

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

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 life³. 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 health¹⁴ 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-being¹⁵.

Methods

We conducted an RER following guidelines provided by the National Collaborating Centre for Methods and Tools¹⁶. Additionally, our study adhered to a modified version of the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) checklist¹⁷ (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 resiliency

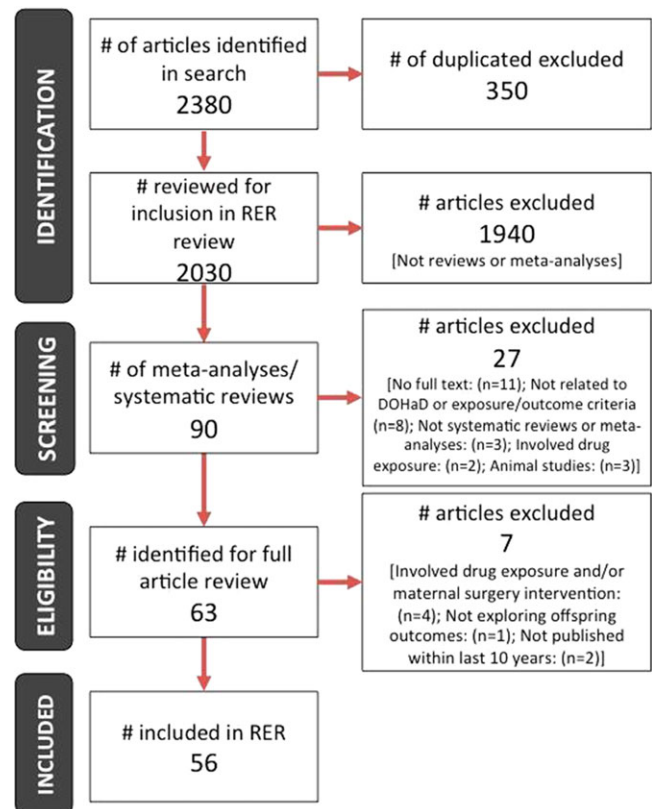


Fig. 1. Flow diagram of the review of citations identified by the search the initial capture resulted in 2380 articles using identified search terms. After deduplication, abstracts and title of records underwent level 1 screening to identify which were systematic reviews or meta-analysis, where 1940 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.

outcomes, and (5) access to full text. Studies of drug effects on adult-onset disease pathways were excluded.

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 consortium¹⁸ 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

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 used²¹. 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 RAWGraphs²² (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

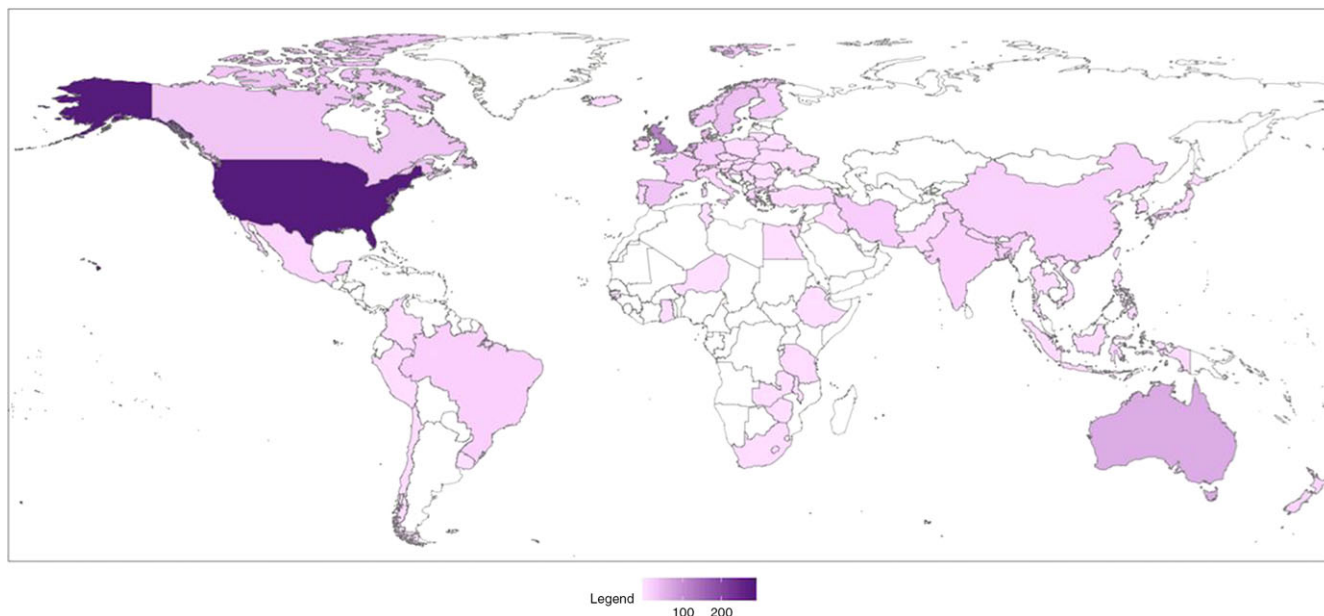


Fig. 2. Heatmap of distribution of each study contained within the systematic reviews/meta-analyses by country where the study took place or where cohort or study population were based. Data values of the country count are represented as colors where the darker to lighter gradient represents higher study 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 Physiologic) 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 offspring³⁸. 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 weight⁵². 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 infants³¹. 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 intelligence⁶⁹ and reduction of allergic disease⁴² 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.

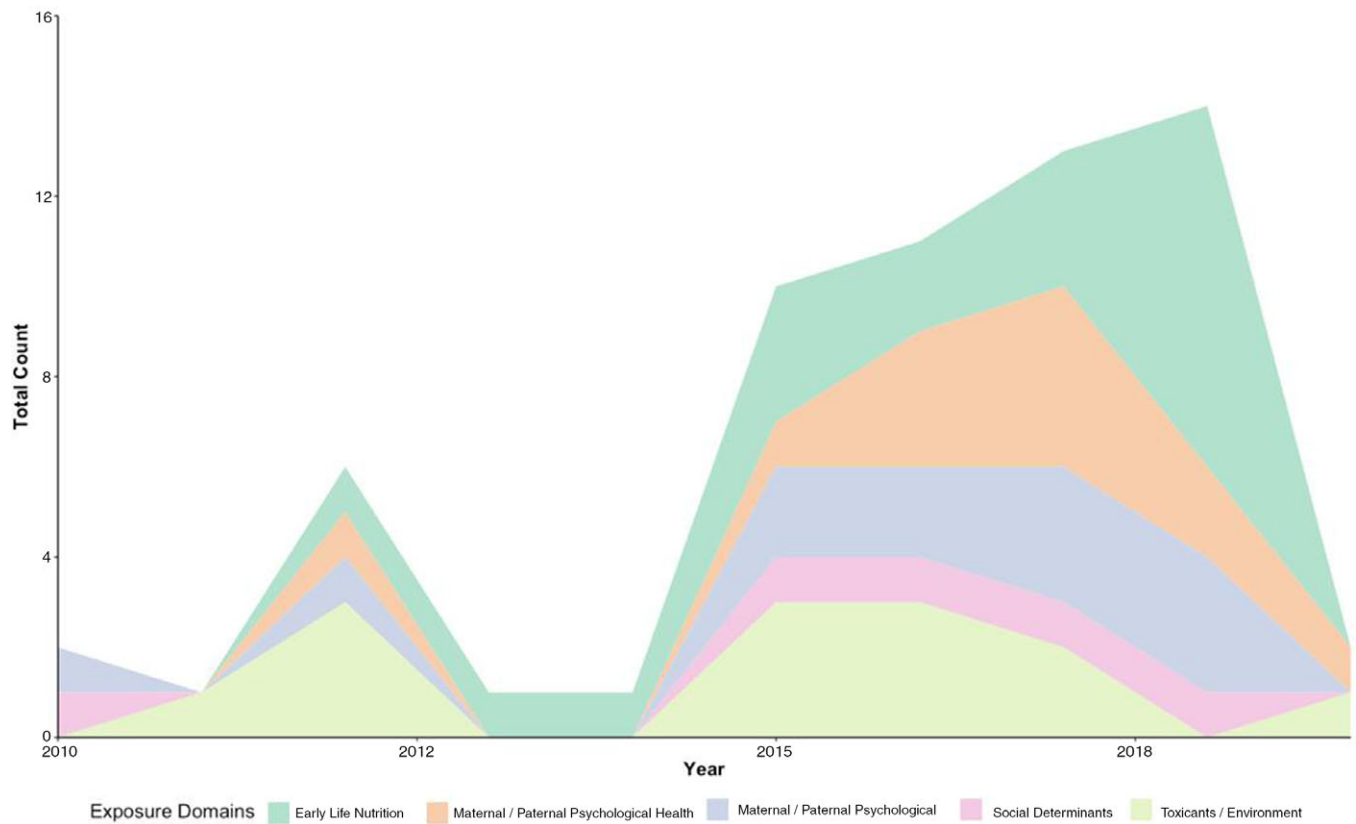


Fig. 3. Stacked area graph displaying the total number of studies published within each exposure domain over time, pulled from studies included in the 56 systematic reviews/ meta-analyses. Each stack as coded by color in the figure legend represents a total count of that particular exposure domain within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

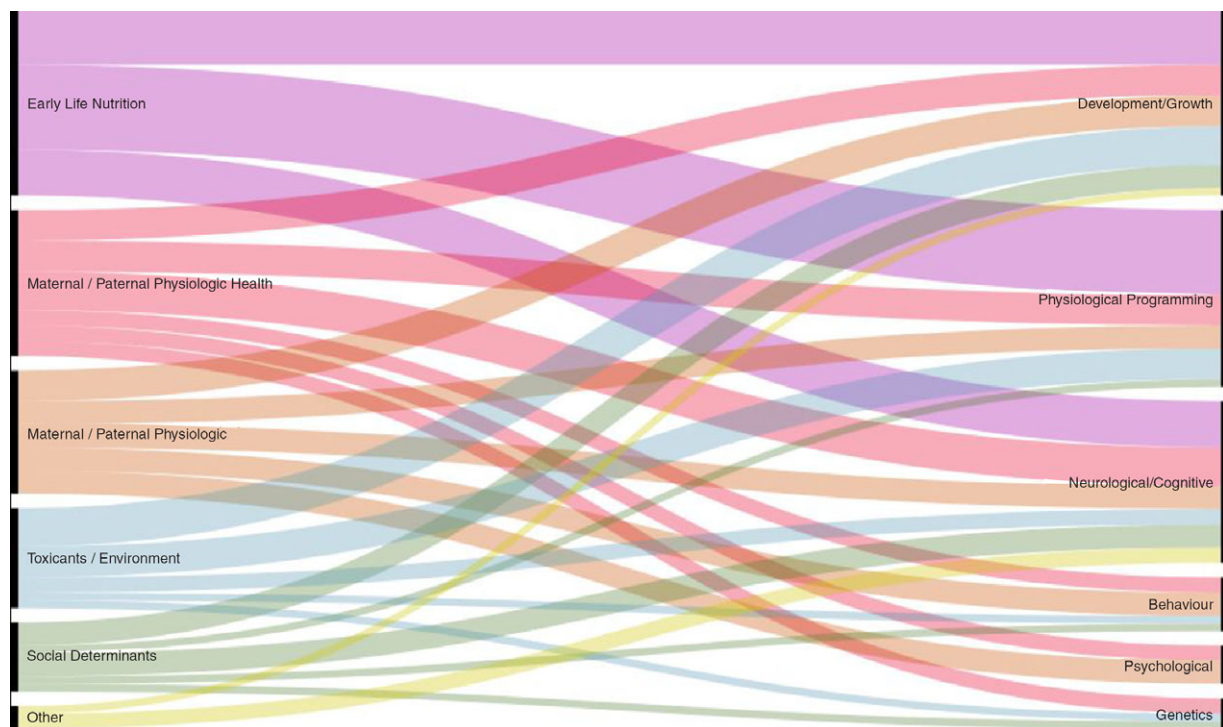


Fig. 4. Alluvial diagram of exposure and outcome domains showing the flow of weighted links between exposure and outcome domains indicating the number of studies included in the RER that explore that particular exposure–outcome relationship.

EARLY LIFE NUTRITION EXPOSURE												
STUDY CHARACTERISTICS		EXPOSURE	FOLLOW-UP TIMELINE					OUTCOME	POOLED ESTIMATES	IMPLICATIONS		
Number of Studies	Study Design <small>Cohort, Case-control, Case-Control, RCT, Longitudinal, Observational, Other</small>		Birth - 4 Y	5 - 10 Y	11 - 14 Y	15 - 20 Y	20+	Summary Statistic	Point estimates; 95% confidence interval	Conclusion	Caveat	
								Physiological programming Development/Growth Neurological/Cognitive Behaviour Genetics Psychological				
Doherty	6	Maternal postpartum levels of human milk oligosaccharides	→								Limited overall evidence that human milk oligosaccharides are associated with allergic and infectious diseases in early life.	Pooling of results was not possible due to the heterogeneity of the reported outcomes.
García-Larsen*	391	Maternal and infant diet during pregnancy, lactation, or first year of life	→						Risk Ratio For eczema related to probiotics Risk Ratio For allergic sensitisation to egg related to fish oil supplementation	0.00 0.40 0.70 0.90 1.00	Maternal probiotic and fish oil supplementation may reduce risk of eczema and allergic sensitisation to food, respectively.	Only most significant findings are shown
Hoang	9	Use of weight loss products in the periconceptional period	→						Risk Ratio Range For birth defects related to weight loss products Odds Ratio Range For neural tube defects related to weight loss products	1.20 1.40 1.60 1.80 2.00	The range provided shows positive but non-significant OR results on increase use of maternal weight loss products and risk of birth defects of neural tube defects.	Few associations were significant (not included in summary estimates). There was notable heterogeneity in the exposures across the included studies.
Zhang*	11	Low glycemic index (GI) diet during pregnancy (more than four weeks)	→						Weighted Mean Difference For birth weight related to low GI diet Risk Ratio For large for gestational age birth related to low GI diet	-1.00 -0.50 0 0.50 1.00	Low-GI diets may be associated with a reduction in large for gestational age and birth weight.	Many pooled statistics were reported in the study. Only two most significant are shown.
Dalrymple	8	Maternal dietary and/or physical activity interventions during second and third trimester of pregnancy	→								Lifestyle interventions during pregnancy in obese women have been associated with reduced measures of obesity in infants up to 12 months of age but no conclusions on measures of adiposity.	Unable to draw conclusions on influence of antenatal interventions on obesity in early childhood due to heterogeneity of methodology of the interventions and reported offspring outcomes.
Lee	10	Maternal nutrition during pregnancy	→								Maternal nutrition before conception and throughout gestation was found to be crucial factor that can influence the risk of renal dysfunction in offspring.	Due to heterogeneity within studies, meta-analysis was not conducted.
Miller	49	Breastfeeding during pregnancy	→								Human Milk provided a possible reduction in late onset sepsis (LOS), severe respiratory tract infection (RPT) and severe necrotising enterocolitis (NEC). Evidence for pasteurisation is inconclusive.	Due to heterogeneity among individual studies and varying outcome definitions, an overall summary statistic was not reported. Multiple pooled statistics were reported.
Santamaria*	30	Prenatal vitamin D status, 25(OH)D assay taken before or at delivery	→						Odds Ratio For small for gestational age birth related to prenatal D status Mean Difference For birth weight (g) related to vit D deficiency Mean Difference For infant weight at 9 months related to vit D deficiency	1.25 1.50 1.75 2.00 2.25 -200.0 -100.0 0 100.0 200.0	Low prenatal 25(OH)D status is found to have an impact on fetal growth and low prenatal vitamin D status may be associated with infant adiposity.	Many pooled statistics were reported in the study. Only the most significant are shown.
Roth	43	Vitamin D supplementation during pregnancy	→						Weighted Mean Difference For mean birth weight (g) related to vit D supplementation Risk Ratio For small for gestational age birth related to vit D supplementation Risk Ratio For asthma/asthma at 3 years related to vit D supplementation	0 25.0 50.0 75.0 100.0 0.40 0.60 0.80 1.00 1.20	Overall, prenatal vitamin D increased mean birth weight and reduced the risk of small for gestational age births and reduced the risk of offspring wheeze by age 3. No effect on preterm birth was found.	Many pooled statistics were reported in the study. Many outcomes were assessed and many sub-analyses were performed. Only the most significant are shown.
Smith	17	Micronutrient supplements containing iron and folic acid during pregnancy	→								Multiple micronutrient supplements reduced mortality in female neonates and increased birth weight and reduced preterm birth among all infants.	A broad range of exposures and outcomes were assessed. Multiple analyses were conducted. An overall summary statistic was not available. Insight into mechanism of action limited by confounders and effect modifiers.
Taylor*	34	Nutritional interventions during pregnancy	→						Standard Mean Difference For crystallized intelligence associated with iron plus zinc plus omega-3 fatty acid supplementation	0 0.25 0.50 0.75 1.00	Marginal association between LCPiFA supplementation and child crystallized intelligence found. Other outcomes were not significantly improved by nutritional interventions.	Many pooled statistics were reported in the study. Only the most significant is shown. Significant heterogeneity among exposure and outcome measures was found.
Veena	38	Maternal nutritional status (BMI, height, weight, macro and microelements) before and/or during pregnancy	→								Some evidence linking maternal obesity and low micronutrient status with poorer offspring cognitive function.	Due to varying methods of measurement for exposures and cognitive tests, a meta-analysis was not conducted.
Wei	6	Maternal vitamin D status during pregnancy comprising maternal serum 25(OH)D, cord serum 25(OH)D and vitamin D intake from food/supplements	→						Odds Ratio For childhood Asthma associated with maternal vit D status Odds Ratio For childhood wheeze associated with maternal vit D status Odds Ratio For childhood eczema associated with maternal vit D status	0.40 0.60 0.80 1.00 1.20	low vitamin D level during pregnancy was associated with the risk of childhood eczema but not with childhood asthma or wheeze.	Methods of vit D assessments/biomarkers in serum were inconsistent across studies.
Delgado-Nogueras	8	Maternal supplementation with long chain polyunsaturated fatty acids during pregnancy and postpartum period	→								Some evidence linking maternal obesity and low micronutrient status with poorer offspring cognitive function.	Due to varying methods of measurement for exposures and cognitive tests, a meta-analysis was not conducted.
Gunaratne	8	Maternal supplementation with n-3 long chain polyunsaturated fatty acids during prenatal and/or postnatal period	→						Risk Ratio For BMI (kg/m ²) (13-26 months) related to LCPiFA supplementation Risk Ratio For child allergy (>6 months) related to LCPiFA supplementation Risk Ratio For IgE mediated allergy (<26 months) related to LCPiFA supplementation Risk Ratio For IgE mediated allergy (>6 months) related to LCPiFA supplementation	0.40 0.60 0.80 1.00 1.20	Overall, there is limited evidence to support maternal n-3 LCPiFA supplementation during pregnancy and/or lactation for the reduction of allergic disease in children because of few differences seen in allergic disease in children of mothers were supplemented with n-3 LCPiFA and those who were not.	Due to variation in reporting between studies, cumulative incidences are not reported.
Thomopoulos	10	Maternal consumption of caffeinated beverages (coffee, tea and cola) and childhood cola consumption (1-2 years)	→						Odds Ratio For childhood leukemia related to maternal coffee consumption Odds Ratio For childhood leukemia related to maternal tea consumption Odds Ratio For childhood leukemia related to maternal cola consumption Odds Ratio For childhood leukemia related to childhood cola consumption	0 0.50 1.00 1.50 2.00	Maternal coffee and cola consumption are detrimentally associated with childhood leukemia risk while tea was found to be inversely associated with risk of childhood leukemia.	Although many sub-analyses for confounding variables were conducted with significant results, only primary findings are shown.
Leventakou	19	Fish intake during pregnancy, fetal growth, and gestational length	→						Risk Ratio For birth weight (g) related to maternal fish consumption (1 < times/week < 3) Risk Ratio For birth weight (g) related to maternal fish consumption (3 times/week) Risk Ratio For preterm birth related to maternal fish consumption (1 < times/week < 3) Risk Ratio For preterm birth related to maternal fish consumption (3-3 times/week)	0 5.0 10.0 15.0 20.0 0.75 0.80 0.85 0.90 0.95	It was found that moderate fish intake during pregnancy is associated with lower risk of preterm birth and a small but significant increase in birth weight.	Some residual confounding mainly related to socioeconomic variables may be present.
Crider	14	Prenatal folic acid intake during periconceptional period, pre-pregnancy and first trimester of pregnancy	→						Risk Ratio For asthma to childhood associated with maternal folic acid supplement use	0.90 0.95 1.00 1.05 1.10	There is no evidence of an association of maternal prenatal folic acid supplement use (compared to no use) in the pre-pregnancy period through the first trimester and asthma or allergy-related outcomes.	Finding was limited by small number of studies. It was not possible to generate summary statistics for other folic measures and asthma or allergy-related outcomes because of heterogeneity within the studies.
McNamara	50	Breastfeeding for at least 2 months	→								Limited evidence showed that breastfeeding may reduce risk of diabetes among the offspring.	Due to heterogeneity of studies and number of exposure and outcomes assessed a meta-analysis was not conducted.

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.

MATERNAL/PATERNAL PHYSIOLOGIC HEALTH														
Year	STUDY CHARACTERISTICS		EXPOSURE	FOLLOW-UP TIMELINE					OUTCOME	POOLED ESTIMATES		IMPLICATIONS		
	Number of Studies	Study Design <small>Cohort, Cross-sectional, Case-Control, RCT, Longitudinal, Observation, Other</small>		Birth - 4 Y	5 - 10 Y	11 - 14 Y	15 - 20 Y	20+		Summary Statistic	Point estimates; 95% confidence interval	Conclusion	Caveat	
2019	Pastorino*	8	7, 1	Maternal leisure time physical activity in early (8-18 weeks) and late pregnancy (30 weeks to 1 day post-delivery)	→						<p>Risk Ratio For birth weight related to moderate to vigorous physical activity (MVPA)</p> <p>Risk Ratio For ponderal index associated with MVPA</p> <p>Odds Ratio For large for gestational age (LGA) birth associated with MVPA</p> <p>Odds Ratio For macrosomia associated with MVPA</p>		Physical activity in late, but not early pregnancy is consistently associated with modestly lower birth weight, ponderal index and risk of large for gestational age and macrosomia, but is not associated with small for gestational age outcome	Many pooled statistics were reported in the study. Only the most significant are represented here. For risk ratio associated with ponderal index, confidence interval is contained within the representative circle.
2018	Guillemette	54	15, 39	Aerobic and/or resistance (strength) training exercises during pregnancy ≥4 weeks in duration	→	→	→				<p>Mean Difference For birth weight associated with prenatal exercise</p> <p>Risk Ratio For large for gestational age status associated with prenatal exercise</p>		Compared to no exercise groups, prenatal exercise does not causally or significantly impact birth weight, fat mass, or large-for-gestational-age status in a clinically relevant way	Direct comparisons between studies cannot be made because of the considerable heterogeneity in research designs, assessment of exercise dose and reported offspring outcomes between studies.
2018	Ludwig-Walz	16	16	Maternal peri-pregnancy Body Mass Index (BMI) or weight	→	→	→						Suggestive, but still limited, evidence was found for an association between maternal pre-pregnancy BMI or weight with offspring's later blood pressure. The effect was found to be mainly mediated via offspring's anthropometry.	Due to the heterogeneity of the outcomes assessed, a pooled summary statistic was not reported for the study.
2018	Alvarez-Bueno	15	15	Pre-pregnancy obesity or overweight	→	→	→				<p>Mean Difference For child neurodevelopment related to maternal overweight pre pregnancy</p> <p>Risk Ratio For child neurodevelopment related to maternal obesity pre pregnancy</p>		Pre-pregnancy maternal obesity, not overweight may have a negative influence on the offspring's neurocognitive development	Pooled estimate for pre-pregnancy maternal overweight is not statistically significant
2017	Figueiró-Filho	27	27, 27	Preeclampsia (between second trimester and term) and maternal hypertension (during pregnancy)	→	→	→						Offspring of mothers who developed preeclampsia (PE-FTs) show cognitive and behavioural differences compared to offspring from non-complicated pregnancies. PE-FTs should be seen as a population at risk during brain development.	No meta-analysis was conducted. There is limited neuroimaging findings for paediatric populations.
2017	Sharp	19	19	Maternal BMI at the start of pregnancy	→	→	→						Overall, maternal BMI at the start of pregnancy is associated with small variation in newborn blood DNA methylation at 86 sites throughout the genome, after adjusting for cell proportions.	Numerous effect sizes were reported in review. Effect sizes for significant loci were small but were widespread.
2017	Wang	17	5, 12	Gestational hypertension, gestational diabetes, preeclampsia	→	→	→						Out of the many exposure factors assessed, gestational hypertension, gestational diabetes and preeclampsia were found to be associated with high risk of autism.	The factors related to autism in this study were examined individually, therefore causality can not be established owing to confounding and mediation. Due to the many exposures assessed an overall summary statistic was not available.
2016	Faucher*	6	6	Gestational weight gain in obese women	→	→	→				<p>Odds Ratio For preterm birth associated with maternal obesity</p>		There was an increased risk of indicated preterm birth in obese women with gestational weight gain above the Institute of Medicine's recommendations	Many other pooled estimates present, but only statistically significant main finding reported here
2016	Jiang	15	2, 13	Maternal infection during pregnancy	→	→	→				<p>Odds Ratio For Autism Spectrum Disorder associated with maternal infection during pregnancy</p>		Maternal infection during pregnancy was associated with an increased risk of ASD in offspring, particularly among mothers requiring hospitalization. Risk varies by the type of infectious agent, time of exposure, and site of infection.	There is a possibility of uncontrolled confounding variables and a limited number of high quality studies included in the review which could affect the accuracy of the results.
2015	Joubert	2	2	Maternal plasma folate levels during pregnancy	→	→	→						Four-hundred forty-three false discovery significant CpGs (320 genes) in newborn DNA are associated with maternal plasma folate levels during pregnancy	Meta-analysis done for multiple CpG loci. An overall summary statistic can not be reported.
2015	Zijlmans	27	4, 5, 18	Maternal prenatal cortisol concentrations	→	→	→						A weak relation was found between maternal prenatal cortisol levels and offspring psychological/behavioural problems (12% of analyses were significant). The relations between maternal prenatal cortisol and other outcome variables (health, cognitive development, infant cortisol) appear to be stronger.	Due to varying methods of measurement for independent and dependent variables, a meta-analysis was not conducted. Confounders and mediators were not taken into consideration for many individual studies.
2012	McNamara	50	43, 7	Maternal obesity and diabetes in utero	→	→	→						Exposure to maternal diabetes was strongly associated with type 2 diabetes and metabolic abnormalities, whereas the association with adiposity was low.	Due to heterogeneity of studies and number of exposure and outcome measures assessed a meta-analysis was not conducted.

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.

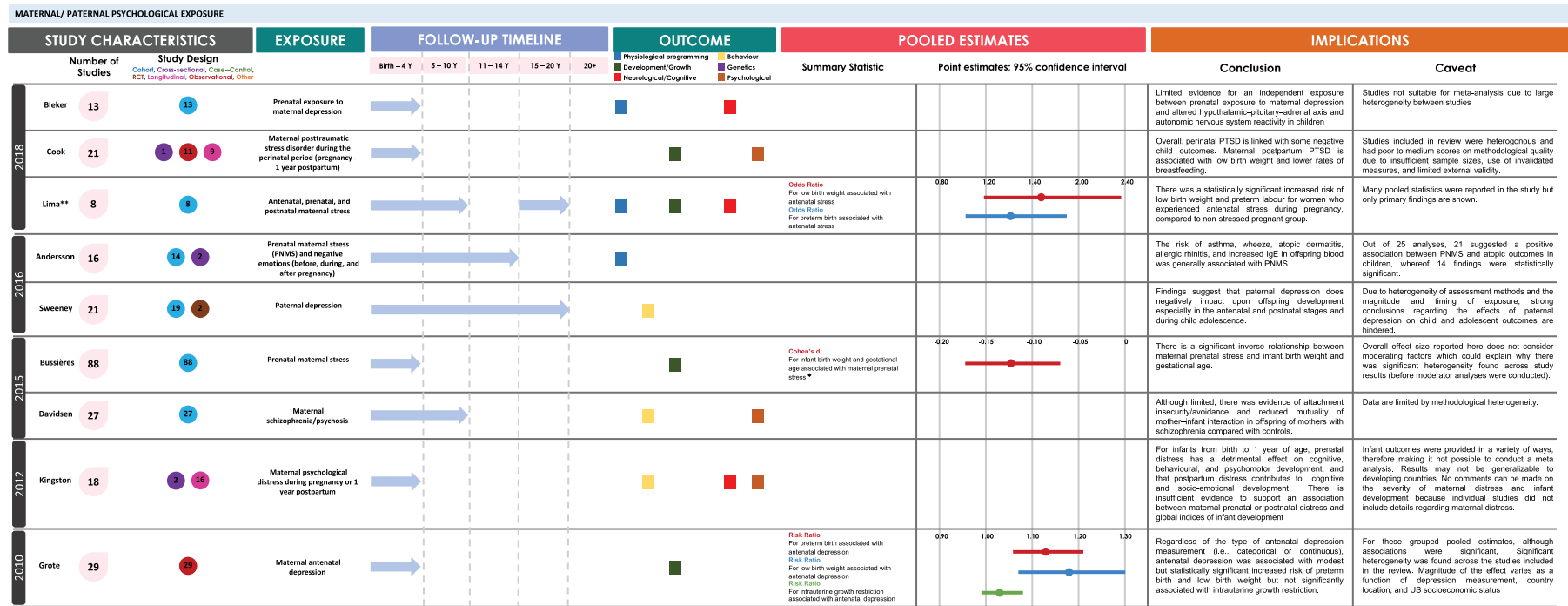


Fig. 7. Summary of studies within maternal/paternal psychological exposure domain. Study characteristics, specific exposures, and outcomes explored within each study, major findings, and implications are summarized. Follow-up timelines include the range of ages during which results were ascertained. 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.

TOXICANT/ENVIRONMENTAL																	
Year	Number of Studies	Study Design <small>Cohort, Cross-sectional, Case-Control, RCT, Longitudinal, Observational, Other</small>	EXPOSURE	FOLLOW-UP TIMELINE					OUTCOME <small>Physiological programming, Development/Growth, Neurological/Cognitive, Behavior, Genetics, Psychological</small>	POOLED ESTIMATES					IMPLICATIONS		
				Birth-4 Y	5-10 Y	11-14 Y	15-20 Y	20+		Summary Statistic	Point estimates; 95% confidence interval					Conclusion	Caveat
2019	Melody 11	9, 1, 1	Maternal exposure to short-medium-term outdoor air pollution (during gestation and after birth)	→					■						Overall, there is some evidence that maternal exposure to acute changes in air quality of short-to medium-term duration can increase the risk of fetal growth restriction and preterm birth.	Findings could not be synthesized quantitatively via a meta-analysis because of limited study numbers and heterogenous methodology.	
2017	Gruzjeva 4	4	Prenatal exposure to NO ₂ air pollution	→					■					Epigenome-wide significant associations (false discovery rate p-value < 0.05) between NO ₂ exposure and DNA methylation in newborns for 3 CpG sites in mitochondria related genes. Exposure to NO ₂ was also related to differential methylation, as well as expression of genes involved in antioxidant defense pathways.	This study reported findings for multiple gene sites. Results could not be synthesized into an overall summary statistic.		
2016	Birks 13	13	Maternal exposure to Endocrine-Disrupting Chemicals (EDC) during pregnancy	→					■	Odds Ratio For low birth weight at term associated with exposure to one or more EDC group	0.75	1.00	1.25	1.50	1.75	Occupational exposure during pregnancy to one or more EDC (classification group) was associated with an increased risk of term low birth weight. Association is fairly consistent across cohorts in the study. Preterm delivery was not significantly associated with estimated exposure to any EDC group in the study	Although study reported many effect sizes for relationships, only main significant finding was presented here as a pooled estimate.
	Xuan 29	6, 23	Active maternal smoking during periconception (6 months before conception and during pregnancy)	→					■	Odds Ratio For cleft lip with or without cleft palate associated with smoking in pregnancy Odds Ratio For cleft palate associated with smoking in pregnancy Odds Ratio For oral clefts associated with smoking in pregnancy	1.00	1.20	1.40	1.40	1.60	Maternal smoking during pregnancy at a moderate, but statistically significant risk can result in child with cleft palate (CP) or cleft lip with or without cleft palate (CL ± P).	Study could not confirm whether there was a positive dose-response effect between maternal smoking and clefts.
2016	Joubert 13	13	Maternal smoking during pregnancy	→					■						There are numerous significant CpG methylation loci in newborn's DNA with persistence into later childhood, involved in the response to maternal smoking in pregnancy.	Meta-analysis done for numerous CpG loci; no report of overall summary effect size.	
2015	Ejaredar 11	8, 2, 1	Phthalates exposure during prenatal period (25-42 weeks) and childhood	→					■					Prenatal phthalate exposure is associated with poorer cognitive and behavioural outcomes in children aged 0-12 years. Boys are at higher risk for poorer neurodevelopmental outcomes with respect to phthalate exposure.	Several studies in the review used the same cohorts and data points to examine neurodevelopmental outcomes and were therefore not independent of each other and could not be included in the meta-analysis.		
	Tsuji 24	8, 15, 1	Child low-level arsenic exposure	→					■						The overall evidence supporting a causative association of arsenic exposure at low doses with neurodevelopmental effects in children is relatively weak.	Issues include non-comparability of outcome measures across studies, possible inaccuracies in measurements of arsenic exposures, insufficient adjustment for some confounders and limited generalizability to non-Bangladesh populations	
2015	Pearson 19	19	Fetal exposure to alcohol, tobacco, drugs and/or stress (during second and third trimester)	→					■	Standard Mean Difference For child cortisol secretion and maternal prenatal stress and alcohol, drug or cigarette use	0.10	0.20	0.30	0.40	0.50	All programming variables were found to be related to cortisol secretion but exposure to alcohol yielded greater effect sizes than either tobacco use or maternal prenatal stress and anxiety	Possibility of other variables influencing relationship not being addressed across studies in reviews which could have a bearing of results and can affect the strength of associations.
2012	Burke* 79	79	Maternal smoking during pregnancy and prenatal or postnatal passive smoke exposure	→					■	Odds Ratio For wheeze associated with postnatal maternal smoking Odds Ratio For asthma associated with prenatal maternal smoking	0.50	1.00	1.50	2.00	2.50	The strongest effect on risk of wheeze in children <2 years was from postnatal maternal smoking. The strongest effect for risk of asthma in children aged <2 years was from prenatal maternal smoking. Overall, exposure to passive smoking increases the incidence of wheeze and asthma in children and young people by at least 20%.	Only strongest significant effect estimates reported out of multiple pooled estimates.
	Kliment-opoulou 22	1, 21	Maternal smoking during pregnancy	→					■	Odds Ratio For childhood acute lymphatic leukemia (ALL) related to maternal smoking Odds Ratio For childhood acute myelocytic leukemia (AML) related to maternal smoking	0.90	1.00	1.10	1.20	1.30	There is no observation of a statistically significant increased risk of either ALL or AML for children whose mothers were smoking during pregnancy.	Pooled effect estimates of the meta-analysis were based on adjusted and crude effect measures available from individual studies included in meta-analysis.
2012	McNamara 50	43, 7	Maternal smoking during pregnancy (prenatal and postnatal period)	→					■						Maternal smoking was associated with risk of adiposity in children but not in adults. No association between maternal smoking and cardiovascular outcomes was found.	Due to heterogeneity of studies and number of exposure and outcome measures assessed a meta-analysis was not conducted.	
2011	Zwink* 22	19	Parental exposure to smoking, alcohol, caffeine, illicit drugs, overweight/obesity, diabetes and occupational hazards during prenatal period	→					■	Odds Ratio For anorectal malformations related to paternal smoking Odds Ratio For anorectal malformations related to maternal overweight Odds Ratio For anorectal malformations related to maternal obesity Odds Ratio For anorectal malformations related to gestational diabetes	1.00	1.50	2.00	2.50	3.00	Paternal smoking, maternal overweight, obesity and diabetes (pregestational and gestational) are all associated with increased risks for anorectal malformations (ARM).	Pooled estimates shown are only of those that are significant. Although pooled estimate for pre-gestational diabetes was also significant, only the gestational diabetes pooled estimate is shown. Evidence on risk factors for ARM are limited overall with only few studies, but nonetheless indicating a significant relationship on these parental risk factors.

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.

SOCIAL DETERMINANTS and OTHERS (for other exposures the year is highlighted in Orange)														
STUDY CHARACTERISTICS		EXPOSURE	FOLLOW-UP TIMELINE					OUTCOME	POOLED ESTIMATES			IMPLICATIONS		
Number of Studies	Study Design <small>Cohort, Case-control, Case-Control, RCT, Longitudinal, Observational, Other</small>		Birth-4 Y	5-10 Y	11-14 Y	15-20 Y	20+	Physiological programming Development/Growth Neurological/Cognitive	Behaviour Genetics Psychological	Summary Statistic	Point estimates; 95% confidence interval	Conclusion	Caveat	
2019	Krishna	11	11										Eight of 11 reviewed studies indicated that in high income settings, there is a modest association between lower birth weight and lower cognitive function in later life.	Limited generalizability due to population setting. Meta-analysis of summary statistics not conducted due to the heterogeneity.
2018	Oh	35	35										Selected studies indicated that exposure to childhood adversity was associated with delays in cognitive development, asthma, infection, somatic complaints, and sleep disruption.	Relationships between a wide variety of adversities and health outcomes were investigated. Due to varying definition of childhood adversity and general variability among studies, a meta-analysis was not conducted.
2017	Lean	74	62	12						Odds Ratio For stillbirth associated with advanced maternal age Odds Ratio For fetal growth restriction associated with advanced maternal age	1.00 1.25 1.50 1.75 2.00	Overall, advanced maternal age is associated with increased risk of the coprinary outcomes stillbirth and fetal growth restriction. Stillbirth risk increased with increasing maternal age.	There was significant heterogeneity with the data. If greater than 80% for both estimates which is considered as "classification severe" in terms of heterogeneity.	
2017	Wang	6	5	12									Out of the many exposure factors assessed, maternal and paternal race, White and Asian, maternal and paternal education (college graduate +), and parental age (>35 years) were associated with increased risk for autism.	The factors related to autism in this study were examined individually; therefore, causality cannot be established owing to confounding and mediation. Due to the many exposures assessed an overall summary statistic was not available.
2016	Mech	30	15	12	3								High Parent BMI, ethnicity, child-care attendance, high TV time (mother and child), breastfeeding (early weaning), food intake behavior, and birth weight were identified as potential mediators between SES and childhood overweight and obesity	Due to the broad scope of the study statistical analysis was not conducted.
2015	Ruiz	12	12							Relative Index of Inequality (RII) For preterm birth associated with maternal education Relative Index of Inequality (RII) For small for gestational age birth associated with maternal education	1.20 1.40 1.60 1.80 2.00	Low education of mothers was associated with poor health outcomes for offspring at birth.	A socioeconomic measure (Relative index of inequality) was used to infer associations between maternal education and birth outcomes. Owing to missing data for some cohorts, residual confounding may be present.	
2010	Lucas	69	13	9	47					Pearson correlation r For achievement outcomes related to early maternal employment \blacklozenge Pearson correlation r For behavioral outcomes related to early maternal employment \blacklozenge	-0.20 -0.15 -0.10 -0.05 0	With a few exceptions, early maternal employment was not significantly associated with later achievement or internalising and externalising behaviors in offspring.	Some sub analysis conducted did show significance; however, only overall findings reported here do not show significance.	

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. \blacklozenge Odds Ratio = 1.004. \blacklozenge 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 development³⁷ 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 disorders²⁴. 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 offspring⁶⁸. Another study explored maternal schizophrenia and found it to be linked to attachment insecurity/avoidance in offspring³².

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 outcomes³⁵. 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 asthma²⁷ and childhood adiposity⁵⁵), development/growth outcomes, specifically birth defects (i.e. cleft lip, cleft palate⁷⁵, and anorectal malformations⁷⁸), and genetic outcomes (i.e. differential DNA methylation⁴⁵).

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 disruptions⁶⁰. One meta-analysis reported parent education and race (White and Asian) to be associated with increased risk of autism⁷³. 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 obesity⁵⁶. 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 settings⁴⁹. Another meta-analytic study looking at advanced maternal age found it to be associated with increased risk of stillbirth and fetal growth restriction⁵⁰. 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-analysis⁷³.

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 pregnancy⁶¹.

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 documented⁷⁹. 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 nutrition²⁰. 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 literature⁸⁰.

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

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 outcomes⁸¹. 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 research⁸². 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 policy⁶.

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-being⁸⁵, human capital, and the ability to integrate into society⁸⁶. 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 established⁸⁷, 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 resilience⁸⁸. 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 lifecycle factors⁸⁹⁻⁹¹. 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 cohorts⁹². 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 effects⁹³, even though early life programming of development and health is not limited to maternal contributions⁹².

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 factors⁹³⁻⁹⁵.
 - Additionally, increased focus on long-term effects of household dynamics, including maternal and paternal stress on child emotional and cognitive development⁹⁶.
- 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 children⁹⁷.
 - For example, the benefits of maternal vitamin D supplementation have been established⁹⁸⁻¹⁰⁰ and more recently, recommendation on increased vitamin D supplementation for pregnant women has been explored¹⁰¹. This information can be used by health professionals to determine specific micronutrient requirements for pregnant women and accommodate them accordingly.

- 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 measured¹⁰⁵.

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 care¹⁰⁶.

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