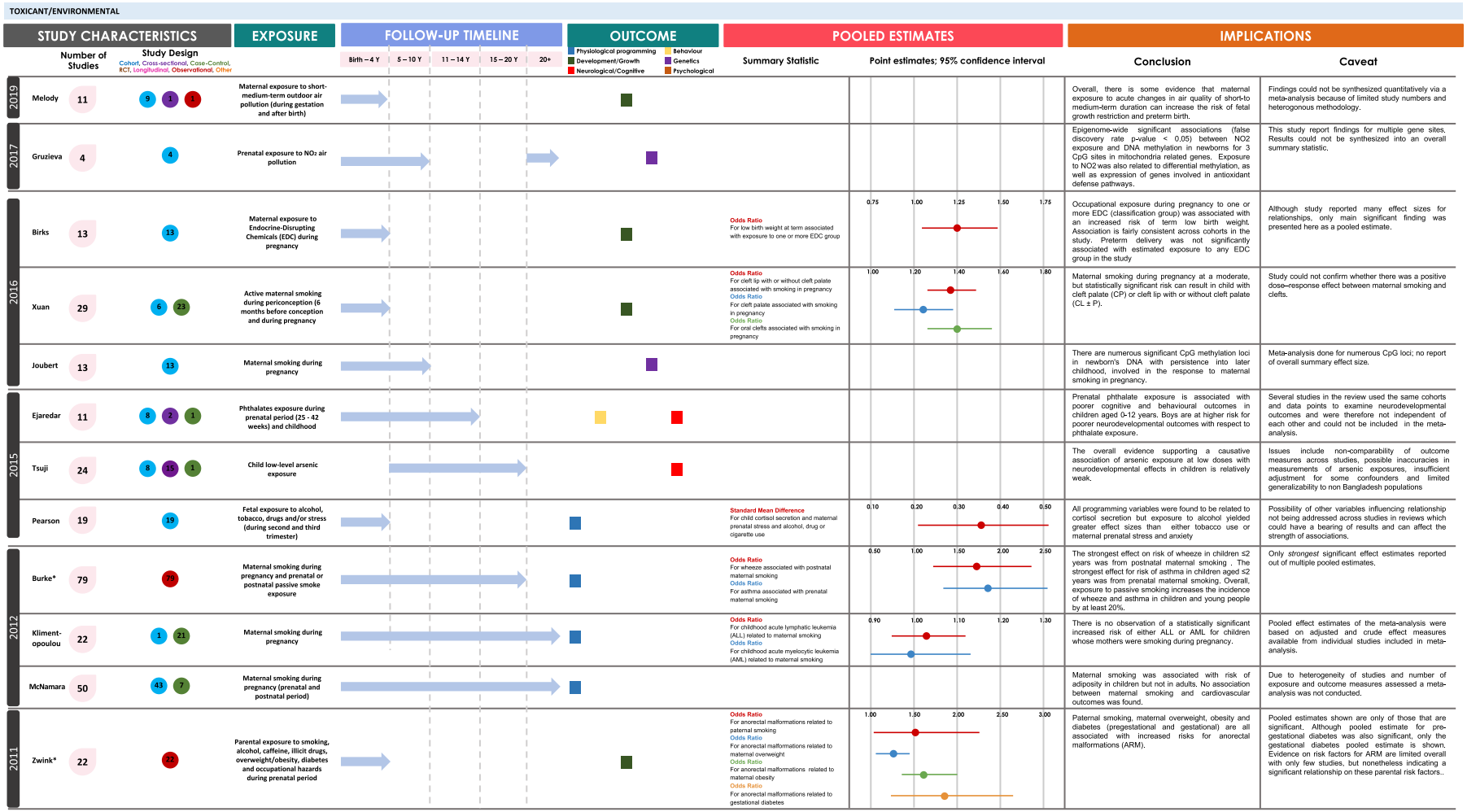

Fig. 8. Summary of studies within toxicant/environment exposure domain. Study characteristics, specific exposures, and outcomes explored within each study, major findings, and implications are summarized. Follow-up timelines include the range of ages during which results were ascertained. The outcome column identifies the domains of outcome which were tested for association with the corresponding exposure. For studies that reported 1–4 primary/significant summary statistics or ranges, pooled estimates are presented. Studies that did not conduct a meta-analysis, did not report a summary statistic, or reported 5 or more primary/significant statistics are identified under "caveat" in the implications column. * Only the most significant pooled estimates, as identified by the systematic review/meta-analysis, are reported for these studies; refer to Supplementary Table S2 for more information.

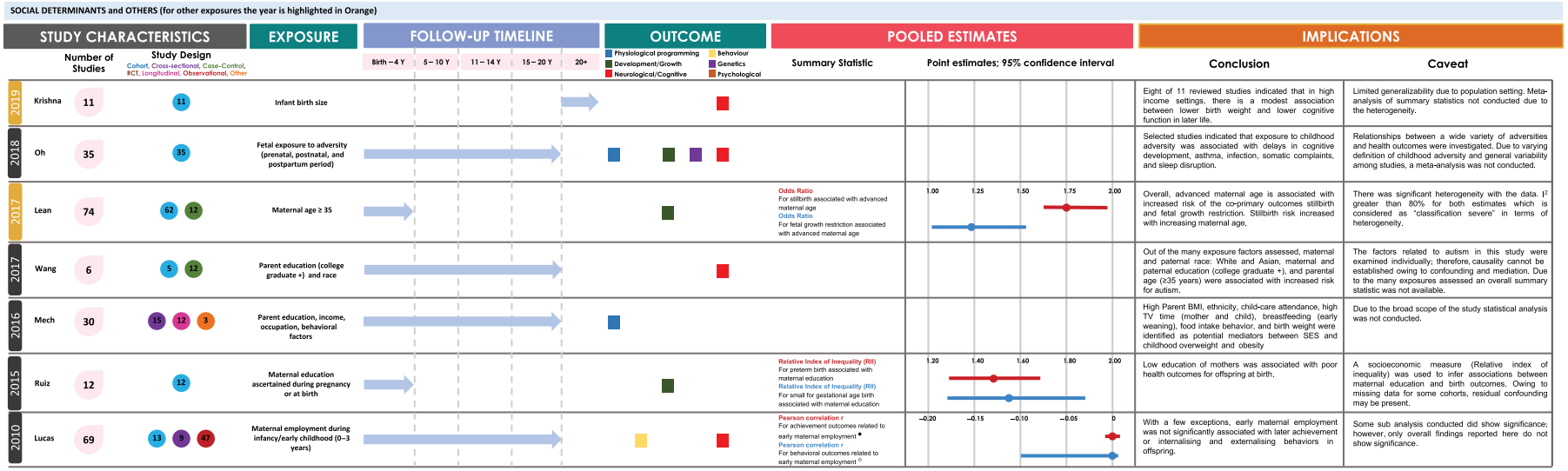

Fig. 9. Summary of studies with Social Determinants and Others exposure domains. Studies under the domain Others are represented by year of publication highlighted in orange. Study characteristics, specific exposures, and outcomes explored within each study, major findings, and implications are summarized. Follow-up timelines include the range of ages during which results were ascertained. The outcome column identifies the domains of outcome which were tested for association with the corresponding exposure. For studies that reported 1–4 primary/significant summary statistics or ranges, pooled estimates are presented. Studies that did not conduct a meta-analysis, did not report a summary statistic, or reported 5 or more primary/significant statistics are identified under "caveat" in the implications column. ◆ Odds Ratio = 1.004. ◇ Odds Ratio = 1.018.

Within this domain, obesity and overweight during pregnancy were commonly investigated. High maternal BMI and obesity were found to be associated with development/growth (e.g. risk of preterm birth)[36] and, according to meta-analysis results, genetic (e.g. variation in DNA methylation)[66] and physiological programming (e.g. increased risk of Type II diabetes)[55]. Preeclampsia, maternal hypertension, and infection during pregnancy were found to be risk factors for neurocognitive development[37] and, as determined through meta-analyses, for autism spectrum disorders as well[44,73]. The most studied outcome domain in this exposure domain was neurological/cognitive, with autism and neurocognitive measures appearing as specific common variables.

The exposure domain maternal/paternal psychological, contained articles exploring features of parental psychological exposures, such as stress during preconception to the postpartum period (Fig. 7). Nine studies were grouped in this domain, where eight found moderate to strong associations. Prenatal maternal stress was studied in three articles and found to be associated with physiological programming and development/growth outcomes in offspring, specifically increased risk of allergic disorders[24]. Two of these three studies were meta-analytic studies that observed an association between prenatal maternal stress and low birth weight and preterm labor[28,59]. One study examined paternal depression during the antenatal and postnatal period and found an association with poor behavioral development in offspring[68]. Another study explored maternal schizophrenia and found it to be linked to attachment insecurity/avoidance in offspring[32].

Studies exploring exposures to environmental risk factors or toxicants during the prenatal period or through childhood were categorized under the toxicant/environment domain (Fig. 8). A total of 12 articles studied exposures within this domain with 11 reporting moderate to strong associations with outcome variables. Air pollution as an exposure was found to be associated with development/growth (e.g. fetal growth restriction, preterm birth)[40] and genetic outcomes (e.g. differential DNA methylation determined through meta-analytic evidence)[57]. Phthalate exposure was found to be associated with poor cognitive and behavioral outcomes[35]. Maternal smoking during pregnancy was the most common studied exposure in this domain, with six studies exploring its effects on health outcomes through the lifecourse. Through mainly meta-analyses results, smoking was found to be associated with offspring physiology and metabolic outcomes (i.e. wheeze and asthma[27] and childhood adiposity[55]), development/growth outcomes, specifically birth defects (i.e. cleft lip, cleft palate[75], and anorectal malformations[78]), and genetic outcomes (i.e. differential DNA methylation[45]).

Five studies involving social determinant exposures were grouped under the social determinants domain (Fig. 9). Studies in this domain explored factors such as exposure to adversity during pregnancy (e.g. abuse, neglect, trauma, household dysfunction), parent education, race, income, occupation, and behavioral factors. Exposure to childhood adversity was associated with delays in cognitive development, asthma, infection, and sleep disruptions[60]. One meta-analysis reported parent education and race (White and Asian) to be associated with increased risk of autism[73]. The reasons for these associations are not evident. This finding should, therefore, be interpreted with caution, and future studies to confirm or contradict those results must be conducted and, if findings were confirmed, mechanistic studies should be carried out to explain observed associations. Another study found that ethnicity, childcare attendance, and high TV time were mediators of childhood overweight and obesity[56]. Three studies were grouped under the domain "Other" (Fig. 9). One of these studies examined birth size as the exposure and found an association between lower birth weight and lower cognitive function in high-income settings[49]. Another meta-analytic study looking at advanced maternal age found it to be associated with increased risk of stillbirth and fetal growth restriction[50]. In the third study, exposures such as fetal distress, labor type, and cesarean delivery were associated with increased risk of developing autism as determined through a meta-analysis[73].

Risk vs. resiliency

Of the 56 articles, most explored risk factors for poor development and adverse health outcomes are summarized for each domain in Fig. 5–9. Resiliency factors were explored in 11 articles in the early life and nutrition domain (Fig. 5) and two articles in the Maternal/Paternal Health domain (Fig. 6). Factors that conferred resiliency factors included maternal dietary-related items (i.e. fish, tea)[31,52,70]; dietary interventions, micronutrient supplementation (established through a meta-analysis) such as vitamin D, iron folate, and fish oil supplements[38,63,67]; and as determined by meta-analytic evidence, breastfeeding compared to formula (exclusive vs. any)[58], and physical activity in pregnancy[61].

Critical assessment

Information regarding critical appraisal reports by authors of the studies were extracted and organized into broad categories. Of the 56 studies, 15 did not perform or report concrete critical appraisal or quality assessment information. Of the 39 studies that did perform quality assessment, 12 included high-quality studies, 8 articles rated their studies as low quality, and the remaining articles (21) rated included studies as moderate quality.

Discussion

This analysis of systematic reviews and meta-analyses provides the first comprehensive perspective on the known early life exposures across biomedical, social, and environmental contexts affecting developmental and health trajectories. Here we analyzed the existing evidence on the complex relationships between early life exposures and offspring outcomes, aiming to pinpoint factors that could be used to predict health and disease.

Results from GOfER analyses revealed that the three most studied exposure domains were early life nutrition, maternal/paternal (physiologic/metabolic) health, and toxicants/environment. The three major outcome domains studied were development/growth, physiologic programming, and neurological/cognitive. Social determinants exposures and psychological, behavioral, and genetics outcomes were least represented. The importance of nutrition for a healthy pregnancy, fetus, and child has been well documented[79]. Although early life nutrition emerged as the most commonly studied domain, there is a need for increased research involving culturally/geographically influenced dietary practices, and breastfeeding behaviors. The increased global consumption of processed food warrants research in risks related to those dietary items, as part of early nutrition[20]. Similarly, studying population-specific diet and nutrition, as well as breastfeeding behavior, mother–father/child bonding, and other differences found across cultures, would contribute to the growing DOHaD literature[80].

Within the psychological exposure domain, most studies provided a qualitative synthesis related to psychological and behavioral outcomes. One study within this domain investigated

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maternal schizophrenia as an exposure, whereas most others focused on maternal stress and depression. In regard to mental health, it is important to consider the complex challenges associated with development and treatment to improve care and prevent adverse outcomes[81]. This RER highlights the need for more research in the origins and outcomes of psychological and mental health-related exposures beyond parental depression and stress, such as mood, personality, and addiction disorders.

Health risk prevention was found to be a dominant theme within the toxicant/environment domain. Many studies explored maternal smoking as an exposure, which is expected since adverse offspring outcomes related to smoking have been consistently identified in research[82]. More novel findings revealed that air pollution is a potential risk factor for fetal growth restriction, preterm birth, and differential methylation patterns[40,57]. This is important for understanding the effects of environmental disruption on fetal health programming and may have implications for clinical interventions and public policy[6].

Geographical trends revealed a higher research focus in high-income countries. The effect of early life exposures on developmental trajectories and health is vastly underexplored in Asian (12.8% of the studies reviewed) and African populations (only 1.7% of the studies reviewed), suggesting that less attention has been paid to the developmental programming hypothesis in these regions[83,84]. In the global context, this bias toward Western, Educated, Industrialized, Rich, and Democratic (WEIRD) populations leaves gaps in our understanding of DOHaD. More DOHaD research in developing countries and traditional societies is needed to explore different population characteristics, experiences, and environment influences for the subsequent development of context-sensitive policy and population-specific interventions that can reduce disease risks and enrich for resiliency[83,84].

Trends on published research over time revealed gaps in certain outcome domain representation. For example, studies evaluating the effects of early life nutrition did not investigate psychological, genetics, and behavior outcomes in offspring. Exploring the relationship between early life nutrition and psychological and behavioral outcomes is very important since diet has been linked with mental health, where healthy nutrition can improve mental health and well-being[85], human capital, and the ability to integrate into society[86]. These findings highlight the importance of developing models that can capture the complexity of multiple interactions between exposures and outcomes. Despite the link between socioeconomic determinants and mental health being well established[87], psychological and behavioral outcomes are underrepresented by studies exploring the social determinants of health.

Importantly, research in the DOHaD field has begun to shift from entirely exploring developmental factors that affect the onset of disease pathways to those that promote health and resilience[88]. Nonetheless, we still found a higher proportion of studies focused on DOHaD risk factors (78.3%) compared to resiliency factors (21.7%). Of those that have been recognized for providing resiliency or have the potential to correct suboptimal development in early life, diet and exercise are the most well-represented factors in our review. Yet, studying resiliency factors and understanding how they interact with risk factors are paramount to informing interventions tailored to prevent or mitigate adverse health outcomes. For example, while one study in the early life nutrition domain looked at vitamin D deficiency and found an association with decreased fetal growth, another article found vitamin D supplements to be associated with improved birth size[63,65]. While the findings in our evidence synthesis are limited for resiliency factors, several studies have emerged that provide recommendations on building resilience throughout the lifecyclefactors[89–91]. Yet, it is our understanding that the evidence in this area is still not clear, and more research on resiliency needs to be conducted to identify and test productive interventions.

The largest limitation observed within the 56 included studies relates to the heterogeneity in the methodology, interventions, characteristics of controls, and data collection and analysis procedures used. For example, regarding intervention and outcome differences, studies would vary in how they defined "stillbirth"[50] or "employed individual"[53,56]. Subsequently, these studies used different methodologies to obtain and report the magnitude of effect for exposure–outcome relationships with some reviews not obtaining a pooled summary statistic due to the high heterogeneity cited by study authors. Additionally, few studies included a longitudinal follow-up in adulthood; most explored outcomes in birth or infancy. A lack of follow-up data limits our understanding of whether outcomes observed in early life persist into adulthood, knowledge that is critical to better understand lifecycle health and develop tools to predict long-term health and disease outcomes. This limitation could be explained by the high cost of conducting follow-up studies, attrition over time, and complexity of working with large longitudinal cohorts[92]. Additionally, many study cohorts were recently initiated; thus, many cohort participants in follow-up studies are still younger. There was also a lack of studies accounting for paternal effects[93], even though early life programming of development and health is not limited to maternal contributions[92].

While our analysis of the existing literature suggests that there are several areas in which information remains limited, the data available suggest this preliminary set of initial recommendations for research and policy consideration:

- Increased focus on research exploring decisive early life exposures and health outcomes in low income and developing countries as well as marginalized groups, a concern identified as important in literature[83,84,94].
- Increased focus on paternal factors that contribute to offspring health outcomes to identify major early life exposures that may have been overlooked due to a larger focus on maternal factors[93–95].
    - Additionally, increased focus on long-term effects of household dynamics, including maternal and paternal stress on child emotional and cognitive development[96].
- Increased study of resiliency factors, which can help inform public policy and public health interventions that support resiliency throughout the lifecycle and allow individuals to reach their full potential.
- Tailored recommendations for micronutrient supplementation to specific groups or for specific needs for optimal benefit for mothers, fathers, and children[97].
    - For example, the benefits of maternal vitamin D supplementation have been established,[98–100] and more recently, recommendation on increased vitamin D supplementation for pregnant women has been explored[101]. This information can be used by health professionals to determine specific micronutrient requirements for pregnant women and accommodate them accordingly.

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- Prioritize emotional intelligence, conflict resolution, and mental health-specific education, screening and treatment of new mothers and fathers to improve health outcomes for both mother and child, since maternal and paternal stress and mental health exposures have been shown to be highly correlated with negative outcomes during pregnancy[102–104].

Despite the comprehensive nature of our study, there were some limitations to our review. First, due to the large number of articles initially captured ($n = 2380$), we limited further screening and analyses to only systematic reviews and meta-analyses. This prevented the exploration of other studies that could have provided additional insight and data on DOHaD relationships. Nonetheless, our findings represent a necessary first step to understanding the breadth of current research and to identify major risk and resiliency factors. Additionally, certain relationships identified in the RER were found to be underrepresented, for example, studies with social determinant-related exposures and psychological and behavioral outcomes were few. Yet, we know from the Research Advancement through Cohort Cataloguing and Harmonization (ReACH) cohort database that cognition/personality and psychological outcomes are commonly measured[105].

There was a high degree of heterogeneity between the included studies. The approach used in each of the 56 studies to analyze and report the magnitude of effect varied, making a consistent analysis of effect sizes difficult. As a result, a summary statistic for studies included in the RER could not be generated. Instead, pooled estimates were reported when the original review provided them. Furthermore, we were limited in comparing effect sizes within an exposure domain because of the various ways studies reported them (i.e. as odds ratios, as standard or weighted mean differences, etc.). Finally, a critical appraisal could not be performed in a rigorous and consistent manner due to the diversity in methodology and analysis within the systematic reviews and meta-analyses. Instead, the quality assessments reported by the original reviews (if available) were used for our assessment, potentially biasing the validity of our synthesis.

Although included studies were limited to systematic reviews and meta-analyses, these reviews help in summarizing the research landscape in a comprehensive way. They enable decision-makers to quickly gain knowledge of synthesized evidence, allowing for a better assessment of current research and existing gaps. This is particularly advantageous for an incredibly diverse field like DOHaD, where heterogeneity in the topics studied can create barriers for their use by non-experts and those making policy-related decisions. Moreover, this review synthesized evidence on exposure–outcome associations and identified where gaps in evidence exist, or associations are under investigated. These findings are important to consider when translating DOHaD research into practice, including its applications in education, public health, and policy fields. Additionally, due to the rapid research output and diverse nature of DOHaD publications, data mining and interpretation become increasingly difficult. Future studies may necessitate the use of artificial intelligence and/or machine learning to leverage knowledge synthesis and translation toward improved practice and policy. As a next step, research in the field should focus on using the available evidence to generate predictive models integrating risk and resiliency variables. Informative tools that predict health trajectories can be used to aid in health decision making, develop targeted interventions that optimize development in early life, and to promote participatory and bottom-up health care[106].

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References

1. Barker DJP, Osmond C. Infant mortality, childhood nutrition, and Ischaemic heart disease in England and Wales. *The Lancet* 1986; 327, 1077–1081.
2. Barker DJP, Osmond C, Winter PD, Margetts B, Simmonds SJ. Weight in infancy and death from Ischaemic heart disease. *The Lancet* 1989; 334, 577–580.
3. Barker DJP, Godfrey KM, Gluckman PD, Harding JE, Owens JA, Robinson JS. Fetal nutrition and cardiovascular disease in adult life. *The Lancet* 1993; 341, 938–941.
4. Wadhwa PD, Buss C, Entringer S, Swanson JM. Developmental origins of health and disease: brief history of the approach and current focus on epigenetic mechanisms. *Semin Reprod Med.* 2009; 27, 358–368.
5. Barker DJP. Developmental origins of adult health and disease. *J Epidemiol Commun Health.* 2004; 58, 114–115.
6. Heindel JJ, Balbus J, Birnbaum L, *et al.* Developmental origins of health and disease: integrating environmental influences. *Endocrinology* 2015; 156, 3416–3421.
7. Jacob CM, Baird J, Barker M, Cooper C, Hanson M. The Importance of a Life Course Approach to Health: Chronic Disease Risk from Preconception through Adolescence andAdulthood. WHO promoting health through the life-course; 2017. p. 41.
8. Hertzman C. Putting the concept of biological embedding in historical perspective. *Proceedings of the National Academy of Sciences of the United States of America* 2012; 109 Suppl 2: 17160–17167.
9. Boyd A, Golding J, Macleod J, *et al.* Cohort Profile: the 'children of the 90s'–the index offspring of the Avon Longitudinal Study of Parents and Children. *Int J Epidemiol.* 2013; 42, 111–127.
10. Dontje ML, Eastwood P, Straker L. Western Australian pregnancy cohort (Raine) Study: generation 1. *BMJ Open* 2019; 9, e026276.
11. Lahelma E, Aittomäki A, Laaksonen M, *et al.* Cohort profile: the Helsinki health study. *Int J Epidemiol.* 2012; 42, 722–730.
12. Lumey LH, Stein AD, Kahn HS, *et al.* Cohort profile: the Dutch hunger winter families study. *Int J Epidemiol.* 2007; 36: 1196–1204.
13. Richter L, Norris S, Pettifor J, Yach D, Cameron N. Cohort profile: Mandela's children: the 1990 birth to twenty study in South Africa. *Int J Epidemiol.* 2007; 36: 504–511.
14. Bircher J, Kuruvilla S. Defining health by addressing individual, social, and environmental determinants: new opportunities for health care and public health. *J Public Health Policy.* 2014; 35, 363–386.
15. Suzuki K. The developing world of DOHaD. *J Dev Orig Health Dis.* 2018; 9, 266–269.
16. National Collaborating Centre for Methods and Tools. Methods: Synthesis 1. Rapid reviews: Methods and implications [Internet]. Hamilton ON: National Collaborating Centre for Methods and Tools. Available from: http://www.nccmt.ca/pubs/Methods_Sythesis1.pdf.
17. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol.* 2009; 62, 1006–1012.
18. Wazana AD, Evans J, Pearson R, Tiemeir H, Meaney M. Dream Big: Developmental Research in Environmental Adversity, Mental health, Biological susceptibility and Gender [Internet].[cited 2019, Sep 11]. Available from: http://dreambigresearch.com/

19. Cecil CAM, Lysenko LJ, Jaffee SR, *et al.* Environmental risk, Oxytocin Receptor Gene (OXTR) methylation and youth callous-unemotional traits: a 13-year longitudinal study. *Mol Psychiatry*. 2014; 19, 1071–1077.
20. Rico-Campà A, Martínez-González MA, Alvarez-Alvarez I, *et al.* Association between consumption of ultra-processed foods and all cause mortality: SUN prospective cohort study. *BMJ*. 2019; 365, l1949.
21. Stahl-Timmins W, Peninsula Technology Assessment Group, European Center for Environment and Human Health. GOfER Guide v2.6 [Online]. Exeter: University of Exeter; [cited 2019 July 19]. p. 4. Available from: http://blogs.exeter.ac.uk/gofer/.
22. Mauri M, Elli T, Caviglia G, Uboldi G, Azzi M. RAWGraphs: A Visualisation Platform to Create Open Outputs. *Proceedings of the 12th Biannual Conference on Italian SIGCHI Chapter*. Cagliari, Italy: ACM; 2017. p. 1–5.
23. Alvarez-Bueno C, Cavero-Redondo I, Lucas-de la Cruz L, Notario-Pacheco B, Martinez-Vizcaino V. Association between pre-pregnancy overweight and obesity and children's neurocognitive development: a systematic review and meta-analysis of observational studies. *Int J Epidemiol*. 2017; 46, 1653–1666.
24. Andersson NW, Hansen MV, Larsen AD, Hougaard KS, Kolstad HA, Schlunssen V. Prenatal maternal stress and atopic diseases in the child: a systematic review of observational human studies. *Allergy*. 2016; 71, 15–26.
25. Birks L, Casas M, Garcia AM, *et al.* Occupational exposure to endocrine-disrupting chemicals and birth weight and length of gestation: a European meta-analysis. *Environ Health Perspect*. 2016; 124, 1785–1793.
26. Bleker LS, van Dammen L, Leeflang MMG, Limpens J, Roseboom TJ, de Rooij SR. Hypothalamic-pituitary-adrenal axis and autonomic nervous system reactivity in children prenatally exposed to maternal depression: a systematic review of prospective studies. *Neurosci Biobehav Rev*. 2018; 5, 33.
27. Burke H, Leonardi-Bee J, Hashim A, *et al.* Prenatal and passive smoke exposure and incidence of Asthma and Wheeze: systematic review and meta-analysis. *Pediatrics*. 2012; 129, 735–744.
28. Bussières E-L, Tarabulsy GM, Pearson J, Tessier R, Forest J-C, Giguère Y. Maternal prenatal stress and infant birth weight and gestational age: a meta-analysis of prospective studies. *Dev Rev*. 2015; 36, 179–199.
29. Cook N, Ayers S, Horsch A. Maternal posttraumatic stress disorder during the perinatal period and child outcomes: a systematic review. *J Affect Disord*. 2018; 225, 18–31.
30. Crider KS, Cordero AM, Yan Ping Q, Mulinare J, Dowling NF, Berry RJ. Prenatal folic acid and risk of asthma in children: a systematic review and meta-analysis. *Am J Clin Nutr*. 2013; 98, 1272–1281.
31. Dalrymple KV, Martyni-Orenowicz J, Flynn AC, Poston L, O'Keeffe M. Can antenatal diet and lifestyle interventions influence childhood obesity? A systematic review. *Matern Child Nutr* 2018; 14, e12628.
32. Davidsen KA, Harder S, MacBeth A, Lundy J-M, Gumley A. Mother–infant interaction in schizophrenia: transmitting risk or resilience? A systematic review of the literature. *Soc Psychiatry Psychiatr Epidemiol*. 2015; 50, 1785–1798.
33. Delgado-Noguera MF, Calvache JA, Bonfill Cosp X. Supplementation with long chain polyunsaturated fatty acids (LCPUFA) to breastfeeding mothers for improving child growth and development. *Cochrane Database Syst Rev*. 2015; 7, CD007901.
34. Doherty AM, Lodge CJ, Dharmage SC, Dai X, Bode L, Lowe AJ. Human milk oligosaccharides and associations with immune-mediated disease and infection in childhood: a systematic review. *Front Pediatr*. 2018; 6, 91.
35. Ejaredar M, Nyanza EC, Ten Eycke K, Dewey D. Phthalate exposure and childrens neurodevelopment: A systematic review. *Environ Res*. 2015; 142, 51–60.
36. Faucher MA, Hastings-Tolsma M, Song JJ, Willoughby DS, Bader SG. Gestational weight gain and preterm birth in obese women: a systematic review and meta-analysis. *BJOG*. 2016; 123, 199–206.
37. Figueiró-Filho EA, Mak LE, Reynolds JN, *et al.* Neurological function in children born to preeclamptic and hypertensive mothers - a systematic review. *Pregnancy Hypertens*. 2017; 10, 1–6.
38. Garcia-Larsen V, Ierodiakonou D, Jarrold K, *et al.* Diet during pregnancy and infancy and risk of allergic or autoimmune disease: a systematic review and meta-analysis. *PLoS Med*. 2018; 15, e1002507.
39. Grote NK, Bridge JA, Gavin AR, Melville JL, Iyengar S, Katon WJ. A meta-analysis of depression during pregnancy and the risk of preterm birth, low birth weight, and intrauterine growth restriction. *Arch Gen Psychiatry*. 2010; 67, 1012–1024.
40. Gruzieva O, Xu C-J, Breton CV, *et al.* Epigenome-wide meta-analysis of methylation in children related to prenatal NO2 air pollution exposure. *Environ Health Perspect*. 2017; 125, 104–110.
41. Guillemette L, Hay JL, Kehler DS, *et al.* Exercise in pregnancy and children's cardiometabolic risk factors: a systematic review and meta-analysis. *Sports Med Open*. 2018; 4, 35.
42. Gunaratne AW, Makrides M, Collins CT. Maternal prenatal and/or postnatal n-3 long chain polyunsaturated fatty acids (LCPUFA) supplementation for preventing allergies in early childhood. *Cochrane Database Syst Rev*. 2015; 7, CD010085.
43. Hoang TT, Agopian AJ, Mitchell LE. Maternal use of weight loss products and the risk of neural tube defects in offspring: a systematic literature review. *Birth Defects Res*. 2018; 110, 48–55.
44. Jiang H-y, Xu L-l, Shao L, *et al.* Maternal infection during pregnancy and risk of autism spectrum disorders: a systematic review and meta-analysis. *Brain Behav Immun*. 2016; 58, 165–172.
45. Joubert BR, den Dekker HT, Felix JF, *et al.* Maternal plasma folate impacts differential DNA methylation in an epigenome-wide meta-analysis of newborns. *Nat Commun*. 2016; 7, 10577.
46. Joubert BR, Felix JF, Yousefi P, *et al.* DNA methylation in newborns and maternal smoking in pregnancy: genome-wide consortium meta-analysis. *Am J Hum Genet*. 2016; 98, 680–696.
47. Kingston D, Tough S, Whitfield H. Prenatal and postpartum maternal psychological distress and infant development: a systematic review. *Child Psychiatry Hum Dev*. 2012; 43, 683–714.
48. Klimentopoulou A, Antonopoulos CN, Papadopoulou C, *et al.* Maternal smoking during pregnancy and risk for childhood leukemia: a nationwide case-control study in Greece and meta-analysis. *Pediatr Blood Cancer*. 2012; 58, 344–351.
49. Krishna M, Jones S, Maden M, *et al.* Size at birth and cognitive ability in late life: a systematic review. *Int J Geriatr Psychiatry*. 2019; 34, 1139–1169.
50. Lean SC, Derricott H, Jones RL, Heazell AEP. Advanced maternal age and adverse pregnancy outcomes: a systematic review and meta-analysis. *PLoS One*. 2017; 12, e0186287.
51. Lee YQ, Collins CE, Gordon A, Rae KM, Pringle KG. The relationship between maternal nutrition during pregnancy and offspring kidney structure and function in humans: a systematic review. *Nutrients*. 2018; 10, 241.
52. Leventakou V, Roumeliotaki T, Martinez D, *et al.* Fish intake during pregnancy, fetal growth, and gestational length in 19 European birth cohort studies. *Am J Clin Nutr*. 2014; 99, 506–516.
53. Lucas-Thompson RG, Goldberg WA, Prause J. Maternal work early in the lives of children and its distal associations with achievement and behavior problems: a meta-analysis. *Psychol Bull*. 2010; 136, 915–942.
54. Ludwig-Walz H, Schmidt M, Gunther ALB, Kroke A. Maternal prepregnancy BMI or weight and offspring's blood pressure: systematic review. *Matern Child Nutr*. 2018; 14, e12561.
55. McNamara BJ, Gubhaju L, Chamberlain C, Stanley F, Eades SJ. Early life influences on cardio-metabolic disease risk in aboriginal populations–what is the evidence? A systematic review of longitudinal and case-control studies. *Int J Epidemiol*. 2012; 41, 1661–1682.
56. Mech P, Hooley M, Skouteris H, Williams J. Parent-related mechanisms underlying the social gradient of childhood overweight and obesity: a systematic review. *Child Care Health Dev*. 2016; 42, 603–624.
57. Melody SM, Ford J, Wills K, Venn A, Johnston FH. Maternal exposure to short-to medium-term outdoor air pollution and obstetric and neonatal outcomes: a systematic review. *Environ Pollut*. 2019; 244, 915–925.
58. Miller J, Tonkin E, Damarell RA, *et al.* A systematic review and meta-analysis of human milk feeding and morbidity in very low birth weight infants. *Nutrients*. 2018; 10, 707.
59. Molina Lima SA, El Dib RP, Kron Rodrigues MR, *et al.* Is the risk of low birth weight or preterm labor greater when maternal stress is experienced during pregnancy? A systematic review and meta-analysis of cohort studies. *PLoS One* 2018; 13, e0200594.

https://doi.org/10.1017/S2040174420000689 Published online by Cambridge University Press

60. Oh DL, Jerman P, Marques SS, *et al.* Systematic review of pediatric health outcomes associated with childhood adversity. *BMC Pediatr*. 2018; 18, 1–19.
61. Pastorino S, Bishop T, Crozier SR, *et al.* Associations between maternal physical activity in early and late pregnancy and offspring birth size: remote federated individual level meta-analysis from eight cohort studies. *BJOG*. 2019; 126, 459–470.
62. Pearson J, Tarabulsy GM, Bussieres EL. Foetal programming and cortisol secretion in early childhood: a meta-analysis of different programming variables. *Infant Behav Dev*. 2015; 40, 204–215.
63. Roth DE, Leung M, Mesfin E, Qamar H, Watterworth J, Papp E. Vitamin D supplementation during pregnancy: state of the evidence from a systematic review of randomised trials. *BMJ*. 2017; 359: j5237.
64. Ruiz M, Goldblatt P, Morrison J, *et al.* Mother's education and the risk of preterm and small for gestational age birth: a DRIVERS meta-analysis of 12 European cohorts. *J Epidemiol Commun Health*. 2015; 69, 826–833.
65. Santamaria C, Bi WG, Leduc L, *et al.* Prenatal vitamin D status and offspring's growth, adiposity and metabolic health: a systematic review and meta-analysis. *British J Nutr*. 2018; 119, 310–319.
66. Sharp GC, Salas LA, Monnereau C, *et al.* Maternal BMI at the start of pregnancy and offspring epigenome-wide DNA methylation: findings from the pregnancy and childhood epigenetics (PACE) consortium. *Hum Mol Genet*. 2017; 26, 4067–4085.
67. Smith ER, Shankar AH, Wu LSF, *et al.* Modifiers of the effect of maternal multiple micronutrient supplementation on stillbirth, birth outcomes, and infant mortality: a meta-analysis of individual patient data from 17 randomised trials in low-income and middle-income countries. *Lancet Global Health*. 2017; 5: E1090–E1100.
68. Sweeney S, MacBeth A. The effects of paternal depression on child and adolescent outcomes: a systematic review. *J Affect Disord*. 2016; 205, 44–59.
69. Taylor RM, Fealy SM, Bisquera A, *et al.* Effects of nutritional interventions during pregnancy on infant and child cognitive outcomes: a systematic review and meta-analysis. *Nutrients*. 2017; 9, 1265.
70. Thomopoulos TP, Ntouvelis E, Diamantaras A-A, *et al.* Maternal and childhood consumption of coffee, tea and cola beverages in association with childhood leukemia: a meta-analysis. *Cancer Epidemiol*. 2015; 39, 1047–1059.
71. Tsuji JS, Garry MR, Perez V, Chang ET. Low-level arsenic exposure and developmental neurotoxicity in children: a systematic review and risk assessment. *Toxicology*. 2015; 337, 91–107.
72. Veena SR, Gale CR, Krishnaveni GV, *et al.* Association between maternal nutritional status in pregnancy and offspring cognitive function during childhood and adolescence; a systematic review. *BMC Pregnancy Childbirth*. 2016; 16, 1–24.
73. Wang C, Geng H, Liu W, Zhang G. Prenatal, perinatal, and postnatal factors associated with autism: a meta-analysis. *Medicine (Baltimore)*. 2017; 96, e6696.
74. Wei Z, Zhang J, Yu X. Maternal vitamin D status and childhood asthma, wheeze, and eczema: a systematic review and meta-analysis. *Pediatr Allergy Immunol*. 2016; 27, 612–619.
75. Xuan Z, Zhongpeng Y, Yanjun G, *et al.* Maternal active smoking and risk of oral clefts: a meta-analysis. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2016; 122, 680–690.
76. Zhang R, Han S, Chen G-C, *et al.* Effects of low-glycemic-index diets in pregnancy on maternal and newborn outcomes in pregnant women: a meta-analysis of randomized controlled trials. *Eur J Nutr*. 2018; 57, 167–177.
77. Zijlmans MAC, Riksen-Walraven JM, de Weerth C. Associations between maternal prenatal cortisol concentrations and child outcomes: a systematic review. *Neurosci Biobehav Rev*. 2015; 53, 1–24.
78. Zwink N, Jenetzky E, Brenner H. Parental risk factors and anorectal malformations: systematic review and meta-analysis. *Orphanet J Rare Dis*. 2011; 6, 25.
79. Rando OJ, Simmons RA. I'm eating for two: parental dietary effects on offspring metabolism. *Cell*. 2015; 161, 93–105.
80. Gutierrez YM. Cultural factors affecting diet and pregnancy outcome of Mexican American adolescents. *J Adolescent Health*. 1999; 25, 227–237.
81. Lake J, Turner MS. Urgent need for improved mental health care and a more collaborative model of care. *Perm J*. 2017; 21, 17–24.
82. Wehby GL, Prater K, McCarthy AM, Castilla EE, Murray JC. The impact of maternal smoking during pregnancy on early child neurodevelopment. *J Hum Cap*. 2011; 5, 207–254.
83. Mandy M, Nyirenda M. Developmental origins of health and disease: the relevance to developing nations. *Int Health*. 2018; 10, 66–70.
84. Miranda JJ, Kinra S, Casas JP, Davey Smith G, Ebrahim S. Non-communicable diseases in low- and middle-income countries: context, determinants and health policy. *Trop Med Int Health*. 2008; 13, 1225–1234.
85. Lim SY, Kim EJ, Kim A, Lee HJ, Choi HJ, Yang SJ. Nutritional factors affecting mental health. *Clin Nutr Res*. 2016; 5, 143–152.
86. Akhter S, Wohab A. Health, nutrition and human resource development: a crucial link. *BRAC Univ J*. 2006; III, 125–132.
87. Maselko J, Bates L, Bhalotra S, *et al.* Socioeconomic status indicators and common mental disorders: evidence from a study of prenatal depression in Pakistan. *SSM – Popul Health*. 2017; 4, 1–9.
88. Hanson M, Gluckman P. Commentary: developing the future: life course epidemiology, DOHaD and evolutionary medicine. *Int J Epidemiol*. 2016; 45, 993–996.
89. Hanson MA, Cooper C, Aihie Sayer A, Eendebak RJ, Clough GF, Beard JR. Developmental aspects of a life course approach to healthy ageing. *J Physiol*. 2016; 594, 2147–2160.
90. Aagaard-Hansen J, Norris SA, Maindal HT, Hanson M, Fall C. What are the public health implications of the life course perspective? *Glob Health Action*. 2019; 12, 1603491.
91. Cosco TD, Howse K, Brayne C. Healthy ageing, resilience and wellbeing. *Epidemiol Psychiat Sci*. 2017; 26, 579–583.
92. Hoffman DJ, Reynolds RM, Hardy DB. Developmental origins of health and disease: current knowledge and potential mechanisms. *Nutr Rev*. 2017; 75, 951–970.
93. Sharp GC, Lawlor DA, Richardson SS. It's the mother!: how assumptions about the causal primacy of maternal effects influence research on the developmental origins of health and disease. *Soc Sci Med (1982)*. 2018; 213, 20–27.
94. Snow ME, Tweedie K, Pederson A. Heard and valued: the development of a model to meaningfully engage marginalized populations in health services planning. *BMC Health Ser Res*. 2018; 18, 181.
95. Sharp GC, Schellhas L, Richardson SS, Lawlor DA. Time to cut the cord: recognizing and addressing the imbalance of DOHaD research towards the study of maternal pregnancy exposures. *J Dev Orig Health Dis*. 2019; 10, 509–512.
96. Härkönen J, Bernardi F, Boertien D. Family dynamics and child outcomes: an overview of research and open questions. *Eur J Popul*. 2017; 33, 163–184.
97. Oh C, Keats EC, Bhutta ZA. Vitamin and mineral supplementation during pregnancy on maternal, birth, child health and development outcomes in low- and middle-income countries: a systematic review and meta-analysis. *Nutrients*. 2020; 12, 491.
98. Mithal A, Kalra S. Vitamin D supplementation in pregnancy. *Indian J Endocrinol Metab*. 2014; 18, 593–596.
99. Wall CR, Stewart AW, Camargo CA, Jr., *et al.* Vitamin D activity of breast milk in women randomly assigned to vitamin D3 supplementation during pregnancy1,2. *Am J Clin Nutr*. 2015; 103, 382–388.
100. Thiele DK, Senti JL, Anderson CM. Maternal Vitamin D supplementation to meet the needs of the breastfed infant: a systematic review. *J Hum Lactat*. 2013; 29, 163–170.
101. Palacios C, Trak-Fellermeier MA, Martinez RX, *et al.* Regimens of vitamin D supplementation for women during pregnancy. *Cochrane Database Syst Rev*. 2019; CD013446.

https://doi.org/10.1017/S2040174420000689 Published online by Cambridge University Press

102. Satyanarayana VA, Lukose A, Srinivasan K. Maternal mental health in pregnancy and child behavior. *Indian J Psychiat*. 2011; 53, 351–361.
103. Bruce L, Béland D, Bowen A. MotherFirst: developing a maternal mental health strategy in Saskatchewan. *Healthcare Policy = Politiques de sante* 2012; 8, 46–55.
104. Fisher SD. Paternal mental health: why is it relevant? *Am J Lifestyle Med*. 2016; 11, 200–211.
105. O'Donnell KA, Gaudreau H, Colalillo S, *et al.* The maternal adversity, vulnerability and neurodevelopment project: theory and methodology. *Can J Psychiat*. 2014; 59, 497–508.
106. Sagner M, McNeil A, Puska P, *et al.* The P4 health spectrum – a predictive, preventive, personalized and participatory continuum for promoting healthspan. *Prog Cardiovasc Dis*. 2017; 59. 506–521.

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