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The Impact of Early-Life Exposures on Women's Reproductive Health in Adulthood

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Abstract

Purpose of Review To review the effects of early-life, preconception, and prior-generation exposures on reproductive health in women.

Recent Findings Women's early-life factors can affect reproductive health by contributing to health status or exposure level on entering pregnancy. Alternately, they can have permanent effects, regardless of later-life experience. Nutrition, social class, parental smoking, other adverse childhood experiences, environmental pollutants, infectious agents, and racism and discrimination all affect reproductive health, even if experienced in childhood or in utero. Possible transgenerational effects are now being investigated through three- or more-generation studies. These effects occur with mechanisms that may include direct exposure, behavioral, endocrine, inflammatory, and epigenetic pathways.

Summary Pregnancy is increasingly understood in a life course perspective, but rigorously testing hypotheses on early-life effects is still difficult. In order to improve the health outcomes of all women, we need to expand our toolkit of methods and theory.

Keywords Pregnancy · Transgenerational · Early-life · Life course · Birth outcomes · Preconception

Introduction

Traditionally research on pregnancy has been focused on the 9 months prior to birth. However, there is increasing recognition of the effects of preconception, early-life, and transgenerational exposures on reproductive outcomes. Such ideas have been developed from perspectives that range from sociological and life-course [1] to next-generation and technological (such as epigenetic analysis of DNA methylation [2]), and are incorporated into the concept of the exposome, addressing the totality of particularly environmental exposures throughout the life course [3]. Preconception can be construed narrowly as the period when pregnancy is planned, or broadly, as any point in the life span prior to pregnancy, while "early-life" usually indicates a focus on childhood and adolescence [4]. Exposures from both time periods affect pregnancy and infant health (e.g., folic acid supplementation [5] or adverse childhood experiences [6]). Adverse health behaviors, whether smoking, sedentary lifestyle, or poor diet, rarely start during pregnancy. They are usually in place well before pregnancy, so that pregnancy begins under less optimal conditions and potentially leads to chronic diseases for both mother and child [7]. In addition, social class, stress, and trauma, whenever experienced, affect both biology and behavior, with consequences for pregnancy health, fecundability, and fertility decisions [8]. Developmental Origins of Health and Disease theory and research, while primarily focused on cardiometabolic health, also have been applied to reproductive outcomes [9].

Early-life exposures (whether in childhood, adolescence, or a previous generation) set a trajectory of risk. In some cases, this trajectory indicates an association between the early-life risk factor and risk factor levels during pregnancy (or at conception attempt) (Fig. 1a). Knowledge about early-life exposures is therefore important for

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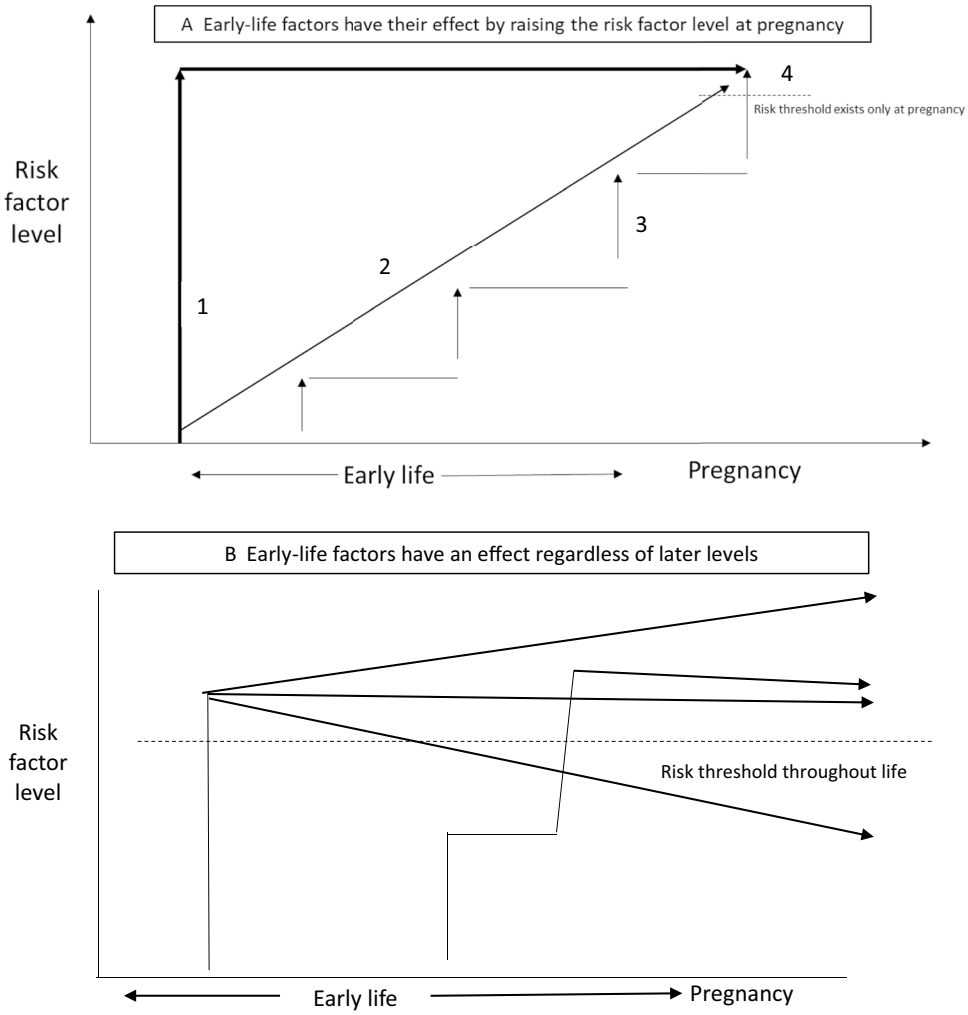

Fig. 1 Schematic for possible effect trajectories of early-life exposures on pregnancy and reproduction. **a** Early-life risk factors stay at a high level throughout the preconception period (trajectory 1), gradually rise (trajectory 2), or accumulate (trajectory 3). However, the important risk level only occurs at pregnancy (4). If we measured only at time 4, we would have the same degree of predictive power. **b** Early-life risk factors have an independent effect, regardless of their levels at the time of pregnancy. Once a risk threshold is crossed, whether levels of the risk factor stay constant, increase, or decrease, the early-life risk factor is still predictive

understanding the course of disease, identifying women who are at high risk, and determining interventions that will have the greatest impact. However, measuring early-life risk factors does not provide additional predictive power beyond what is measured during pregnancy; the threshold for risk is met only when the pregnancy happens. For example, adolescent smoking might predict reproductive outcomes, but only because it is associated with smoking during pregnancy. If a woman quit smoking prior to pregnancy, the early-life smoking would not predict outcomes. In other cases, early-life exposures have independent effects on reproductive and pregnancy outcomes (Fig. 1b), and predict and cause these outcomes. For these, an early-life exposure has a permanent effect, regardless of later exposures: early-life smoking predicts reproductive outcomes, regardless of smoking during pregnancy. The exposures considered in this review may be of either type, but we will focus on possible mechanisms for independent, permanent effects of early-life exposures (Table 1).

Early-Life Influences on Women's Reproductive Health

Nutrition

Childhood nutrition has long been recognized for its far-reaching effects on adult health. At the most basic level, sufficient calories are necessary for menarche and normal gynecological development to occur [10], and this can extend to lifelong influences; for example, low early-life crop yields in preindustrial societies [11] and early-life exposure to the Dutch Hunger Winter were associated with reduced fertility [12]. Other early deficiencies also cause long-term problems, e.g., rickets in early life leading to

Table 1 Mechanisms of early-life effects on reproductive outcomes

Pathway	Example exposure	Example mediator	Example outcomes
Direct effects	Syphilis	Transplacental infection	Stillbirth, miscarriage [80]
	Pb	Release from bone during pregnancy	Hypertension during pregnancy [81]
Structural	Vitamin D deficiency	Pelvic deformities	Obstructed labor and stillbirth
	Chlamydia	Tubal damage	Infertility
Health behaviors	Adverse childhood experiences	Smoking	Low birthweight [82]
	Low neighborhood SES	Gestational weight gain	Preterm birth [83]
Endocrine	Sexual abuse	HPA axis activation and insulin resistance	Gestational diabetes [84]
	Parental smoking	Anti-Mullerian hormone[85]	Fertility
Inflammatory	Social class	C-reactive protein, IL-6 [86]	Intra-amniotic infection and preterm delivery [87]
	Maternal infection	Pro-inflammatory cytokines	ovarian function and development [88]
Epigenetic	Warzone stress	Methylation of NR3C1 gene promoter[89]	Birthweight [90]
	Maternal overnutrition and obesity	Methylation of aryl-hydrocarbon receptor repressor	Birthweight and gestational age [91]

SES, socioeconomic status; *HPA*, hypothalamic–pituitary–adrenal

pelvic deformities inconsistent with carrying a pregnancy to term [13]. Other micronutrient deficiencies, including iron, thiamine, and vitamin B12, have long-term physiological sequelae that can be permanent [14]. Women with a history of eating disorders are at higher risk of miscarriage and low birthweight (LBW) [15]. High-calorie and low-nutrient density diets lead to obesity in childhood and later, associated with infertility, gestational diabetes, and complicated labor [16].

Social Class

Early-life social class predicts reproductive health. Economic hardship during the mother's childhood is associated with negative outcomes in neonates, including lower birthweight, longer hospital stays, and higher rates of neonatal intensive care unit admissions [17]. Maternal socioeconomic decline from childhood has been associated with infant mortality and preterm birth (PTB) [18, 19], while lifetime improved SES has been associated with reduced risk of small-for-gestational-age (SGA) and PTB [20, 21]. Recent work has extended this idea from individual SES to the wider community; for instance, neighborhood SES [22] modified age-related patterns of LBW and SGA [23], while inequality and polarization in childhood neighborhood was associated with greater likelihood of PTB in adulthood [24].

Abuse and Other Adverse Childhood Experiences

Women who experience physical abuse in childhood are at increased risk of PTB and LBW [25]. Sexual abuse during childhood has a particularly strong association with pregnancy complications, including increased hospitalization, premature contractions, cervical insufficiency, and PTB [26]. Abuse is also strongly associated with mental health issues, which raise the risk for several poor outcomes, both directly and via health behaviors, substance use, and partner violence during the pregnancy [27]. Experiencing out-of-home care (foster or residential care) as a child is associated with increased risk of PTB [28]. More generally, adverse childhood experiences (ACEs), such as abuse, parental substance use, or neglect, are linked to adverse birth outcomes [29, 30], unintended pregnancy [31], and risky reproductive health behaviors, including early sexual debut and prenatal substance use [32–34]. It should be noted that positive experiences in earlier life may also have long-term effects; women with greater athletic opportunities in adolescence (due to Title IX) gave birth to babies with higher Apgar scores and who were less likely to be LBW [35].

Parental Smoking

Tobacco smoke is composed of hundreds of toxins, many of which affect reproduction. Exposure to parental smoking in childhood is associated with stillbirth, spontaneous abortion, and ectopic pregnancy, and reduced success in fertility treatment [36, 37], even among women who never smoked themselves. In utero exposure to maternal smoking has been associated with reduced fertility [38] and miscarriage [39], though effects are small and inconsistent [40].

Environmental Pollutants

Many environmental pollutants are retained in the body. Lipophilic chemicals accumulate in fat tissues and heavy metals are taken up in bones. Such toxicants may be released during pregnancy even if exposure occurred many years previously; this has been clearly demonstrated with studies of lead (Pb) isotopes [41]. Arsenic, to which several worldwide populations are highly exposed, is associated with alterations in hormonal levels and may cause anemia, exacerbated during pregnancy [42]. Preconception and prenatal exposure to endocrine disruptors can impact a woman's reproductive health, altering hormonal signaling in reproductive organs by, for instance, antiestrogenic effects. The focus of this research has generally been on organogenesis and neonatal periods, and then again during the reproductive years [43]; for instance, prenatal exposure to dioxins and polychlorinated biphenyls (PCBs) has been associated with longer time to pregnancy [44]. Few studies have directly linked childhood and adolescent exposures to later-life pregnancy outcomes. Young women living in the Chernobyl region had a higher risk of miscarriage, premature birth, and menstrual disturbances approximately 20 years after the nuclear disaster there, although in that case there were long-lasting and ongoing exposures to radiation and other pollutants [45].

Infections

HIV and Other Sexually Transmitted Infections Proper treatment of chronic infections is crucial in management of infectious sequelae impacting reproductive health. Although research on non-congenitally inherited early-life exposure to sexually transmitted diseases is extremely limited, infections occurring years prior to child-bearing can significantly impact fecundity. Women living with HIV are at increased odds of developing coinfection with other sexually transmitted infections including human papillomavirus, genital herpes, syphilis, trichomonas, gonorrhea, and chlamydia, which may progress to pelvic inflammatory disease, with deleterious effects on reproductive health and fecundity [46, 47]. Women with HIV are more likely to experience anovulation and amenorrhea [48]. Preconception treatment with antiretroviral therapy increases the risk of both PTB and LBW, compared to women treated with antiretroviral therapy after conceiving [49]. Other long-term infectious diseases, such as tuberculosis, also carry reproductive sequelae, including infertility, miscarriage, and ectopic pregnancy [50].

COVID-19 At this point, nothing can be said conclusively about the long-term effects of COVID-19 on reproductive health. Several changes in reproductive physiology observed with COVID-19 have effects on later fertility and pregnancy, but it will be many years before we can truly assess the effects of early-life exposure to COVID-19. Patients infected with COVID-19 have been found to have a prolonged menstrual cycle, but these changes did not extend beyond a few months after resolution of infection [51]. Alterations of Angiotensin-Converting Enzyme (ACE-2) have led to cases of orchitis and infertility in males with COVID-19 infection, and researchers have hypothesized that gonadotropin-dependent expression of ovarian ACE-2 could affect female gametogenesis including ovarian function, oocyte quality, and later pregnancy outcomes [46], although initial studies of hormone concentrations are reassuring [51]. Pro-inflammatory ACE-2 can lead to damage of endometrial epithelial cells, which may affect early embryo implantation [52, 53], and ACE-2 effects on angiotensin-II could also lead to dysfunctional uterine bleeding secondary to hyperplastic endometrium. Parental treatment of COVID-19-induced pneumonia, including antiviral therapy, has been hypothesized to influence later development of the fetus, leading to a recommendation that contraception be encouraged for a time after active infection [54], although current evidence suggests no association between medical treatments and birth defects or preterm delivery [55]. Beyond possible effects of the virus and related treatments, the social, economic, educational, and emotional toll of the pandemic may be substantial and lifelong or transgenerational. The 1918 influenza pandemic led to reduced income and health for at least two generations [56].

Racism and Other Forms of Discrimination

Structural racism and discrimination produce a situation where the abovementioned risk factors are more likely to be seen in populations of color and disadvantaged populations. The high prevalence of these early-life risk factors is likely a major contributor to disparities in reproductive outcomes. Studies of lifetime experiences of interpersonal racism or ethnic discrimination have generally found associations with adverse birth outcomes [57] or with potential mediators of such associations, such as depressive symptoms or psychological distress [58]. Experiences of stigma and discrimination among sexual minority women contribute to worse reproductive health [59].

Mechanisms

These early-life risk factors could lead to poorer reproductive and pregnancy outcomes through several pathways (Table 1). Certain exposures (infectious agents or environmental pollutants) are retained in the body, so that the early-life exposure is still present during pregnancy even when there was no recent exposure. Others have direct effects on the structure of the reproductive system. Some exposures, particularly social ones, may lead to adverse health behaviors. Many types of exposures produce long-term hormonal or inflammatory changes [60]. For instance, micronutrient deficiencies cause subtle changes such as cortisol levels and rhythms [14]; adverse childhood experiences have also been shown to alter hypothalamic–pituitary–adrenal axis function [61, 62]; in utero exposure to maternal smoking changes ovarian developmental signaling [63]; and prenatal exposure to perfluoroalkyl substances has been associated with anti-Müllerian hormone levels, associated with ovarian reserve [64]. Increasingly, there is interest in possible epigenetic changes that persist across the life course, carry into pregnancy, and impact reproduction [65], although evidence for causal effects is still limited.

Multigenerational Effects

Developmental origins of health and disease (DOHaD) research have made us aware that early life can encompass the period in utero, or even prior to conception, and studies are now beginning to address transgenerational effects. Such studies provide powerful evidence for life experiences affecting health and disease across the life course and generations, and how "life circumstances, health, and disease are linked at a molecular scale" [66]. PubMed, EMBASE, and CINAHL were searched for papers with keywords related to transgenerational effects (transgenerational, multigenerational, three-generation) and reproductive health (birthweight, preterm, gestational age, fertility, miscarriage; see supplementary material for details). Several three- or more-generation studies exist addressing reproductive health (Table 2). Perhaps because the original focus among DOHaD studies was birthweight (and likely because it is easily measured and reported), this remains the primary reproductive outcome studied. However, a few studies have also addressed infant mortality, preterm birth, birth defects, or hypertensive disorders (Table 2). Results from the multigenerational studies are inconclusive. Generally, grandparents' exposures were related to grandchildren's birth outcomes, but often that was mediated by known risk factors in the intermediate generation, such as maternal BMI, smoking, or birthweight.

Conducting a multigenerational study is difficult. Randomized trials are impossible and prospective cohort studies are nearly as hard. The Uppsala study is the closest to a prospective design, identifying F0 births (first-generation, grandparents) at a single hospital (1915–1929), then linking to F1 (children) and F2 (grandchildren) [67]. Few other studies started with a multigenerational design, and many include both prospective and retrospective components. Several studies began as birth cohorts, enrolling either pregnant women or children at birth and following the children until they had their own children. Others are linkages of existing data sources (e.g., Swedish and Norwegian medical registries [68, 69], vital statistics data [70–72], or medical records [73]). Some focus on a defined exposure (e.g., famine, traumatic experience, diethylstilbestrol (DES), the atomic bomb); others were developed as studies of social and economic development in youth, and expanded to include biological measures [74]. For some, the focus is on change in risk factors across generations, particularly those with a focus on social or neighborhood exposures [18, 19]. All the study designs share issues with completeness of measurement across generations and informative missing data [75]. Interpretation of these studies is additionally complex in that it is generally easier to follow the maternal line, but many epigenetic and transgenerational effects in both humans and animals have been shown to be paternal [76]. Perhaps because of these difficulties, many studies that have collected information on three generations appear to have published primarily on two-generation associations.

Conclusions

Pregnancy is increasingly understood in a life course perspective, but rigorous methods for researching this are still difficult. Retrospective studies are subject to recall bias and selective fertility [77]. Prospective life course studies require a long-term investment of time and money, and information relevant to hypotheses of most interest decades or generations later may not have been measured initially. Even when data are collected at regular time points, statistical methods may not be sufficient for determining critical periods, while measurement error may not allow determining independent effects [78]. Parental — particularly paternal — information may be missing, especially for important confounders. These concerns are magnified in multigenerational studies. Technological developments in both statistical methods [75] and epigenetics [79] will be

Table 2 Three- or more generation studies of transgenerational exposures and reproductive or pregnancy outcomes

Study or author name; Country, state, or region	Primary outcome	F0 exposure(s)	Study design/data source	Multigenerational results*
1958 National Child Development Study [92] England, Scotland, Wales	Birthweight	Smoking during pregnancy (up to or after the fourth month)	Cohort enrolled at birth. Grandmothers reported on smoking during pregnancy. Maternal report on offspring numbers and birthweight	Grandmother's smoking associated with reduced birthweight via maternal smoking. If mother did not smoke, adjusted association between smoking and birthweight was positive
3G Multigenerational Cohort of Nova Scotian women [93] Nova Scotia, Canada	Birthweight, gestational age, neonatal complications	Sociodemographics, weight, smoking	Population database linkage	
Aberdeen children of the 1950s [94] Scotland, UK	Birthweight	Occupation	Interview and medical record	Those in the highest quintile of SES (F0) had higher birthweight for mother (F1) and children (F2)
Agius [73] Malta	Birthweight	BMI and metabolic syndrome	Linkage of clinical datasets	No associations between F0 metabolic syndrome and F2 birthweight
ALSPAC (Avon Longitudinal Study of Parents and Children), Avon, UK [95]	Birthweight	Smoking, diabetes	Parents reported during their pregnancies on grandparents' smoking and diabetes status; children were followed prospectively	Grandchildren of maternal grandparents with type 2 diabetes were more likely to be in the top tertile of birth weight than grandchildren of non-diabetics Inverted U-shaped association between birth weight of grandchildren and diabetes in paternal grandmothers
Andrasfay [70] Florida, USA	Birthweight, LBW	Race/ethnicity and foreign/domestic birth	Linked vital statistics	Hispanic foreign-born F0 associated with less LBW in F2; black foreign-born F0 LBW advantage much reduced
Bogalusa Heart Study and Bogalusa Daughters [96, 97] Louisiana, USA	Birthweight, gestational age	Cardiometabolic health	Cohort follow-up and F1 interview/linkage to birth certificates for F2	F0 higher glucose levels associated with higher F2 birthweight; F0 triglycerides and LDL associated with lower F2 birthweight
Children of 1997 [98] Hong Kong	Birthweight	Education	Birth cohort with report on grandparental information	F0 education not associated with birthweight
Consortium of Health Outcomes Research in Transitioning Societies (COHORTS) [99, 100] Cebu, Philippines	Birthweight	Nutritional status	Birth cohort originally enrolled mothers and infants; children followed up for outcomes of their children	
Danish Perinatal Study [101] Denmark	PTB, SGA	Smoking, BMI	Birth cohort with linkage and follow-up of children	
DES follow-up study combined US studies [102, 103]	Birth defects, menstrual cycle characteristics, fertility, miscarriage, preterm birth, neonatal death	DES in utero	Combination and follow-up of 4 cohorts; DES exposure verified by medical record	Overall birth defects were elevated but possibly reporting bias; higher risk of irregular menses and amenorrhea; preterm delivery

Table 2 (continued)

Study or author name; Country, state, or region	Primary outcome	F0 exposure(s)	Study design/data source	Multigenerational results*
Dutch Famine Birth Cohort Study [104, 105] Netherlands	Infant mortality, birthweight	Famine	Follow-up of birth cohort	Excess F2 perinatal mortality if F0 exposed to famine in the third trimester. F2 birthweight lower if F0 exposed, due primarily to effects on F1 birthweight
Early Life Exposures in Mexico to ENvironmental Toxicants (ELEMENT) [106] Mexico City	Birthweight, head circumference	Lead, endocrine disruptors, pesticides	Follow-up of pregnancy/birth cohort	
Giuntella [107] California and Florida, USA	Birthweight	Assimilation/endogamy	Linked birth certificates (siblings as well as direct line)	F2 children of F1 intermarried Hispanic women are more likely to be LBW
Add Health [108] USA	Birthweight	Education	Maternal report	Grandmaternal education associated with higher grandchild birthweight
Illawarra Born [109] Illawarra-Shoalhaven, Australia	Birthweight, length, head circumference, gestational age	Mental health, personality, quality of life, alcohol use	Pregnant women recruited along with grandmothers and children	
Illinois Transgenerational Study [110–112, 113 and others] USA	Birthweight	Immigration generation Place of birth	Links across generations; limited to existing data on birth certificate	Upward mobility associated with reduced risk of PTB among those not born LBW
Isle of Wight birth cohort [114] UK	Birthweight	BMI and smoking	Birth cohort and medical records	F0 BMI and smoking associated with F2 birthweight via maternal birthweight, smoking, and BMI
Jerusalem Perinatal Family Follow-Up Study [115] Israel	Birthweight	Demographics, socioeconomic status, smoking	Follow-up of a birth cohort	
Lee [116] South Korea	Birthweight, gestational age	Kwangju uprising	Vital statistics	Grandmother exposure during pregnancy (particularly second trimester) associated with lower birthweight and gestational age
Lifecourse Influences on Fetal Environment [20, 117] Michigan, USA	PTB, SGA, LBW	Socioeconomic position, health, BMI, neighborhood	Birth cohort with additional interviewing of F0 mothers	Improved F1 education relative to F0 associated with reduced risk of SGA
Lifelines NEXT [118] Netherlands	Gestational age, birthweight, birth length, birth defects	Anthropometry, blood pressure, pulmonary function, neuropsychiatric health, family, work, physical activity, smoking	F0 recruitment of adults (aged 25 to 50) through general practitioners; recruitment of their children and grandchildren through F0	
Life Span Study Atomic Bomb Survivor Cohort [119] Japan	Birthweight, birth defects, infant mortality	Atom bomb	Cohort follow-up	

Table 2 (continued)

Study or author name; Country, state, or region	Primary outcome	F0 exposure(s)	Study design/data source	Multigenerational results*
Lifeways Cross-generational Study [120, 121] Ireland	BMI at birth Height at birth	Height and BMI	Prospective study of children 2001–2013. Height and BMI collected at 0, 5, and 9 years of age. Retrospective on adults	Offspring height correlated with both parents at birth Adherence to Healthy Eating Index in maternal grandparents associated with lower likelihood of LBW and greater likelihood of macrosomia
Mater-University of Queensland Study of Pregnancy [122] Queensland, Australia	Pregnancy outcomes	Mental illness, physical activity, BMI, substance use, poverty	Birth cohort with added F2 generation	
Michigan Bone Health and Metabolism Study [123] Michigan, USA	Birthweight	Smoking	Study of female adult children of participants community health study; reported on grandmother's and children's health	Birthweight was higher in F2 grandchildren whose grandmother (F0) and mother (F1) both smoked during pregnancy if F0 was born between 1929 and 1945; not found for earlier births
Nurses' Health Study 2, Growing Up Today Study (GUTS), Nurses' Mothers Study [124] USA	Birthweight	Smoking	Children and mothers of NHSII women were recruited. Information on grandpaternal smoking was provided by mothers	Birthweight and child BMI were higher in those whose grandmothers smoked. No association between grandparental smoking and adolescent BMI
Naess [69] Norway	Birthweight	Death certificates for ICD: breast cancer, chronic obstructive pulmonary disease, cardiovascular causes, coronary heart disease, stroke, diabetes, lung cancer	Identified children (F2) births from 1967–2009 and linked parents (Maternal and Paternal) (F1) and grandparents (Maternal and Paternal) (F0);	Grandparents who died of cardiovascular causes associated with lower likelihood of higher birthweight; much of this was due to maternal smoking in pregnancy. U-shaped associations were seen with grandchild birthweight and maternal grandmother mortality from diabetes; inverse associations for all other grandparents
Nebraska Mother Index [125] USA	Birthweight, gestational age, delivery type		Linked vital statistics	
New Jersey [126] USA	PTB	Education, marital status	Linked vital statistics	Grandmother's education predicted PTB for grandchildren
Norwegian Mother and Child Birth Cohort (MoBa) [127] Norway	Birthweight, gestational age, birth defects	Health, medication, smoking	Primarily a birth cohort with child follow-up, but linked to other registries for some analyses	

Table 2 (continued)

Study or author name; Country, state, or region	Primary outcome	F0 exposure(s)	Study design/data source	Multigenerational results*
Pathways to Adulthood [128, 129] Baltimore, USA	Birthweight	Smoking, health, BMI, income	Follow-up of the Collaborative Perinatal Project birth cohort; includes interviews and medical records	Higher F0 income/needs ratio associated with higher birthweight. Higher F0 education associated with higher birthweight only if F1 education was lower. Effects of F1 smoking moderated by F0 smoking
Qian [130] Taiwan	Birthweight for gestational age	Education, town-level educational status	Linked vital statistics	
Respiratory Health in Northern Europe, Spain, and Australia (RHINESSA) [131]	PTB	Respiratory health, place of residence, exposure to allergens, smoking	Population-based study of adults; grandparents and children recruited through participants	
Song [132] China	Infant mortality	Famine (Chinese Great Leap Forward)	2001 National Family Planning and Reproductive Health Survey (NFPRHS) and the 1982 Chinese Population Census	In regions of low famine severity, mothers' prenatal famine exposure significantly reduced children's infant mortality; in regions of high famine severity, prenatal exposure associated with higher infant mortality
Seattle Social Development Project (SSDP) and the SSDP Intergenerational Project [133] Washington, USA	Birthweight	Socioeconomic disadvantage	Longitudinal study of mothers followed in the Seattle School Development Project starting at age 10 and followed until age 27	Low grandparental SES in maternal childhood associated with birthweight. Abuse in maternal childhood was associated with birthweight, mediated through maternal substance abuse as an adolescent and/or prenatally
South Carolina Multigenerational Linked Birth Dataset [72] USA	Birthweight	Education, social mobility	Linked birth certificates	
Uppsala Birth Cohort Multigenerational Study [67] Sweden	Birthweight Birth length Gestational age	Education, marital status, occupational class	Birth cohort study F0 born 1915–1929 linked to grandchildren who were born after 1972	Shared environment had a small but significant effect on birthweight and birth length
US National Longitudinal Study of Youth [74] USA (nationally representative)	Birthweight, controlled for gestational age	Education (self-reported) Nonmarital childbearing	Mother is index subject. Grandmother and mother interviewed at baseline, information collected about child from mother or directly from child at follow-ups. Birthweight measured on grandchildren of original study participants	
Utah Population Database [134, 135] USA	Fertility, birth defects	Age, chemotherapy exposure	Linked birth, death, cancer registry	No association between grandmaternal age and F2 trisomy 21

Table 2 (continued)

Study or author name; Country, state, or region	Primary outcome	F0 exposure(s)	Study design/data source	Multigenerational results*
Vägerö [136] Sweden	Birthweight, PTB	Childhood trauma: parental (F0) death during F1 childhood	Linked information from several Swedish national registers, including the Population and Housing Census 1960, Cause of Death Register 1961–2002, the Swedish Register of Education 1990 and the Swedish Medical Birth Register (MBR) 1973–2002	Grandparental death during parental childhood predicted lower birthweight and PTB in generation 3
Virginia Intergenerational Linked Birth File [137] USA	Birthweight		Linked vital statistics	
Wallace [138] New York, USA	LBW	Housing destruction	Birth records and vital statistics	1970–1980 percent population change associated with socioeconomic factors that were associated with low birthweight in 2008
Washington State Intergenerational Cohort [139] USA	LBW, PTB	Education, residence in a deprived area, smoking	Linked vital statistics	

*Generations are referred to as F0 (grandparent), F1 (parent), F2 (child) for consistency, regardless of how they were referred to in the paper. Last column blank for studies that present a 3-generation study design but for which we did not find papers on effects of F0 exposures on F2 outcomes

LBW, low birthweight; *PTB*, preterm birth; *SES*, socioeconomic status; *DES*, diethystilbestrol

needed to improve our understanding of patterns of disease and of mechanisms. However, given the lack of efficacy for many interventions implemented during pregnancy, improving health in this crucial period may not be possible without improving health throughout life.

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Declarations

Conflict of Interest The authors declare no competing interests.

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