

Early life exposure and its association with diseases in adulthood: review of longitudinal studies

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Abstract

Background: We describe the evidence of the effects of early life exposures on health and aging during adulthood. **Methods:** A narrative review of cohorts and systematic reviews of studies initiated early in life and followed up to adulthood was conducted. **Results:** Most studies were carried out in developed countries. The long-term effects of birth weight and, to a lesser extent, height at birth on chronic-degenerative diseases, functionality, bone, renal and respiratory pathology, and mortality have been consistent. Breastfeeding is associated with metabolic and cardiovascular diseases and functionality. Adiposity, bone pathophysiology, functionality in old age, and high blood pressure are associated with socioeconomic status at birth. **Conclusions:** Several exposures from intrauterine life to adolescence that exert discrete but significant effects on adult health have been consistently described. It is necessary to carry out these studies in developing countries.

Key words: Life history. Growth. Infant. Adult. Health. Chronic diseases.

Exposiciones tempranas en la vida y su asociación con enfermedades en la edad adulta: revisión de estudios longitudinales

Resumen

Introducción: En este artículo se describe la evidencia acerca de los efectos de las exposiciones tempranas sobre la salud y el envejecimiento en la edad adulta. **Métodos:** Revisión narrativa de cohortes y revisiones sistemáticas de estudios iniciados en la vida temprana y seguidos hasta la edad adulta. **Resultados:** La mayoría de los estudios se realizaron en países desarrollados. Los efectos a largo plazo del peso al nacer, y en menor medida de la talla al nacer, en las enfermedades crónico-degenerativas, la funcionalidad, la fisiopatología ósea, renal y respiratoria, y la mortalidad, han sido consistentes. La lactancia materna se ha asociado con enfermedades metabólicas y cardiovasculares, y con la funcionalidad. La adiposidad, la fisiopatología ósea, la funcionalidad en la vejez y la hipertensión arterial están asociadas con el nivel socioeconómico al nacer. **Conclusiones:** Diferentes exposiciones desde la vida intrauterina hasta la adolescencia ejercen efectos discretos, pero significativos, sobre la salud de los adultos. Se requiere realizar estos estudios en las poblaciones que viven en países en desarrollo.

Palabras clave: Historia de vida. Crecimiento. Lactante. Adulto. Salud. Enfermedad crónica.

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Introduction

It is known that early environmental conditions affect the growth and development in the early stages of life, which later affects adult morbidity¹. These associations are relevant to public health^{2,3}. When associated with morbidity, they sometimes are confused with the progression of aging-related changes⁴. The harmful effects of early life exposures can also hamper the so-called “healthy biological aging,” which is understood as “surviving to old age with delayed onset of chronic diseases and with optimal functioning of the individuals in their physical and cognitive abilities, as well as at the systemic and cellular levels⁵.”

Some early developmental factors influence different aging phenotypes and their related diseases^{6,7}. Sometimes, the adaptations may confer advantages to the environment that will be faced later. However, according to the antagonistic pleiotropy theory, these adaptations become adverse as the individual ages^{8,9}. Barker’s hypothesis links the decrease of fetal growth, present in situations of nutrient shortage, with metabolic syndrome as life advances¹⁰. Several studies have shown a relationship between early adverse events during embryonic development and childhood, such as poverty, poor nutrition, sub-optimal health system, and violence, with fragility in adulthood and early development of chronic diseases¹¹. The mechanism by which the external factors modify the internal environment after several years could be DNA epigenetic changes, including methylation patterns during embryonic development¹²⁻¹⁴. Thus, changes in gene expression and their relationship with epigenetics have been associated with various metabolic, immunity, and senescence processes^{15,16}.

In this context, the objective of the present manuscript is to review and describe the evidence about the effects of early life exposures on health in the adult stage and aging.

Methods

A narrative review of cohorts and systematic reviews of studies initiated in the early stages of life and followed up to adulthood was conducted. The search was carried out in PubMed and Virtual Health Library using the MeSH terms indicated in [Table 1](#).

Results

The summarized results are shown in [Table 2](#).

Effects of early life exposures (in utero and childhood) on adult life

MORTALITY AND LIFE EXPECTANCY

The Helsinki Birth Cohort 1934-1944 (n = 4943)¹⁷ showed that the changes in the body mass index (BMI) from 0 to 11 years of age were related to adult mortality: women with high BMI or who gained weight and increased their BMI showed a higher risk of death from any cause; men with an average or reduced BMI in childhood had a higher risk of cancer mortality¹⁷. Another analysis of this cohort (n = 13,345) showed that women who increased their BMI between 2 and 11 years and had children, as well as men with high height at 7 years of age, were associated with longer life expectancy¹⁸. A Danish cohort (n = 216,464) showed that adult mortality (25-68 years) was 17% higher in the group of low birth weight (LBW) (2000-2750 g), and 7% higher in the high birth weight (HWB) group (4251-5500 g), compared to the normal birth weight (BW) group (3251-3750 g). BW was linearly associated with the risk of cancer, but the relationship of this parameter with circulatory diseases and other causes of mortality showed a U-shape distribution¹⁹. In another Danish cohort of men born in 1953 (n = 10,753), LBW and low birth height were directly related to the risk of adult mortality²⁰. The results of these studies are consistent with an increased overall risk of mortality from different causes in adulthood related to early adverse conditions.

Adult height

Several studies showed that developed countries, which have experienced improvements in food access, diet diversification, sanitation, water availability, economic development, the standard of living, education, and less exposure to infectious diseases, had presented increases in adult height since the 19th century. In turn, in low- and middle-income countries, low adult height reflects the growth retardation that occurs mainly from conception up to 2 years of age. The effect of inheritance on height has been variable due to methodological

Table 1. PubMed search for early exposures and adult outcomes in cohort or meta-analysis studies

((breastfeeding OR "breast feeding" OR "exclusive breastfeeding" OR "exclusive breast feeding" OR "complementary diet" OR "complementary feeding" OR "complementary diet start" OR "complementary feeding start" OR "complementary diet age" OR "complementary feeding age" OR "supplementary diet" OR "supplementary feeding" OR "supplementary diet start" OR "supplementary feeding start" OR "supplementary diet age" OR "supplementary feeding age" OR "weaning age" OR "failure to thrive" OR "growth faltering" OR undernutrition OR malnutrition OR "severe acute malnutrition" OR kwashiorkor OR marasmus OR stunting OR stunted OR "growth gain" OR growth OR "growth increment" OR "weight for age" OR "weight gain" OR "weight increment" OR "length gain" OR "length for age" OR "recumbent length" OR "length increment" OR "height increment" OR "height gain" OR "height for age" OR "sitting height" OR "sitting height increment" OR "head circumference" OR "head circumference for age" OR "head circumference gain" OR "head circumference increment" OR "leg length" OR "leg length gain" OR "leg length index" OR "arm circumference" OR "arm circumference for age" OR "arm circumference gain" OR "thoracic perimeter" OR "thoracic perimeter gain" OR "thoracic perimeter for age" OR "thoracic perimeter increments" OR "triceps skinfold" OR "triceps fat tissue" OR "triceps adipose tissue" OR "biceps skinfold" OR "biceps fat tissue" OR "biceps adipose tissue") AND ("adult health" OR "chronic disease" OR "non-transmissible disease" OR "non-communicable disease" OR "non-communicable disease" OR "ageing" OR "aging" OR "leg length index" "body mass index" OR BMI OR "overweight" OR "obesity" OR "waist circumference" OR "central adiposity" OR "fat mass" OR "fat free mass" OR "skeletal muscle mass" OR "bone mass" OR "grip strength" OR "quality of life" OR "functional capacity" OR "functional dependence" OR "functional disability" OR "functional health" OR "functional impairment" OR "functional limitation" OR "functionality capacity" OR "functionality dependence" OR "functionality disability" OR "functionality health" OR "functionality impairment" OR "functionality limitation" OR "physical function" OR "cognition" OR cognitive OR inflammation OR "C reactive protein" OR fibrinogen OR "erythrocyte sedimentation rate" OR "erythrocyte sedimentation rate" OR "blood sedimentation" OR "sedimentation rate" OR "diabetes mellitus" OR "blood glucose" OR hyperglycemia OR "systemic arterial hypertension" OR hypertension OR "high blood pressure" OR "cholesterol" OR "high cholesterol" OR hypercholesterolemia OR hypercholesteremia OR dyslipidemia OR dyslipoproteinemia OR "visual acuity" OR "visual impairment" OR "hearing acuity" OR "hearing loss" OR "hearing impairment" OR audition OR "renal function" OR "kidney function" OR "liver function" OR "hepatic function" OR "heart disease" OR cardiopathy OR "COPD" OR "chronic obstructive pulmonary disease" OR "chronic bronchitis" OR "pulmonary emphysema" OR asthma OR "osteoporosis" OR "socioeconomic classification" OR socioeconomic OR "living standard" OR "social class" OR "socioeconomic status" OR "type of aging" OR "patterns of aging" OR "type of ageing" OR "patterns of ageing" OR "aging type" OR "aging pattern" OR "ageing type" OR "ageing patterns" OR "death" OR "cause of death" OR mortality OR "metabolic syndrome" OR "menopause" OR climacteric)) AND (cohort OR review OR "meta-analysis" OR "meta analysis" OR "metaanalysis") AND "humans" [MeSH Terms] AND ("middle aged" [MeSH Terms] OR "aged" [MeSH Terms]) AND (Spanish [lang] OR English [lang])

Number of retrieved abstracts: 451
 Number of selected articles: 54
 Date of Search: May 10, 2017

diversity; however, some studies have shown that the environment profoundly influences adult height²¹.

Nutrition, body composition, and functionality in adulthood

ADIPOSY AND LEAN BODY MASS

The British Medical Research Council National Survey of Health and Development (MRC NSHD) cohort study (n = 1558) showed that, after adjusting for height, body fat was related to the lifetime socioeconomic position of women and men between 60 and 64 years old. At 4 years of age, a lower fat mass index in women was related to a higher paternal occupational class, whereas an inverse relationship was observed in the android to gynoid fat ratio distribution in both sexes. At 6 years of age, the fat mass index in women showed a negative correlation with maternal education but a positive one with paternal education. Lower lifetime socioeconomic position was associated with lower lean mass in women after adjustment for fat mass. Whereas, in men, lean mass was associated with current household income²².

These observations indicate that the fat and lean mass levels in adulthood are influenced by multifactorial processes early in life. Furthermore, this is coherent with difficulty to prevent and control obesity in adulthood.

Breastfeeding (BF) is an early environmental factor that influences obesity during adulthood. In a study of 9377 people who were followed from birth to 45 years of age in the British Cohort of Births 1958, BF for more than 1 month was associated with lower waist circumference values, waist/hip ratio, von Willebrand factor, and obesity risk during adulthood, compared with people that received formula feeding. This association was maintained when was adjusted to maternal weight before pregnancy, maternal smoking during pregnancy, socioeconomic status in childhood and adulthood, the region of birth, sex, and current smoking status²³.

OBESITY IN ADULTHOOD

In a meta-analysis (n = 642,902, ages 1-75 years), LBW was associated with a long-term lower risk of overweight/obesity, while HBW predisposed to overweight/obesity in later stages²⁴. Another systematic

Table 2. Studies of early life exposures and health outcomes in adulthood

Population (n)	Exposure age (years)	Sex	Exposure	Effect	Outcome	Reference	
Helsinki Birth Cohort, 1934-1944 (n = 4943)	0-11	F	Increased in BMI	Increase	Mortality from any cause	17	
		M	Decrease from average BMI		Mortality from cancer		
Helsinki Birth Cohort, 1934-1944 (n = 13,345)	2-11	F	BMI in their lane and had children	Increase	Life expectancy	18	
	7	M	Height				
Danish Cohort (n = 216,464)	0	F, M	LBW	Increase	Mortality	19	
			HBW	Increase			
		U-shape	Mortality by circulatory diseases and other causes				
			Increase	Cancer risk			
Danish Cohort of born in 1953 (n = 10,753)	0	M	LBW or low birth height	Increase	Mortality	20	
The British MRC NSHD Cohort, 1946 (n = 1558)	4	F	Higher paternal occupational class	Decrease	Fat mass	22	
		F, M			Android/gynoid fat ratio distribution		
	6	F, M	Lower paternal occupational class or lower maternal and paternal education	Increase	Android/gynoid fat ratio distribution		
			Lower maternal education		Fat mass		
Lifetime	F	Lower socioeconomic status	Decrease	Lean mass			
The British Cohort of Births, 1958 (n = 9377)	> 1/12	F, M	BF versus formula feeding	Decrease	Waist, waist/hip ratio and obesity	23	
Meta-analysis (n = 642,902)	0	F, M	LBW	Decrease	Overweight/obesity	24	
			HBW	Increase	Overweight/obesity		
Systematic review	Infancy and childhood	F, M	Fast growth (weight/age)	Increase	Overweight/obesity	25	
Helsinki birth Cohort, 1934-1944 (n = 4515)	0	F, M	HBW	Increase	Obesity	26	
			Prenatal	Higher maternal BMI	Increase		Obesity
				Higher socioeconomic status and education level	Decrease		Obesity
	0.5-12		Higher weight	Increase			
Meta-analysis of 13 Nordic Cohorts (n = 43,482)	0	F, M	BW < 2.75 kg or > 4.76 kg	Decrease	Physical activity performance	27	
Helsinki Cohort, 1934-1944 (n = 1078)	0	F, M	HBW and height	Increase	Physical performance	28	
MRC NSHD Cohort (n = 2850)	0	F, M	BW	Increase	Grip strength	29	
			2				Height for age
			2-7				Height increase
			< 2				Earlier motor development
	Puberty	M	Weight increase				
		F	Height increase				

(Continues)

Table 2. Studies of early life exposures and health outcomes in adulthood (*continued*)

Population (n)	Exposure age (years)	Sex	Exposure	Effect	Outcome	Reference
Hertfordshire Cohort (n = 2983)	1/12 and more	M	BF duration	Increase	Grip strength	30
Japanese Cohort JAGES, 2010 (n = 15,499)	< 15	F, M	Subjective lower socioeconomic status	Increase	Limitations in higher-level functional capacity	31
			Lower height reached	Increase	Functional limitation	
ELSA-Brazil study (n = 12,997)	Lifetime	F, M	Lower level of maternal education	Decrease	Cognitive performance	32
	0		LBW	Decrease	Psychomotor performance	
	Fast growth stages		Trunk length	Increase	Semantic and phonemic verbal fluency	
Helsinki Cohort, 1934-1944 (n = 931 males)	0	M	LBW, height, and head circumference	Decrease	Cognitive capacity	33
			Length at birth	Increase	Cognitive performance	
				Decrease	Cognitive decline after 20 years	
	0 and 2	Lower growth	Decrease	Cognitive ability		
Edinburg study, 1921-1926 (n = 128)	0	F, M	Greater height	Increase	Cognitive ability before old age	34
			Greater socioeconomic status			
Caerphilly Cohort, 1920-1935 (n = 779)	0	M	Weight below the median and formula-fed	Decrease	Reasoning and reading tests	35
MRC NSHD Cohort, 1946 (n = 1741)	Infancy	F, M	BF	Increase	Reading ability	36
NHS Cohort (n = 87,077)	0	F	BW > 4.54 kg	Increase	Rheumatoid arthritis	37
Twins UK Registry (n = 1194)	0	F	HBW	Decrease	Insulin resistance	38
Newcastle TFS Cohort (n = 412)	Infancy	M	BF duration	Decrease	Insulin resistance	39
Meta-analysis (n = 152,084)	0	F, M	HBW	Decrease	T2DM	40
E3N Cohort, 1925-1950 (n = 91,453)	0	F	HBW	Decrease	T2DM	41
	8, menarche age		Self-perception of thinness			
Danish Cohort monozygotic and dizygotic twins (n = 298)	Lifetime	F, M	Monozygotic and dizygotic twins	Increase	Abdominal adiposity, insulin resistance, glucose intolerance, hemoglobin A1C, glycemia, and T2DM	42
Systematic review (n = 76,744)	Infancy	F, M	BF versus formula	Decrease	T2DM	43
NHS Cohort (n = 69,526)	0	F	LBW	Increase	T2DM	44

(Continues)

Table 2. Studies of early life exposures and health outcomes in adulthood (*continued*)

Population (n)	Exposure age (years)	Sex	Exposure	Effect	Outcome	Reference
Meta-analysis (n = 39,641)	0	F, M	LBW	Increase	Hypertension	45
			Weight > 4.0 kg	Decrease		
The Newcastle TFS (n = 412)	0	F, M	LBW	Increase	BMI	46
		M			SBP and DBP	
		F, M	Lower socioeconomic status	Increase	DBP	
British Cohort of Births 1958 (n = 9297)	0	F, M	BW	Decrease	SBP	47
Meta-analysis (n = 56,779)	0	F, M	BW	Decrease	Total cholesterol	48
MRC NSHD Cohort 1946 (n = 2311)	2	F, M	Greater height	Decrease	Cholesterol and LDL	49
	15		Greater growth rate		Cholesterol	
Newcastle TFS Cohort (n = 406)	Infancy	F	Duration of exclusive BF	Increase	Total cholesterol and LDL	50
Systematic review (n = 17,498)	Infancy	F, M	BF versus formula fed	Decrease	Total cholesterol	51
The Helsinki Cohort, 1934-1944 (n = 8760)	0		Smaller height	Increase	Apolipoprotein B and triglycerides	52
	2		Slow weight gain			
	0.5		BMI	Increase	HDL	
	2			Decrease	Non-HDL cholesterol apolipoprotein B and triglycerides	
Review (n = 147,009)	0	F, M	BW	Decrease	CHD	53
WHI Cohort (n = 63,815)	0	F	LBW	Increase	Cardiovascular disease	54
Norwegian Cohort (n = 35,846)	0	F, M	Lower HC and tall mother or high adult BMI	Increase	Death from CHD	55
SWLH Cohort (n = 49,259)	0	F	LBW	Increase	CHD	56
Icelandic Cohort (n = 3614)	Infancy	F, M	Formula-fed	Increase	Erythrocyte sedimentation	57
			BF	Increase	BMI	
Carnegie Cohort (n = 405)	Infancy	F, M	BF versus bottle-feeding	Decrease	Carotid plaque	58
Caerphilly Cohort (n = 1580)	Infancy	M	BF	Increase	BMI	59
NHS Cohort (n = 87,252)	Infancy	F	BF	None	SH, CHD, or stroke	60
Meta-analysis (n = 15,378)	0	F, M	BW	Increase	Glomerular filtration rate	61
Meta-analysis (n = 11,471)	0	F, M	BW	Decrease	Albumin creatinine ratio	
Meta-analysis (n = 110,683)	0	F, M	LBW	Increase	Chronic kidney disease	

(Continues)

Table 2. Studies of early life exposures and health outcomes in adulthood (*continued*)

Population (n)	Exposure age (years)	Sex	Exposure	Effect	Outcome	Reference
Helsinki Cohort, 1934-1944 (n = 13,345)	0	F, M	Placental weight and length and BW	Decrease	Asthma	62
	Childhood	M	Lower socioeconomic status or manual workers sons	Increase		
Newcastle TFS Cohort (n = 412)	0	F, M	HBW	Increase	Forced expiratory volume 1	63
	Infancy		BF > 4 weeks			
	Childhood		Lower respiratory tract infections			
Meta-analysis (n = 3181)	0	F, M	BW	Increase	BMC in spine	64
Meta-analysis (n = 1,795)	0	F, M	BW	Increase	BMC in hip	
British MRC NSHD study 1946 (n = 1658)	0	F, M	BW	Increase	Diaphyseal cross-sectional area of radius	65
	Pre- and post-pubertal		Height and weight increased rate		Cross-sectional area and bone strength of radius	
MrO Cohort (n = 1831)	0	M	HBW	Increase	Length and cross-sectional area of femoral neck	66
Hertfordshire Cohort (n = 966)	0	F, M	BW	Increase	BMC in proximal femur and lumbar spine	67
		M		Increase	BMD in proximal femur	
	1	F, M	Weight	Increase	BMC in proximal femur	
Newcastle TFS (n = 389)	0	F, M	Position in the family, BW and socioeconomic status	Increase	BMD	68
Newcastle TFS (n = 407)	Infancy	M	Duration of exclusive BF	Decrease	Seropositivity for <i>Helicobacter pylori</i>	69
E3N Cohort (n = 15,983)	0	F	HBW	Increase	Risk of colon adenoma	70
	8		Self-perception of the body figure as "large"	Decrease	Risk of rectal adenoma	
Hertfordshire Cohort (n = 3217)	Infancy	F, M	BF	Increase	Prudent diet	71

BF: breastfeeding; BMC: bone mineral content; BMD: bone mineral density; BMI: body mass index; BW: birth weight; CHD: coronary heart disease; DBP: diastolic blood pressure; F: female; HC: head circumference; HWB: high birth weight; LBW: low birth weight; LDL: low density lipoproteins; M: male; T2DM: type 2 diabetes mellitus; SBP: systolic blood pressure; SH: systemic hypertension.

review with participants between 3 and 70 years, rapid growth, defined as a change in Z score > 0.67 of weight for age between two different ages in childhood, was associated with later overweight or obesity²⁵. In the Helsinki Cohort (n = 4515), obesity in adulthood was positively associated with BW.

Furthermore, higher maternal BMI in pregnancy increased the risk of adult obesity; the weight between 6 months and 12 years predicted obesity in later stages. As registered before, socioeconomic status and education are inversely associated with obesity²⁶.

Other adult attributes

PHYSICAL ACTIVITY AND PHYSICAL PERFORMANCE

In a meta-analysis of 13 Nordic cohorts ($n = 43,482$), adolescents and adults with $BW < 2.75$ kg or > 4.76 kg were less likely to perform physical activity²⁷. In turn, in the Helsinki Cohort ($n = 1078$), higher weight and height at birth were associated with greater physical performance at 71 years of age, adjusting for adult anthropometry, lifestyle, and socioeconomic status²⁸. Handgrip strength at 53 years was associated with BW, height at 2 years of age, and height gain between 2 and 7 years (MRC NSHD cohort, $n = 2850$), when adjusting for health status, physical activity, and socioeconomic status. Other associations with adult handgrip strength were earlier motor development, puberty weight gain in men, and height gain in women²⁹. Furthermore, in the Hertfordshire Cohort ($n = 2983$), BF was related to greater handgrip strength in men between 59 and 67 years of age, after adjustment of the effects of BW, infant growth, height, age at measurement, current diet, and physical activity³⁰.

FUNCTIONALITY IN OLD AGE

In the Japanese JAGES Cohort ($n = 15,499$), functional limitations in instrumental self-maintenance activities, intellectual activities, and social roles during old age were associated with socioeconomic status in childhood. A lower subjective socioeconomic status for ages under 15 years was associated with limitations in the higher-level functional capacity; also, a shorter height was associated with functional limitation at 70-74 years. This study highlights the late effects of early social experiences functionality in old age³¹.

COGNITION

The cognitive function in adulthood is a predictor of aging quality. In the ELSA-Brazil study ($n = 12,997$, aged 35-64 years), a lower level of maternal education was associated with poor performance in cognitive tests. LBW decreased psychomotor performance, and the greater trunk length was related to semantic and phonemic verbal fluency; the latter association was observed regardless of sex, age, and educational level³².

The Helsinki Cohort ($n = 931$ men) showed that lower weight, height, and head circumference (HC) at birth were associated with lower cognitive ability at 67.9 years of age. Those subjects who were born larger had

better cognitive performance over time, and lower cognitive decline after 20 years. Besides, slower growth between birth and 2 years of age was related to lower cognitive ability, but not with cognitive decline³³.

In the Edinburg study ($n = 128$), adult cognitive ability before old age correlated with height at birth; also, there was a trend toward an association between social class at birth and cognitive ability before old age. There were no associations of height, weight, and social class at birth, with cognitive ability in old age³⁴. In the Caerphilly Cohort ($n = 779$), men with BW below the median that were formula-fed scored lower in reasoning and reading tests at 60-74 years of age³⁵. In the MRC NSHD Cohort ($n = 1741$), BF was positively associated with reading ability at 53 years, adjusted for sex, parental socioeconomic status, maternal education, birth order, parental interest in education, and material conditions at home³⁶.

CHRONIC MORBIDITIES

The developmental origins of health and disease theory were first postulated for chronic morbidity, which is essential for healthy aging promotion. The following is a short account of the findings of longitudinal studies on chronic diseases.

RHEUMATOID ARTHRITIS

In the NHS Cohort ($n = 87,077$ women), $BW > 4.54$ kg was associated with rheumatoid arthritis, compared to BW of 3.2-3.85 kg, adjusting for maternal diabetes, socioeconomic status in childhood, prematurity, parental smoking, age of menarche, use of oral contraceptives, use of post-menopausal hormones, duration of BF, and BMI at 18 years³⁷.

RESISTANCE TO INSULIN AND THE RISK OF TYPE 2 DIABETES MELLITUS (T2DM)

Several studies have confirmed the impact of early life influences on the risk of developing insulin resistance and T2DM in adult life. In the study of Twins UK Registry ($n = 1194$ twins aged 18-74 years), BW was negatively related to insulin resistance when adjusted for BMI and age³⁸. In the Newcastle TFS Cohort ($n = 412$, aged 50 years old), about 0.1-5.6% of the insulin resistance variation was inversely explained by BF duration in men, when adjusted for body fat and waist/hip ratio. Lifestyle and body composition in adulthood explained the variation in insulin secretion and resistance (11 and 22% in men and 5.9 and 34% in women, respectively)³⁹.

Regarding T2DM, BW was inversely related to T2DM development, when adjusted for age and sex (6090 cases/52,084 individuals)⁴⁰. In the E3N Cohort (91,453 French women, 15 years of follow-up), self-reported BW and self-perceived slimness at 8 years, at menarche, and at 20-25 years of age were inversely associated with T2DM when adjusted for physical activity, education, prematurity, family history of T2DM, smoking, cholesterol, systemic hypertension (SH), menopause, hormone replacement therapy, oral contraceptives, parity, age of the first child, age of menarche, and BMI during follow-up⁴¹. In a Danish Cohort of 298 monozygotic and dizygotic twins who were followed-up until 84 years of age, twins showed higher abdominal adiposity, insulin resistance, glucose intolerance, hemoglobin A1C, and glycemia in the glucose tolerance test, in addition to higher prevalence and incidence of T2DM when compared with 71 controls born of single pregnancies⁴². In a systematic review (n = 76,744), those who received BF had a lower risk of T2DM in adulthood, compared to those who were formula-fed⁴³. In the NHS Cohort (n = 69,526 women; 2123 with T2DM), LBW (< 2.25 kg) was associated with T2DM, when adjusted for age and adult BMI. This association was not modified by ethnic group, socioeconomic status in childhood, or lifestyle in adulthood⁴⁴.

HYPERTENSION

A meta-analysis (n = 39,641) confirmed the association between LBW (< 2.5 kg) and the risk of SH in later stages of life, whereas BW > 4.0 kg was a protective factor⁴⁵. In the Newcastle TFS (n = 412; 49-51 years old), LBW adjusted for sex and gestational age, increased BMI, and male sex were associated with higher systolic blood pressure (SBP) and diastolic blood pressure (DBP). Furthermore, socioeconomic status at birth was associated with DBP. BMI was the most important predictor of high SBP and DBP, with a small contribution of BW⁴⁶. The British Cohort of Births, 1958 (n = 9297), showed that the positive association BMI/BP strengthened with age. BW was inversely associated with BP: SBP reduced by 1.3 mmHg per SD increase in BW, independently of BMI⁴⁷.

DYSLIPIDEMIAS

In a meta-analysis (33,650 men and 23,129 women), BW showed an inverse relationship with total cholesterol, when adjusted for age and BMI⁴⁸. Furthermore, in the MRC NSHD Cohort (n = 2311), both heights at 2 years

of age and the rate of growth between 15 years and adulthood were negatively associated with cholesterol at 53 years of age, adjusted for height and adult BMI. Furthermore, height at 2 years was related to lower levels of LDL, adjusted for height and BMI⁴⁹. In the Newcastle TFS Cohort (n = 406), the duration of exclusive BF correlated with total cholesterol and with LDL only in women, and without effect on HDL or triglycerides⁵⁰. In a systematic review (n = 17,498), those who received BF had lower total cholesterol in adulthood compared to those formula-fed. In seven studies (n = 1244), which compared subjects with exclusive BF to formula-fed, the differences were more significant in comparison to ten studies of subjects non-exclusively formula-fed. These differences were little affected by the adjustment for age, socioeconomic status, BMI, and sex⁵¹. The Helsinki Cohort (n = 8760) showed that smaller birth height and a slow weight gain at 2 years of age were negatively related to the concentrations of apolipoprotein B and triglycerides at 57 and 60 years of age. Once adjusted for sex, current BMI, and current age, BMI at 6 months was positively associated with HDL and negatively associated with non-HDL cholesterol, and with apolipoprotein B. BMI at 2 years was positively associated with HDL levels, and negatively with non-HDL, apolipoprotein B, and triglyceride concentrations⁵². These results confirm that intrauterine, postnatal growth, and the type of lactation influence the adult lipid profile.

CORONARY HEART DISEASE (CHD) AND OTHER CARDIOVASCULAR RISKS

Several Cohort studies and systematic reviews have consistently found associations of intrauterine growth and early feeding patterns with cardiovascular risks. A review (7518 cases/147,009 people) showed an inverse association between BW and CHD, with a 1 kg higher BW associated with a 16% lower risk of ischemic disease⁵³. In a WHI Cohort (63,815 post-menopausal women), self-reported LBW (< 2.7 kg) was associated with a higher incidence of cardiovascular disease, adjusted for smoking, diabetes, SH, age, systolic BP, and BMI⁵⁴. In a Norwegian Cohort (n = 35,846, 630 deaths from CHD), the HC at birth was related to CHD and also was associated with maternal height and adult BMI. Those in the lowest HC tertile who had a tall mother or a high BMI in adulthood had a higher risk of death from CHD⁵⁵. In the SWLH Cohort (49,259 women, at 35-50 years of age), after adjusting for age, health behaviors, diabetes, HS, and obesity at 12 years of follow-up, LBW (< 2.5 kg) was associated with CHD⁵⁶.

In an Icelandic Cohort (n = 3614), those formula-fed (5.2%) had a higher erythrocyte sedimentation rate, while those with BF had 2.9% higher BMI in adulthood. However, the risk of CHD was not different between groups⁵⁷. In the Carnegie Cohort (n = 405, aged 63-81 years), BF protected against carotid plaque development compared to bottle-feeding⁵⁸. In the Caerphilly Cohort (n = 1580 men aged 45-59 years), when adjusted for age, birth order, and child and adult socioeconomic status, retrospectively recorded BF was associated with higher BMI and higher incidence and mortality by CHD⁵⁹. However, in the NHS Cohort (n = 87,252 women aged 46-79 years), no relationship was found between BF and SH, CHD, or ischemic or hemorrhagic stroke, when adjusted for age, BW, smoking, and BMI⁶⁰.

RENAL FUNCTION AND DISEASE

In a meta-analysis, LBW (< 2500 g) was associated with chronic kidney disease later in life, as measured by glomerular filtration rate and microalbuminuria/albumin excretion rate (AER)/urinary albumin creatinine ratio (ACR) parameters. On average, each kg of BW increased the glomerular filtration rate by 2.09 ml/min per 1.73 m² and reduced the albumin/creatinine ratio⁶¹.

ASTHMA

In the Helsinki Cohort (n = 13,345), increased birth length and increased placental surface were associated with less risk of asthma development, after adjusting for gestational age and BW. In the same cohort, it was shown that in later stages, the siblings of manual workers had a higher risk of asthma compared to those of upper-middle-class, regardless of fetal growth; when adjusted for birth length, childhood growth was not related to asthma⁶².

RESPIRATORY FUNCTION

In the Newcastle TFS Cohort (n = 412), increased BW, BF for more than 4 weeks, less frequent childhood respiratory tract infections, non-smoking, lower body fat (in men), no history of asthma, and more considerable adult height were all associated with higher forced expiratory volume in 1 s at 49-51 years of age⁶³.

BONE

In a meta-analysis, BW was positively correlated with adult bone mineral content (BMC) in the lumbar spine (n = 3181) and the hip (n = 1795)⁶⁴. In the British MRC

NSHD study (n = 1658, aged 60-64 years), higher BW increased the diaphyseal cross-sectional area of the radius. Furthermore, a faster increase in height and pre- and post-pubertal weight was associated with a broader cross-sectional area and bone strength in early old age⁶⁵. In the MrO Cohort (n = 1831 men, > 65 years), those with BW ≥ 4 kg had more length and broader cross-sectional area of the femoral neck compared to those with BW between 3.1 and 4 kg⁶⁶. Between 498 men and 468 women of the Hertfordshire Cohort, BW was positively associated with BMC in the proximal femur and lumbar spine; in men, there was a weak correlation with bone mineral density (BMD) in the proximal femur. Weight at 1 year of age was related to BMC in the proximal femur in men and women. The variability of the proximal femur bone area was explained by BW, weight at 1 year, and adult weight by 2.8, 6.8, and 3.9%, respectively, in men; and 6.7, 4.2, and 3.9%, respectively, in women⁶⁷. In the Newcastle TFS (n = 389, 49-51 years of age), fetal life (position in the family, BW, and social class at birth) showed 6% of the variation of BMD in men, but < 1% in women. Adult weight explained 10% of the variability of BMD in men and 6% in women. Almost half of the variability of the bone area in men was explained by early life; however, most of this variation was explained by adult height and weight. For men, the BW was related to total hip and lumbar spine bone area, when adjusted for weight and height; in women, this relationship occurred without adjustment⁶⁸.

INFECTIONS

In the Newcastle TFS (n = 407), the duration of exclusive BF was associated with lower seropositivity for *Helicobacter pylori* in 50-year-old men⁶⁹.

NEOPLASIA

In the E3N Cohort (15,983 women followed to age 58.7 years), BW > 3.5 kg presented a 22% greater risk of colon adenoma; in contrast, the self-perception of a "large" body shape at 8 years of age was associated with 32% less risk of rectal adenoma⁷⁰.

HEALTHY DIET CONSUMPTION

In the Hertfordshire Cohort (n = 3217, 59-73 years old), BF was associated with higher prudent (healthier) diet scores, after adjusting for sex and infant weight gain⁷¹.

Conclusions

In literature, several environmental exposures in early stages of life, from intrauterine to adolescence, have consistently shown to have significant, although discrete, effects on human health in adulthood and old age. We found evidence of combined effects of intrauterine growth indicators such as LBW, height, and HC, and indicators of growth from the first 2 years up to 7 years of age, on different adult health problems such as mortality from various causes. These early influences are modulated by factors such as BF, socioeconomic status, and parental education and are reflected in the incidence of chronic-degenerative pathologies. These influences are also reflected in functional variables during adulthood, such as muscle strength and physical, psychomotor, and cognitive performance. On the other hand, additional studies have shown evidence of BW and BF protective effects against the risk of T2DM and insulin resistance.

As strengths supporting the effects of early influences on adult outcomes are the cohorts design and the systematic review with meta-analysis of the selected publications. However, as limitations, some of the exposures were measured retrospectively and the outcomes, cross-sectionally. Furthermore, the possibility of publication bias is inherent to this type of analysis. Although most of the associations have discrete magnitude effects, they have been consistent and have resisted adjustment to adult factors such as sex, BW, smoking, and physical activity, among others. As Huxley et al. refer⁵³, the potential for growth and intrauterine growth, as well as non-genetic factors that act throughout life (such as intrauterine growth restriction and subsequent weight gain), could mediate the effects of birth size on adult heart disease.

It has been stated that the early environmental influences act through epigenetic mechanisms, especially DNA methylation. DNA experimental modifications were linked to diet, environment, lifestyle, and other phenomena through lifetime⁸. These “epigenetic modifications” can aide in reacting to some environmental changes by regulating genic expression and DNA integrity. The initial establishment of these processes takes place in the early stages of development and differentiation⁷². These early changes have been documented in monozygotic twins, where their epigenetic profiles accumulate changes in an age-related fashion causing diverging patterns, presumably when the twins did not share the same environment⁷³. Such results indicate that aging-related DNA methylation changes are caused in part by environmental factors.

Thus, DNA-methylation levels have been used to estimate an “epigenetic age,” which correlates with the biological age^{13,14}. In this context, frailty studies have indicated that methylation patterns differ between frail and not frail individuals^{74,75}.

Finally, except for the study conducted in a Brazilian population³⁴, almost all the reviewed studies were carried out in industrialized countries, whose populations, at the time of their development, were exposed to environmental and social conditions different from those observed in developing countries at the same historical moment. The lack of historical records explains the lack of information on the developmental origin of adult diseases in populations living in impoverished environments or war exposed countries. The overwhelming evidence that links indicators of intrauterine and early postnatal development and feeding practices to adult diseases is sustained on the available information consigned in the health records from several decades ago.

The role of the early life exposures in poor and developing countries should be confirmed in populations of different ethnic, environmental, and socioeconomic backgrounds. However, given the shared evolutionary and molecular basis of these effects in our species, it is likely that the most consistent results would be replicated. While this happens, it is also possible to investigate the practical implications for cost-effective health care from early stages in life.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient identifying information appears in this article.

Conflicts of interest

The authors declare no conflicts of interest.

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