Establishing a Palestinian Refugee Birth Cohort Using Electronic Health Records to Investigate the Effects of Size at Birth on Child Wellbeing

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Declaration

I, Zeina Bassel Jamaluddine, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Date:09/06/2024

Palestinian refugees living in Lebanon, Shatila Refugee camp

Each box in grey represents 25,000 refugees. The coloured boxes represent the countries where Palestinian refugees are hosted.

 Each box 25,000 refugees

In 2023, Palestinian refugees resided in:

	Jordan	2.3 million
	Lebanon	0.5 million
	Syria	0.6 million
	West Bank	0.9 million
	Gaza	1.5 million

For my grandfather Mohammad Hasan Saadi and the countless other refugees documented in electronic records. You are not forgotten; every vaccine administered, every growth record logged, every school attendance record, serves as a trace of our existence and resistance.

UNRWA REGISTRATION CARD — بطاقة تسجيل - وكالة الغوث الدولية

الرقم الرمزي REGISTRATION No.	الرمز السابق EX-CODE	المنطقة AREA	مركز السكن RESIDENTIAL CENTRE	تاريخ الاصدار DATE OF ISSUE
[redacted]	[redacted]	BEIRUT	MUSEITBE I	04/94

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01	MOHD HASAN	M	MHF	0031	00	0494							
02	HIBA	F	MDA	0660	01	0494							
03	RULA	F	MDA	0661	01	0494							
04	MUNA	F	BDA	0663	01	0494							
05	LINA	F	MDA	1168	01	0494							
06	MUST	M	BSO	1074	01	0494							

Abstract

Background

Size-at-birth is a crucial early endowment with long-term human-capital consequences affecting health, growth, developmental, and educational outcomes. Despite extensive research, knowledge gaps persist in this field, motivating me to investigate the literature and to harness the potential of large-scale electronic health record data to address crucial questions relevant to Palestinian refugees, the Arab World, and global discourse.

The objectives are to:

1. Conduct an umbrella review to assess the effect of various size-at-birth measures on mortality and child health, growth, and developmental outcomes, identifying associations and gaps in evidence.

2. Use data from United Nations Relief and Works Agency for Palestine Refugees in the Near East (UNRWA) to establish a birth cohort of Palestinian refugees born between 2010-2020 by linking obstetric records with child health and education records.

3. Expand the size-at-birth classification (distinguishing between gestational age (preterm, term, post-term) and size-for-gestational age (small, appropriate, and large for gestational age) to investigate the associations between being post-term, and outcomes of small-for-gestational age and infant mortality.

4. Evaluate the effects of birth size and rapid weight gain in the first year of life on childhood overweight/obesity among children aged 24 to 59 months.

Methods

In the umbrella review, I systematically searched four databases to extract systematic reviews and meta-analyses. To build the electronic record dataset, I employed deterministic linkage techniques and used decision-tree analysis to investigate linkage failures. To examine associations, I applied both logistic regression and multilevel logistic regression. Additionally, I employed structural equation models to investigate the mediating role of rapid weight gain.

Findings

The umbrella review identified 154 meta-analyses, underscored significant disparities in exposure definitions, and emphasized the importance of distinguishing gestational age from size-for-gestational age. In the review, I observed inconsistent associations between birth size and childhood overweight/obesity.

I established a birth cohort of Palestinian refugees (n=972,743) since 2010, drawing on UNRWA data across five settings. High linkage rates were achieved. Children who died (adjusted aOR=47.0, 95% CI (44.8-49.3)) or were born to non-refugee mothers (aOR=2.7, 95% CI (2.6-2.8), were least likely to link.

The study introduced a newborn-phenotype classification with nine groupings, highlighting a three times increased risk of being small for gestational age (SGA) (aRR=3.0, 95% CI: 3.0-3.1) among post-term as compared to term, and a doubling in the risk of infant mortality (aRR=2.1, 95%CI 1.7-2.6) among post-term SGA neonates compared to appropriate for gestational age (AGA) term.

Analysis of size at birth found large for gestational age (LGA) newborns had nearly three times the odds of childhood overweight/obesity at 24-59 months (aOR=2.8, 95%CI (2.6-3.1)) compared to those of AGA, but no such association was observed for SGA or preterm births. Importantly, rapid weight gain during the first year of life was identified as a mediating factor in the relationship between birth size and childhood overweight/obesity. Exclusive breastfeeding is associated with a reduced odds of rapid weight gain.

Discussion

Overall, this research a) shows the advantages of leveraging large electronic health record datasets to provide insights into rare exposure or outcomes, b) highlights the importance of separating gestational age and size-for-gestational age, and c) emphasizes the importance of longitudinal assessment of child weight in determining the risk of overweight/obesity. This study underscores the need for targeted interventions during early postnatal phases to mitigate the risks associated with variability in size-at-birth, particularly post-term birth, and rapid weight gain.

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I dedicate this work to my grandfathers, Jedo Ahmad, who was the first to believe in me, and Jedo Mohammad Hassan El Saadi, who is the inspiration of any research I do and to the Palestinian people: your spirit and perseverance inspire me every day. شكرًا

Table of contents

Abbreviations

ACLED	Armed Conflict Location & Event Data
ADHD	Attention Deficit Hyperactivity Disorder
AGA	Appropriate for Gestational Age
ANC	Antenatal Care
aRR	Adjusted Relative Risk
aOR	Adjusted Odds Ratio
BMI	Body Mass Index
BW	Birthweight
C RRIS	Child Refugee Registration ID
CART	Classification and Regression Decision Tree
CI	Confidence interval
CMFN	Child Medical File Number
DHS	Demographic and Health Surveys
DOB	Date of Birth
e-health	Electronic Health
ELBW	Extremely Low Birthweight
EMIS	Education Management Information System
EPT	Extremely Preterm
F RRIS	Family Refugee Registration ID
FGR	Foetal Growth Restriction
GA	Gestational Age
GWG	Gestational Weight Gain
HAZ	Height-for-Age Z-score
HBW	High Birthweight
HIC	High-Income Countries
HR	Hazard Ratio
ID	Identification Number
IMR	Infant Mortality Rate
INTERGROWTH-21	International Fetal and Newborn Growth Consortium for the 21st Century
IOM	Institute of Medicine

IUGR	Intrauterine Growth Restriction
LBW	Low Birthweight
LGA	Large for Gestational Age
LMIC	Low- and Middle-Income Countries
LMP	Last Menstrual Period
M RRIS	Mother Refugee Registration ID
MD	Mean Difference
MEXT	Ministry of Education, Culture, Sports, Science and Technology
MICS	Multiple Indicator Cluster Surveys
MMFN	Mother Medical File Number
MRSA	Methicillin-Resistant Staphylococcus Aureus
NBW	Normal Birthweight
OR	Odds Ratio
PT	Preterm
Ref	Reference
RR	Relative Risk
RRIS	Refugee Registration ID
SGA	Small for Gestational Age
T	Term
UCDP	Uppsala Conflict Data Program
UNICEF	United Nations International Children's Emergency Fund
UNRWA	United Nations Relief Works Agency for Palestine Refugees in the Near East
VLBW	Very Low Birthweight
VPT	Very Preterm
WAZ	Weight-for-Age Z-score
WHO	World Health Organization
WHZ	Weight-for-Height Z-score

 Chapter 1- Size at birth as a human capital endowment for Palestinian refugees

In the first part of this Chapter, I define the key concepts, measures and indicators that underlie the conceptual framework of my thesis. I define size at birth and gestational age, and outline what is already known about the effects of size at birth on child mortality and wellbeing outcomes. I then highlight the potential of electronic health records to generate population-based cohorts for studying these associations, and finally, focus on the population of interest, namely Palestinian refugees.

In this Chapter, I briefly introduce the background of the thesis, I then outline the aims and objectives of this research and present the overall thesis structure.

1.1. Size at birth as a critical early human capital endowment

Size at birth is a crucial early endowment in human capital development with deviations or extremes in size at birth is shown to be major predictors of early mortality and excess morbidity across the life course (1, 2). The World Bank defines human capital as the accumulation of knowledge, skills, and health that enables individuals to realize their potential as productive members of society (3, 4).

Extensive research has shown that in utero conditions, manifested through small size at birth, have long-lasting effects on an individual's life. Low birthweight is associated with increased risks of disabilities, heart diseases, diabetes, poorer educational outcomes, and lower adult earnings (1, 2). This is particularly critical in developing countries, where the combination of small size at birth, under-resourced health and education systems, and adverse environmental exposures can result in long-term losses of human capital, including lower levels of health and educational attainment and poorer economic productivity (1, 2). Recognizing the significance of birthweight as a critical initial endowment, UN agencies including WHO, UNICEF, and the World Bank have set an ambitious target to reduce the incidence of low birthweight by 30% by 2025, although achieving this goal within the next year seems unlikely (5).

1.1.1. Birthweight

The most used measure of size at birth is birthweight. **Birthweight** is the first weight of an infant, measured within an hour of birth. **Low birthweight (LBW)** is defined as a birthweight under 2500 grams, irrespective of gestational age (6), with further sub-categories of **very low birthweight (VLBW**) (1000-1499 grams) and **extremely low birthweight (ELBW**) (500-999 grams). It is argued that a binary cut-off of 2500 grams is arbitrary and does not recognize that developmental and health risks associated with LBW vary by sex, length, head circumference, and gestational age (7). For example, a LBW infant of 2000 grams born at 40 weeks of gestation may have a different etiologic explanation and clinical outcomes than one of 2000 grams born at 33 weeks. LBW results from two primary pathways: 1) **foetal growth restriction (FGR)** (also known as **intrauterine growth restriction (IUGR)**; **or** 2) preterm**.**

1.1.2. Gestational age

Term birth is defined as birth between 37+0 and 42+0 weeks of gestation, while **preterm** refers to birth before 37 weeks (between 22+0 weeks and 36+6 weeks) and **post-term** to birth after 42+0 weeks. Babies born at term have lower risks of complications compared to those born pre-or post-term. Preterm birth is associated with various complications and health challenges for the newborn, including respiratory distress syndrome, developmental delays, and increased risk of mortality (8, 9). On the other hand, post-term infants may face increased risks of complications such as macrosomia, meconium aspiration syndrome, and stillbirth (10).

1.1.3. Birthweight and gestational age phenotypes

Small for gestational age (SGA) is defined as birthweight under the tenth percentile for gestational age and sex, based on standardized foetal growth curves (11-13). Historically, gestational age was not collected reliably in many settings, so few studies had previously examined the long-term health effects of SGA. In a recent series on small vulnerable newborns, data on LBW was available for 158 of 195 WHO member states (81%); in contrast preterm birth data was only available for 113 (58%), while SGA was only generated for 8 countries (14).

FGR/IUGR occurs when the foetus cannot grow at the expected rate due to a variety of factors including (a) social, economic and demographic, (b) maternal health, (c) behavioural, and (d) structural and environmental factors (15). Social, economic and demographic risk factors encompass poverty, lower maternal educational attainment, and extremes of maternal reproductive age (15). Maternal health risk factors involve pre-existing medical conditions (e.g., chronic hypertension, renal disease, diabetes, obesity/undernutrition...), obstetric history (e.g., previous miscarriage, birth interval, parity, previous caesarean section...), and medical conditions arising during pregnancy (such as gestational hypertension, gestational diabetes, multiple pregnancy (e.g., twins, triplets), anaemia, bleeding, infections) (15). Behavioural factors include lifestyle choices such as smoking, alcohol, caffeine, or drug consumption (15). Structural and

environmental risk factors include for example inadequate or poor-quality antenatal care, exposure to toxic substances (e.g., pesticides), and living in poor neighbourhoods (16).

In this thesis I refer to **small size at birth** as including per in Figure 1 the following newborn phenotypes LBW or SGA among preterm or post-term (AGA-PT- LBW, AGA-PT-NBW, SGA-PT-LBW, SGA-T-NBW, SGA-Post-NBW).

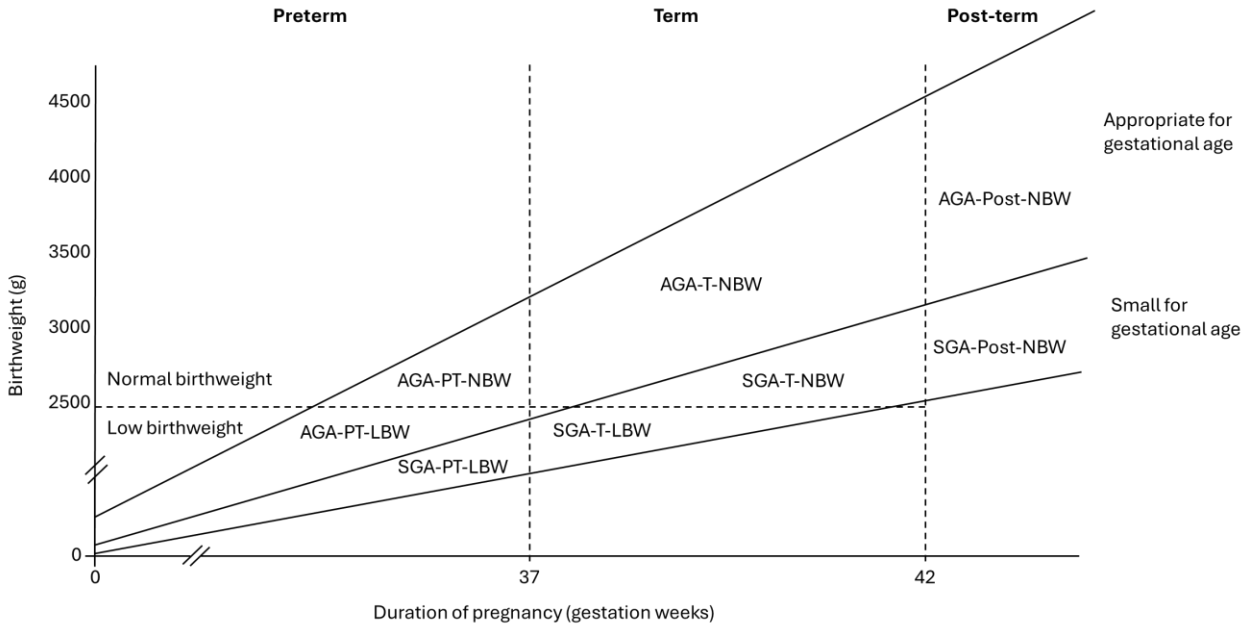

Figure 1- Newborn phenotypes (figure adapted from (17)) (Appropriate for Gestational Age (AGA), Small for Gestational Age (SGA), Preterm (PT), Term (T) Low Birthweight (LBW), Normal Birthweight (NBW)

High birthweight (HBW) or macrosomia is often used interchangeably with **large for gestational age (LGA)**. However, there is distinction between these two terms. HBW specifically refers to infants with a birthweight above a certain threshold, usually set at 4000 grams. Infants classified as HBW may have increased risks of birth complications, including shoulder dystocia and birth injuries, as well as potentially long-term health issues such as obesity and metabolic syndrome (18). On the other hand, LGA refers to infants who are above the ninetieth percentile for weight at a given gestational age (19). LGA encompasses a broader range of birthweights while HBW specifically highlights infants at the highest end of the birthweight spectrum. In comparison to the extensive research on LBW and its associated risks, very limited research has focused on the long-

term implications of **large size at birth**. In recent studies examining birth size, infants classified as LGA or HBW were excluded from the analyses (8).

1.2. Effects of size at birth on child mortality and wellbeing outcomes

Size at birth has implications on both survival and the ability of children to thrive in the long-term. While the focus has traditionally been on the increased mortality risks associated with small size at birth, emerging evidence indicates that deviations from optimal birthweight at either extreme can have lasting impacts on a child's health, development, and overall wellbeing throughout the life course (2, 20).

1.2.1. Mortality

LBW, SGA and preterm birth are well-documented to be associated with increased risks of **infant mortality**. A recent global study (covering 15 countries and 125.5 million live births) quantified the association between small size at birth and risk of neonatal mortality (8, 14). The analysis of six newborn types found that preterm and SGA (preterm-SGA) infants face the highest neonatal mortality risk, with a median rate of 32.0 deaths per 1,000 live births. This group's neonatal mortality relative risk was approximately 70-folds higher compared to term and appropriate for gestational age (term- AGA) infants, underscoring their significant vulnerability. (8, 14). While preterm-SGA had the highest risk, at the population level, preterm and AGA (preterm- AGA) newborns contributed the most to overall neonatal mortality, with a median population attributable risk percentage of 53.7% (8, 14). This study excluded post-term from the analysis of the size at birth phenotype.

1.2.2. Growth and longer-term outcomes

Between 2014 and 2035, nearly 100 million children will not achieve their full development potential (in terms of disability, neurodevelopmental impairment, and stunting outcomes) either because of preterm birth or SGA (21). Children born preterm or SGA are more likely to subsequently have poor nutritional status, poor physical growth, more recurrent infections and more hospitalizations compared to normal birthweight children (2, 22). Small size at birth and consequent undernutrition also affect

neurocognitive development, thus affecting intellectual abilities and educational outcomes (2, 23). Early interventions to prevent or target small-size at birth children can theoretically yield a very high return on investment by supporting children to achieve their fullest human capital potential – in terms of both health and educational endowment (3, 24). Maternal undernutrition and IUGR can perpetuate an **intergenerational cycle** of growth failure, as growth-restricted infants are more likely to become stunted children and subsequently undernourished mothers, perpetuating the cycle to their offspring (20, 24).

A large body of evidence highlights the association between impaired foetal growth (FGR/IUGR) and an elevated risk of chronic health conditions extending into adulthood (2, 25-31). This connection has been illuminated by historical studies, such as those on individuals born during the Dutch Hunger Winter and the siege of Leningrad (29, 32-34). These individuals demonstrated LBW and a higher propensity for non-communicable diseases like type 2 diabetes and cardiovascular disorders in adulthood, laying the foundation for what is now known as the developmental origins of health and disease (35, 36).

The developmental origins of health and disease framework stems from observations that early-life adversity—particularly nutritional deprivation/or stress in utero (measured using a proxy of LBW)—can predispose individuals to health challenges later in life. Research on populations exposed to famine during critical developmental windows revealed that nutritional deficits lead to adaptive changes in foetal physiology and metabolism (29, 32-34). While these adaptations may enhance short-term survival, they often prove maladaptive in environments of nutritional abundance, contributing to an increased risk of metabolic diseases in adulthood.

Thrifty phenotype hypothesis

Proposed by Hales and Barker in 1992 (37), the thrifty phenotype hypothesis provides a foundational explanation for the link between FGR and later metabolic disorders. This hypothesis posits that poor foetal and infant growth, thought to be driven by adverse maternal nutrition or stress, induces permanent changes in glucose-insulin metabolism

(37). These changes, including reduced insulin sensitivity and production, enhance energy conservation. Building on the thrifty phenotype hypothesis, the foetal salvage model emphasizes nutrient redistribution as a survival strategy (38). In response to limited maternal nutrition, the foetus prioritizes the development of vital organs, particularly the brain, at the expense of others such as skeletal muscle and liver life (38). This adaptive mechanism is associated with peripheral insulin resistance, reduced skeletal muscle glucose transporter function, and increased insulin production. While beneficial for foetal survival, these adaptations can lead to pancreatic β-cell exhaustion and impaired glucose metabolism later in life (38, 39). Some other studies note that epigenetic changes, including DNA methylation and histone modification, mediate the effects of early-life adversity (FGR/IUGR) by altering gene expression patterns, particularly those involved in glucose, lipid, and insulin metabolism, also leading to an increased risk of metabolic disorders (40).

Rapid catch-up growth hypothesis

The rapid catch-up growth hypothesis focuses on the compensatory growth observed in SGA infants (41, 42). These infants often exhibit accelerated postnatal weight gain, driven by hormonal changes such as increased levels of insulin-like growth factor-1(43, 44). While this rapid growth helps normalize weight and height, it is associated with long-term health risks, including obesity, insulin resistance, and cardiovascular diseases in adulthood (41). Mechanisms like lipoprotein lipase mediated lipolysis of very-low-density lipoprotein and triglyceride and postnatal fat accumulation further underscore the complexity of this adaptive response (42, 45). Rapid weight gain can lead to increased fat deposition, insulin resistance, and elevated blood lipid levels in adulthood. In addition, accelerated growth trajectories in infancy are predictive of higher body mass index (BMI) of children (28). Some overweight children/adolescents are more likely to become overweight or obese adults (46), increasing their risk of type 2 diabetes, metabolic syndrome, non-alcoholic fatty liver disease, higher blood pressure, abnormal lipid profiles, and increased risk of heart disease later in life. Obesity-related health issues can lead to more frequent school absences, negatively affecting school performance (47), and mixed evidence of association with lower self-esteem and increased risk of depression and anxiety disorders (48).

The timing of catch-up growth plays a critical role in determining long-term outcomes. Rapid growth occurring in infancy may have different implications compared to similar growth patterns later in childhood (41, 49, 50). Studies suggest that early catch-up growth is often associated with better cognitive outcomes but higher metabolic risk. Delayed or slower growth trajectories may reduce long-term metabolic risks but could impact physical development (49, 50). Further research is needed to elucidate the precise mechanisms linking rapid growth to overweight and obesity and metabolic risks in childhood or adulthood.

There is also an extensive body of literature examining the effects of birth size on subsequent mortality and child wellbeing outcomes. Given the multitude of effects, it is important to synthesize this literature to highlight research gaps and identify areas requiring further investigation. This comprehensive understanding aligns with the global health community's evolving focus, which has shifted from a narrow emphasis on child survival to a broader agenda encompassing "survive, thrive, and transform" (51).

1.3. Electronic records of Palestinian refugees

1.3.1. Electronic health records and cohort studies

Electronic health records offer an opportunity to establish birth cohorts that can track obstetric outcomes and long-term child health and development. Notable examples include the UK birth cohorts (52) and the 100 million Brazilian birth cohort studies (53, 54), which have used electronic health records and linked records of obstetric and child outcomes to investigate the relationships between prenatal and perinatal factors, birth outcomes, and subsequent mortality and child health, growth, and development.

In low- and middle-income countries (LMICs), where resources for large-scale cohort studies are limited, the use of individual electronic health records presents a promising path for conducting research. Electronic health records can facilitate the collection and integration of data from various healthcare facilities, enabling the creation of large, diverse cohorts that can provide insights into the unique challenges and risk factors faced by populations in these regions. Additionally, electronic health records can help

overcome barriers related to data fragmentation and loss to follow-up, which are common challenges in traditional cohort studies.

1.3.2. Population of interest: Palestinian refugees

The world is witnessing the highest levels of population displacement on record. In 2022, there were 35.3 million refugees worldwide, 75% of whom had been displaced for more than five years (55). Palestinian refugees represent 17% of the global refugee population.

The نكبة (Nakba), meaning "catastrophe", refers to the forced displacement and dispossession of hundreds of thousands of Palestinians during and after the 1948 establishment of the State of Israel (56). This event marked the beginning of a protracted refugee crisis that has spanned over seven decades, with generations of Palestinians denied their fundamental right of return to their ancestral homes and lands.

Since its establishment in 1949 by the United Nations General Assembly, **UNRWA** (the United Nations Relief and Works Agency for Palestine Refugees in the Near East) has played a vital role for generations of Palestinian refugee children and their families. Its mandate is to provide humanitarian assistance to Palestinian refugees pending a just and durable solution to their plight, which remains elusive due to the ongoing Israeli occupation and lack of political will to address the legitimate rights of Palestinians (57). Today, UNRWA provides essential services (health, education, and assistance) to around 5.9 million Palestinian refugees, living in 62 camps and many informal gathering points in Jordan, Lebanon, Syria, the West Bank and the Gaza Strip (Figure 2) (58).

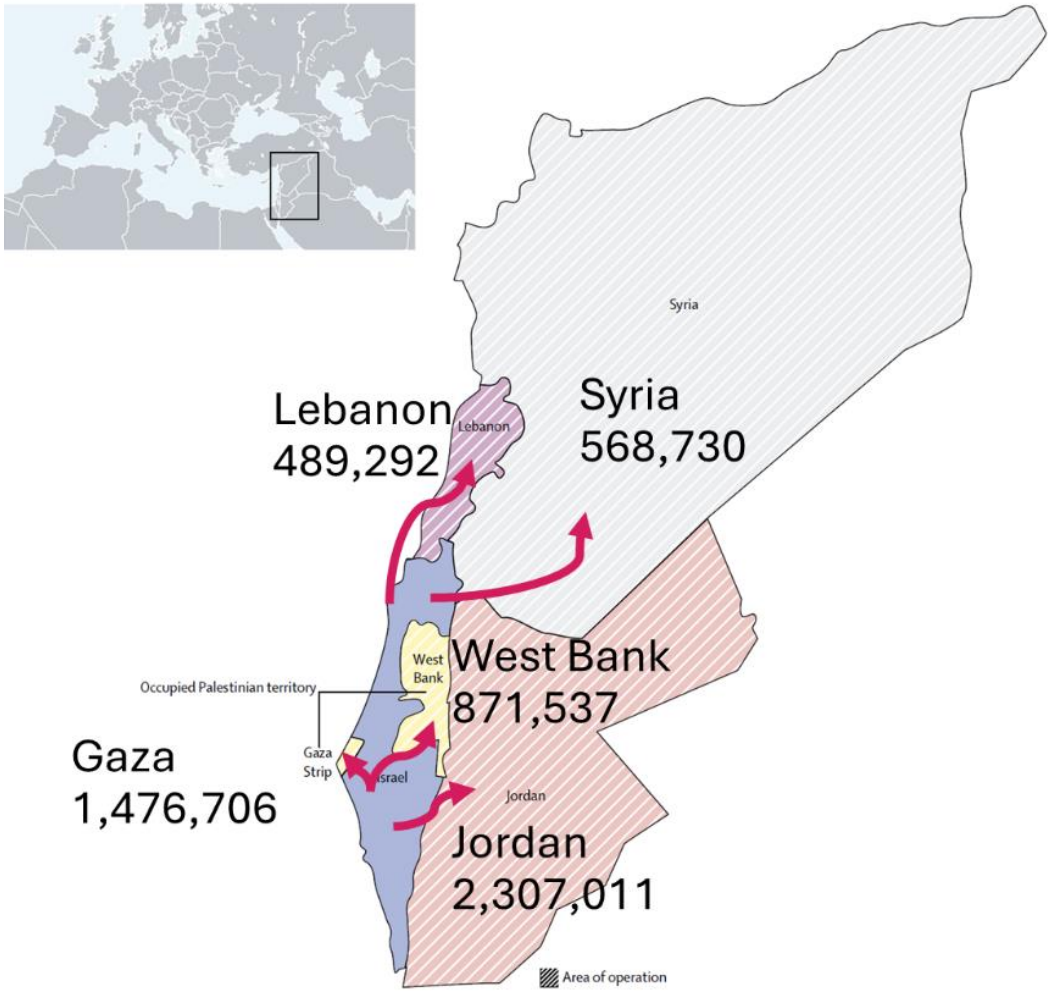

Figure 2- Palestinian refugees in five settings in 2023 (adapted from (58)) (shaded area of operation of UNRWA).

Despite their long-standing presence in neighbouring Arab countries to which they fled, Palestinian refugees continue to face significant marginalization and a denial of basic rights. The context of Palestinian refugee populations is complex and varies significantly across different host countries, presenting unique features compared to other urban low/middle-income populations. Most Palestinian refugees do not live in tents or in temporary structures; rather the majority of reside in urban settings, often in densely populated former “camps” that have evolved into permanent neighbourhoods with concrete structures. These areas frequently face challenges such as overcrowding, poor infrastructure, and inadequate housing quality.

In Jordan, Palestinians were granted citizenship and access to certain rights and services, but they still grapple with social and economic disparities (59, 60). As of 2024, poverty rates in Jordan's refugee camps have sharply increased, with 67% of registered refugees now classified as poor, compared to 45% in 2021 (61).

In Lebanon, the situation is even more dire: Palestinian refugees have endured systemic marginalization, including restrictions on employment, education, and property ownership, exacerbating their vulnerability and perpetuating cycles of poverty (62). As of 2024, poverty rates among Palestine Refugees in Lebanon have reached around 80% (63). The ongoing economic crisis in Lebanon has exacerbated their situation, with at least 168,000 Palestine Refugees relying on emergency cash assistance for basic needs.

The Syrian war has further compounded the difficulties experienced by Palestinian refugees in Syria, with many fleeing the violence and seeking refuge in Lebanon and Jordan (64, 65). About 438,000 Palestine Refugees remain in Syria, with 40% displaced and more than 90% living below the poverty line (63).

In the West Bank and Gaza, there are Palestinian refugees who were forcibly displaced from other areas during the 1948 and 1967 wars, as well as non-refugee Palestinians who have lived in these territories for generations. The latter are not eligible for UNRWA services. In the West Bank, the system of checkpoints, roadblocks, and the separation barrier erected by Israel has severely hindered the freedom of movement for all Palestinians, restricting their access to essential services, employment, and education (66, 67). The Gaza Strip, has endured multiple Israeli military operations and offensives, resulting in significant civilian casualties, widespread destruction of homes and infrastructure, and mass displacement. The 2008-2009, 2012, 2014, and 2021 Gaza wars, as well as the current ongoing war since October 2023, have exacerbated the already dire humanitarian situation in the besieged Gaza Strip, where residents have endured a crippling blockade imposed by Israel, leading to severe shortages of essential goods, medical supplies.

Across all these settings, Palestinian refugees face psychological stressors that likely contribute to variability in birth outcomes. These include chronic exposure to different

levels of conflict and violence, displacement, restricted freedom of movement, limited access to essential services, economic hardship and unemployment, overcrowded living conditions and uncertainty about legal status and prospects. The cumulative impact of these stressors on maternal health and foetal development is likely to be significant. Studies have shown that maternal stress during pregnancy can lead to increased cortisol levels, which may affect foetal growth and development, potentially resulting in lower birth weight and increased risk of preterm birth (68, 69).

There is also variability across setting in terms of access and utilization of maternal health care. For example of pregnant Palestinian refugee women registered with UNRWA take up antenatal services within the UNRWA health system to varying extents: 35% in Jordan, 54% in West Bank, 73% in Gaza, 42% in Syria; 63% in Lebanon (70). This mainly depends on the availability and eligibility for other services in each setting (detailed further in Chapter 3).

UNRWA provides essential services across 144 health centres and 708 schools, maintaining electronic administrative databases to facilitate the delivery of health, education, and social services (71). Despite operating amidst complex conflicts and resource constraints, UNRWA has consistently invested in its health records and electronic data infrastructure since 2010 (Figure 3 shows a screenshot of e-health records), recognizing the importance of accurate and accessible data for addressing the needs of this vulnerable population.

UNRWA's e-health system provides comprehensive, electronic health records which consolidate each refugee's medical history, test results, and treatment plans in one place. This enables healthcare providers to quickly access critical information, ensuring better continuity of care and informed decision-making. According to UNRWA, the e-health system has streamlined operations and reduced physicians' daily consultations (72). The system promotes consistent, high-quality care through built-in clinical guidelines and standardized disease classifications (including the ICD 11 classification for outpatient care). Notably, the system empowers refugees to access their personal health records in real-time through smartphone applications. UNRWA also leverages the e-health system to disseminate health awareness and education materials more

effectively, improving health literacy and promoting preventive care. Moreover, the system's web-based architecture allows UNRWA to provide consistent healthcare services to this highly mobile population, even when they are displaced or move between settings.

The electronic health records of UNRWA provides an opportunity to study the effects of size at birth on longer term growth outcomes in a largely understudied population.

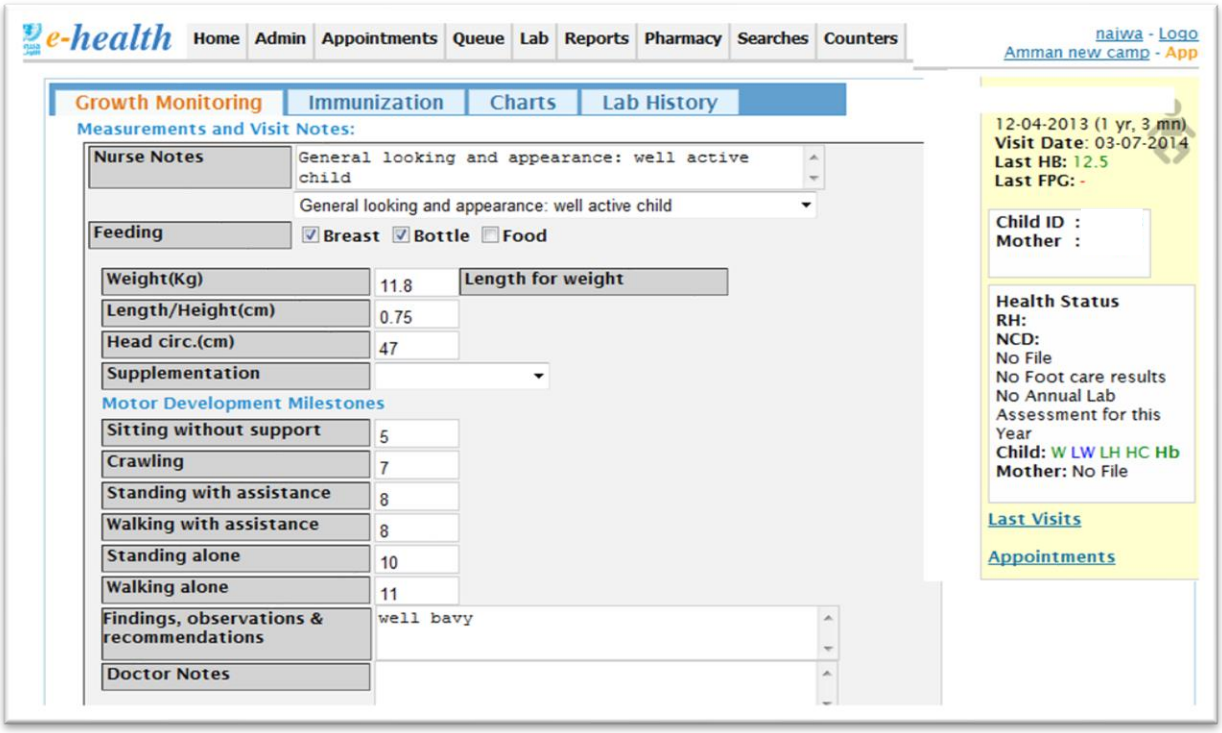

Figure 3- Screenshot example of UNRWA e-health system (example of dummy data).

1.4. Summary

The literature on the **long-term effects of size at birth** has received considerable attention, yet evidence **gaps** persist, both in terms of the populations studied and specific sub-topics.

Some research gaps and potential research opportunities include that there is:

- Limited research **distinguishing between SGA and LBW and preterm infants** when examining the effects of small size at birth.
- A scarcity of research that **simultaneously focuses on LGA and SGA infants.** Instead of examining nine phenotypes of size at birth the literature tends to mostly look at six phenotypes (combination of preterm/term SGA/AGA excluding post-term and LGA)
- While there is a large body of literature on the effect of size at birth on child outcomes, there is a need to **review the evidence and identify gaps in evidence across different outcome domains**.
- Despite the global community's shift in focus from child survival to the "survive, thrive, and transform" agenda, relatively little is known in **refugee settings** about children's outcomes, particularly **beyond the first months of life.**
- A lack of existing cohorts in the Arab region, with **potential of using electronic health records to establish a Palestinian refugee birth cohort.**

1.5. Aim and objectives

The aim of this thesis is to investigate the effects of size at birth on infant mortality and child wellbeing outcomes by using electronic health records to establish a Palestinian refugee birth cohort. In this thesis, I use existing data to establish a historic cohort of Palestinian refugee children living in protracted refugee situations in five settings and examine the effects of gestational age on size at birth and on the effects of gestational age and size at birth on multiple subsequent outcomes, in terms of mortality and overweight/obesity.

1.5.1. Objectives

The objectives are to:

1) Conduct an umbrella review to assess the effect of various size-at-birth measures on child mortality, health, growth, and developmental outcomes, identifying associations and gaps in evidence.
2) Establish a birth cohort of Palestinian refugees born between 2010-2020 by linking obstetric records with child health and education records.
3) Expand the size-at-birth classification into nine phenotypes (distinguishing between gestational age (preterm, term, post-term) and size-for-gestational age (small, appropriate, and large for gestational age) to investigate the associations between post-term and small-for-gestational age and infant mortality.
4) Evaluate the effects of birth size and rapid weight gain in the first year on childhood overweight/obesity among children aged 24 to 59 months.

These were investigated via (a) an umbrella review to determine of the state of knowledge and scope the literature on size at birth and effects on mortality and child wellbeing (Chapter 2), (b) developing methods and assembling a large, linked dataset to answer the some key questions (Chapter 3), (c) analysing phenotypes at birth (the main outcome and exposure of interest in the thesis) and consequences of post-term on SGA and mortality (Chapter 4); (d) an assessment of the effects of size at birth and rapid growth in the first year of life on childhood overweight/obesity (Chapter 5).

1.6. Thesis structure

Chapter 1- Size at birth as a human capital endowment for Palestinian refugees

This chapter is an overview of the study, including its aim and objectives. I delve into the significance of birth term and size at birth as crucial factors in shaping human capital. Additionally, I explore the potential of utilizing electronic health records for research purposes and provide some minimal context on UNRWA and Palestinian refugees.

Chapter 2- Survive and thrive: the effect of size at birth on children's mortality and sixty-six additional subthemes of health, growth, and development

Here, I conduct an umbrella review of the existing literature to comprehensively examine the effects of size at birth on various aspects of child outcomes. The focus is on summarizing the evidence and identifying gaps in the literature in the association between size at birth and mortality and 66 subthemes related with health, growth, and development outcomes.

Chapter 3- Establishment of a birth-to-education cohort of 1 million Palestinian refugees using electronic medical records and electronic education records

This Chapter outlines the process of establishing a cohort of Palestinian refugees using electronic health records. I detail the structure of the data and methods of linking obstetric records (including exposure of interest size at birth) with child health and education records.

Chapter 4- Post-term births as a risk factor for small-for-gestational-age and infant mortality, using 45.7 million electronic birth records from Brazil, Mexico, and Palestinian refugees

Based on the results emerging from the umbrella review on gaps and appropriate comparators, in this Chapter, I analyse the exposure of interest, size at birth, using nine different phenotypes. I then explore the associations between these phenotypes and small size at gestational age and infant mortality, paying careful attention to use term AGA as the comparator. This paper also includes data from Mexico and Brazil, which are not the focus of this thesis, but which are in similar stages of the epidemiologic and nutrition transitions as the settings hosting Palestinian refugees.

Chapter 5- Examining size at birth and rapid weight gain in first year of life as a risk factor in childhood overweight/obesity

Based on a gap in the evidence identified in the umbrella review and my previous interests, I investigate the association between size at birth and rapid weight gain in the first year of life and the risk of childhood overweight/obesity among Palestinian refugees.

Chapter 6- Discussion of themes covered in the project related to measurement, electronic health records and childhood overweight/obesity

Finally, in this Chapter, I discuss key themes emerging from this thesis, highlighting strengths and limitations. I also consider the implications of our findings for implementation. Additionally, I outline some future research directions in this area.

Chapter 2- Survive and thrive: the effect of size at birth on children's mortality and sixty-six additional subthemes of health, growth, and development

To understand the large literature related to the association between size at birth and various aspects of child mortality, health, growth, and development outcomes, I first conducted an umbrella review. The umbrella review allowed me to synthesise evidence from several systematic reviews and meta-analyses, and to identify gaps in research and areas needing further investigation. Additional supplementary material from the umbrella review is included in the Thesis Appendix 1.

RESEARCH PAPER COVER SHEET

SECTION A – Student Details

Student ID Number	2004086	**Title**	Ms
First Name(s)	Zeina		
Surname/Family Name	Jamaluddine		
Thesis Title	Establishing a Palestinian Refugee Birth Cohort Using Electronic Health Records to Investigate the Effects of Size at Birth on Child Wellbeing		
Primary Supervisor	Oona Campbell		

SECTION B – Paper already published.

Where was the work published?	Archives of Disease in Childhood		
When was the work published?	20/06/2023		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	Not applicable		
Have you retained the copyright for the work? *	Yes	Was the work subject to academic peer review?	Yes

*Attach evidence of permission from the copyright holder (publisher or other author) to include this work.

SECTION C – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper.	ZJ, OC conceived the review and designed and conducted the search. ZJ, GS, NEH screened the titles and abstracts, ZJ, ES, NER screened the full-texts, ZJ, ES, VH, GS, NEH extracted data, NER assessed data quality, ZJ, OC interpreted the results, designed the tables and figures. ZJ wrote the first draft. ZJ, ES, VH, NER, GS, NEH, HG, MS, HB, OC authors contributed to writing the final version. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

SECTION D

Student Signature	
Date	27/05/2024
Supervisor Signature	
Date	16/06/2024

OPEN ACCESS

Effects of size at birth on health, growth and developmental outcomes in children up to age 18: an umbrella review

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ABSTRACT

Background Size at birth, an indicator of intrauterine growth, has been studied extensively in relation to subsequent health, growth and developmental outcomes. Our umbrella review synthesises evidence from systematic reviews and meta-analyses on the effects of size at birth on subsequent health, growth and development in children and adolescents up to age 18, and identifies gaps.

Methods We searched five databases from inception to mid-July 2021 to identify eligible systematic reviews and meta-analyses. For each meta-analysis, we extracted data on the exposures and outcomes measured and the strength of the association.

Findings We screened 16 641 articles and identified 302 systematic reviews. The literature operationalised size at birth (birth weight and/or gestation) in 12 ways. There were 1041 meta-analyses of associations between size at birth and 67 outcomes. Thirteen outcomes had no meta-analysis.

Small size at birth was examined for 50 outcomes and was associated with over half of these (32 of 50); continuous/post-term/large size at birth was examined for 35 outcomes and was consistently associated with 11 of the 35 outcomes. Seventy-three meta-analyses (in 11 reviews) compared risks by size for gestational age (GA), stratified by preterm and term. Prematurity mechanisms were the key aetiologies linked to mortality and cognitive development, while intrauterine growth restriction (IUGR), manifesting as small for GA, was primarily linked to underweight and stunting.

Interpretation Future reviews should use methodologically sound comparators to further understand aetiological mechanisms linking IUGR and prematurity to subsequent outcomes. Future research should focus on understudied exposures (large size at birth and size at birth stratified by gestation), gaps in outcomes (specifically those without reviews or meta-analysis and stratified by age group of children) and neglected populations.

PROSPERO registration number CRD42021268843.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ A search in PubMed returns nearly half a million articles - an unwieldy and unmanageable field to navigate.
⇒ Eight previous umbrella reviews focused on specific subtopics; none was comprehensive in examining different risk factors or a broad range of outcomes.

WHAT THIS STUDY ADDS

⇒ It provides a comprehensive overview of reviews on the effects of size and gestation at birth on all subsequent health, growth and developmental outcomes in children.
⇒ It identifies outcomes with no meta-analyses and topics where there is a large, conclusive literature, and areas needing further or more conclusive research.

INTRODUCTION

Size at birth is affected both by in utero growth and by length of gestation. Researchers have been quantifying the relationship between size at birth and subsequent outcomes for over a century, resulting in a vast, nearly unmanageable, literature.[1–3] A quick PubMed search on size at birth generates almost half-a-million articles (online supplemental material 1), shaped by contemporaneous topics or theories of interest and by prevailing measurement capabilities.

The observation that small neonates were at substantially higher risk of dying than larger babies was quantified by early studies which defined 'prematurity' as low birth weight (LBW).[1 2] By the 1950s, prematurity was redefined using gestational age (GA) cut-offs; table 1 shows these and other definitions used as risk factors in our review. Research expanded from mortality outcomes to other potential consequences of being born with immature lung, neurological or immune-system development. At the other end of the size spectrum, macrosomia or high birth weight (HBW) was explored as a predictor of traumatic delivery or adverse growth outcomes. By the mid-1960, LBW, prematurity and intrauterine growth restriction (IUGR) were being distinguished, and modellers began looking at distributional components and developing population-specific and custom birthweight curves (late 1960s–1990s). The 1990s also saw the 'developmental origins of disease' theory, which suggested that small size at birth, quantified as LBW, increased disease risks in later life. This led to a burgeoning literature examining in utero shocks

Table 1 Measurements and threshold used for size-at-birth definitions

Risk factors (exposures)	Measurement units and thresholds used in definitions
Continuous measures	
Gestational age (GA)*	The duration of gestation is usually reported in completed weeks with additional days, or in completed days.
Birth weight (BW)†	Weight at birth measured in gram or kg. Reported using birth weight thresholds below or as mean birth weight with standard deviation
Small size at birth	
Extremely preterm (EPT)	<28 gestational weeks
Very preterm (VPT)	<32 gestational weeks
Preterm (PT)	<37 gestational weeks
Extremely low birth weight (ELBW)	<1000 g
Very low birth weight (VLBW)	<1500 g
Low birth weight (LBW)	<2500 g
Small for gestational age (SGA)	<10th percentile of birth weight for GA
Intrauterine growth restriction (IUGR)	Defined in the footnotes of online supplemental material 3 tables 1 a-g
Large size at birth/post term	
Post term	>41 gestational weeks
High birth weight (HBW)/ macrosomia	>4000 g
Large for gestational age (LGA)	>90th percentile of weight for GA

*GA is counted in calendar days from the first day of gestation, with the number of completed weeks calculated as the number of days divided by 7, presented as a whole integer plus a remainder, for example, day 258 is 36+6. Methods used to assess GA vary by study, which can affect reliability and comparability between studies. Methods using ultrasound assessment in the first trimester are most accurate.
†Birth weight is the first weight of the fetus or neonate obtained after birth. For live births, birth weight should preferably be measured within the first hour of life before significant postnatal weight loss has occurred.
GA, gestational age.

and their effects on cardiovascular and metabolic outcomes in adults and on early markers of these diseases in young children.[1 2] Starting in 2013, the International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21) used eight geographically diverse populations to develop global standard curves for fetal growth by sex and by GA.[3]

Despite a large literature and eight previous umbrella reviews,[4–11] there is no comprehensive summary of the main associations between size at birth and health, growth and developmental (including motor, cognitive and educational) outcomes, or of the literature gaps. Previous umbrella reviews (1) do not examine the full size-at-birth spectrum (neglecting larger neonates)[4 5 7–10]; (2) focus primarily on specific associations, for example, on the effects of LBW on mortality or chronic diseases[11] or of preterm birth on developmental outcomes[4 5]; (3) limit reviews to young children or adults and neglecting older children; and most importantly, to our knowledge, only one umbrella review (4) examines size for GA stratified by gestation, making it difficult to elucidate the relative importance of IUGR versus prematurity.

Our umbrella review aims to serve as a primary source of up-to-date compiled evidence on the effect of the full range of size-at-birth measures on a wide range of subsequent child and adolescent well-being outcomes.

Our umbrella review objectives are to (1) identify systematic reviews on the effects of size at birth on health (including mortality, acute ill health, lung-related ill health, chronic ill health and mental health), growth, developmental outcomes in children and adolescents; (2) map the evidence from reviews with meta-analyses, highlighting the magnitude, direction and consistency of the associations; (3) indicate evidence gaps; in addition, (4) we will suggest approaches needed for future empirical studies and meta-analyses.

METHODS

We conducted an umbrella review, gathering information from existing systematic reviews and meta-analyses which examined the effects of size at birth on health, growth and developmental outcomes in children up to 18 years of age.

We systematically searched MEDLINE, Embase, ERIC and Cochrane Library databases for articles published until 15 July 2021, without restricting on date, language or location. The search was limited to peer-reviewed systematic reviews or meta-analyses. Key search concepts included ("birth weight" OR "gestational age" OR "intrauterine growth restriction" OR "prematurity") AND ("systematic review" OR "meta-analysis"). To maximise the eligible reviews, we did not limit the outcomes or the study population. We also hand-searched the reference lists of the eight identified umbrella reviews to ensure we did not miss any reviews. The full search strategy and the steps for data extraction are included in online supplemental material 2.

In Online supplemental material 3 tables 1 a-g, we mapped the evidence on the effects of 12 different size-at-birth risk factors on a wide range of outcomes, grouped in seven themes: mortality and hospitalisation (theme a); neonatal and early childhood acute ill health (theme b); allergies and lung-related ill health (theme c); chronic ill health (theme d); behavioural and mental health (theme e); growth and nutrition (theme f); and developmental (motor, cognitive and educational) (theme g). The 7 themes had 67 subthemes. The subthemes in the behavioural and mental health themes (theme g) were grouped based on *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM5), classifications.[12]

The direction of the association was indicated using different colours in online supplemental material 3 tables 1 a-g with dark blue denoting a harmful effect, yellow denoting no statistically significant effect, and green denoting a beneficial effect.

RESULTS

We screened 16641 articles and identified 367 systematic reviews, of which 65 focused on outcomes in adults. This left 302 eligible systematic reviews of outcomes in children or in children and adults: 148 without meta-analyses, 141 with meta-analysis and 13 with meta-analyses of primary data (figure 1). Studies were published between 1989 and 2021.

We identified 7 themes and 67 subthemes of outcomes. Of the 67 subthemes, 13 were systematically reviewed without a meta-analysis (via 29 reviews)[13–41] (figure 2). Out of the 141 reviews with meta-analyses, 52 had a high-quality appraisal score, 61 medium and 28 low (online supplemental material 4a). Most of the meta-analyses (100 of 141) assessed publication bias (online supplemental material 4b).

Online supplemental material 3 tables 1 a-g shows the associations grouped by themes and subthemes. A total of 1041 associations were summarised from the 150 studies with meta-analyses

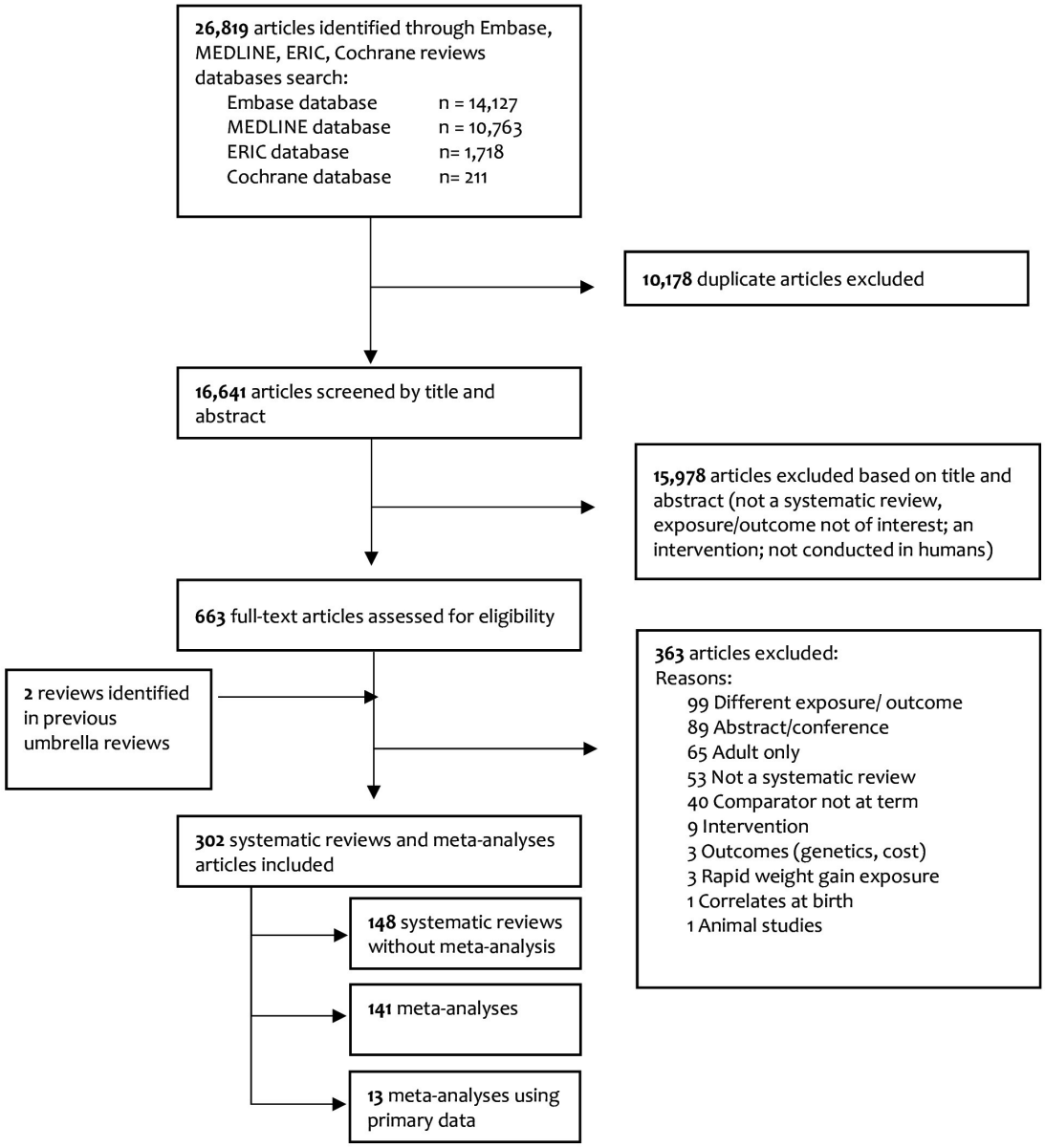

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart for study selection.

(including those with primary data): 772 with small size at birth as risk factor (including extremely preterm, very preterm, preterm, extremely low birth weight (ELBW), very low birth weight (VLBW), LBW and small for gestational age (SGA)), 144 with large size at birth/post-term (including post-term, HBW and large for gestation age (LGA)) and 125 with size as a continuous risk factor (weight and gestation). Only 85 of 1041 associations used SGA or LGA as risk factors. Of the 1041 associations, 225 focused on children under 5, 487 focused on children under 18, and 329 focused on mixed children and adults. The magnitude, direction and consistency of these associations are presented in online supplemental material 3 tables 1 a-g with a detailed narrative summary to explain the results by theme.

The main manuscript contains table 2 as an example of online supplemental table 1 f showing the associations between size at birth and nutrition and growth outcomes. Table 3 shows a subset of seven reviews which measured size for GA stratified by gestation, including four reviews missing from online supplemental material 3 tables 1 a-g because they included only stratified exposures.[42–45]

Figure 3 summarises findings on the direction of the association by subtheme of online supplemental material 3 tables 1 a-g .[46–195] Except for a few subthemes like undernutrition, most studies were conducted in high-income countries (online supplemental material 5).

Small size at birth (extremely preterm, very preterm, preterm, late preterm, ELBW, VLBW, LBW, SGA and IUGR) associations comprised most of the outcomes assessed (32 of 50) (online supplemental material 3 tables 1 a-g and figure 3). Seventeen of the 32 outcomes had been identified previously in eight published umbrella reviews as being associated with size at birth: mortality,[11 46–48 50] dental caries,[8 56–59] infection,[11 50 52 60–63] quality of life,[4 5 65] atopic dermatitis,[5 11 67 68] lung function,[4 5 11 70–73] asthma/wheezing,[11 52 73–80] including hypertension,[4 11 84–88 94] type 2 diabetes type,[9 11 113 114] physical activity,[6 143 144] undernutrition,[11 160] attention-deficit/hyperactivity disorder,[4 5 140–142 149–151] cerebral palsy,[5 170–173] neurodevelopmental,[4 5 164–167] motor development,[4 5 146 147 168] intellectual disabilities[10 11 138 139 141 146 148 151 174 177 179 181–184] and IQ.[10 11 141 142 146 177 181–183 185–189] Unlike most previous umbrella

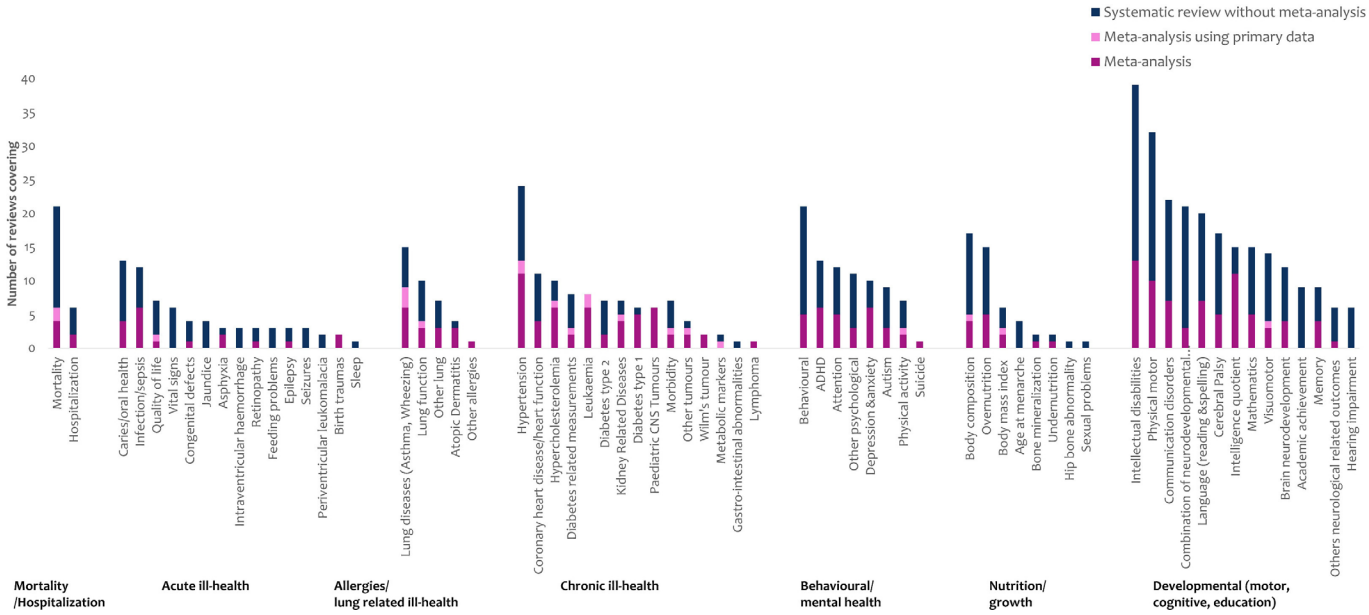

Figure 2 Themes and subthemes identified in 302 reviews.

reviews, we mapped the specific associations between different small size-at-birth risk factors and specific detailed outcomes. We also identified 15 subthemes which were consistently associated with small size at birth that had not been included in previous umbrella reviews of associations with hospitalisation,[52] asphyxia,[54] retinopathy,[55] epilepsy,[64] other lung related measurements,[51 82 83] kidney related diseases,[85 87 105–107] attention,[138 139 146–148] autism spectrum disorder,[140 152 153] body composition,[85 155–158] working memory,[138 141 146 182] communication,[138 148 174 183 190–192] educational outcomes language learning disorder,[138 141 184 190 191 193 194] mathematics learning disorder,[138 141 173 184 193] non-right handedness[195] and combined neurological measurements.[176] We found two subthemes (hypercholesterolaemia[84] and lymphoma[128]) which consistently showed no association. We also identified 16 associations with mixed evidence of association: congenital defects,[53] coronary heart disease heart function,[101 102] type 1 diabetes,[108–111] diabetes-related measurement,[84 115] paediatric central nervous system tumours,[116–120] leukaemia,[121 122 124 126 127] Wilms' tumour,[129] other tumours,[130] metabolic syndrome,[132] depressive/anxiety disorders,[133–138] other psychological,[132 135 139] adverse behaviours,[138 140–142] suicidal behaviour,[154] body mass index,[77 84] overnutrition[156 161 162] and visuomotor.[146 147 168]

Large size at birth/post-term/continuous measurement of birth weight and GA were consistently associated with 11 subthemes: increased risk of hospitalisation,[49] birth trauma,[49] atopic dermatitis,[69] lung function,[70] body composition,[158] overnutrition,[161–163] cerebral palsy,[170] Wilms' tumour,[112 129] intellectual disabilities,[151] and decreased quality of life[66] and working memory.[182] Meta-analyses showed mixed evidence for 24 subthemes.

In table 3, only 11 reviews and 73 meta-analyses within these compared risks by size for GA stratified by gestation. Four reviews[46 48 160 174] (37 meta-analyses) compared term SGA, preterm SGA and preterm- appropriate for gestational age (AGA) to term-AGA babies. These ideal comparisons elucidated the relative magnitude of the effect of SGA matching on preterm/term status and the relative magnitude of the effect of GA matching on AGA status.

DISCUSSION

This umbrella review provides the most recent synthesis of evidence from multiple fields exploring associations of size at birth with a wide range of subsequent health, growth and developmental outcomes in children under 18. This umbrella review summarised 302 reviews and mapped the magnitude and consistency of 1041 meta-analyses (from 150 reviews). The umbrella review also showed 73 meta-analyses (from 11 reviews) which compared risks by size for gestational age, stratified by preterm and term. We revealed gaps in research and an absence of meta-analyses for some exposures and outcomes. We elucidated analytical and measurement approaches which, if replicated, could better reveal the relative importance of preterm and IUGR (SGA) in the aetiology of adverse outcomes in children.

Our findings indicate some of the potential mechanisms underlying the associations. There is a body of theory seeking to distinguish the causes and the consequences of prematurity from those of IUGR.[46 196 197] Prematurity and fetal growth restriction are influenced by some similar factors, many of them maternal, such as weight, height, weight gain during pregnancy, smoking and age among others. Preterm delivery interrupts in utero development of neurological, immunological and lung function.[198 199] By contrast, poor fetal intrauterine growth, reflected in IUGR (SGA), links to subsequent metabolic and growth issues reflected in undernutrition and poorer cognitive development,[200 201] while rapid in utero growth, reflected by LGA, links to subsequent obesity and cancers. Analyses such as those shown in table 3, distinguishing the co-occurrence of preterm and SGA from the occurrence of preterm alone or SGA alone, and comparing these to term AGA babies, enable greater understanding of the relative importance of the prematurity and IUGR (and their respective causes) in the causation of specific adverse outcomes. This review suggests that prematurity mechanisms are the key aetiologies linked to mortality and cognitive development, while IUGR mechanisms are the key ones linked to underweight and stunting. Improved understanding of the relationship of these two different aetiologies to subsequent adverse outcomes will ensure we develop more appropriate interventions to address

Table 2 Associations between size at birth and nutrition and growth outcomes

Ref	Exposures (size at birth)												Population	Outcomes	Effect size (CI), direction of the association
	Small							Cont		Large					
	EPT (<28 weeks)	ELBW (<1000 g)	VPT (<32 weeks)	VLBW (<1500 g)	PT (<37 weeks)	LBW (<2500 g)	SGA (<10th percentile)	BW (cont.)	GA (cont.)	Post term (>41 weeks)	HBW (>4000 g)	LGA (>90th percentile)			
														Body composition	
155					X								Infants	Length (cm)	MD=−3.71 (−4.60 to −2.81)
85		X											11 years	Height (cm)	z-score difference=−0.92 (−0.03), p<0.001
155					X								Infants	Weight (kg)	MD=−0.59 (−0.75 to −0.44)
85		X											11 years	Weight (kg)	z-score difference=−0.61 (0.18), p<0.001
155					X								Infants	Head circumference (cm)	MD=−1.03 (−1.52 to −0.54)
85		X											11 years	Head circumference (cm)	z-score difference=−1.52 (0.44), p<0.001
85		X											11 years	Body surface area	z-score difference=−0.10 (−0.01), p<0.001
155					X								Infants	Total body fat (%)	MD=3.06 (0.25 to 5.88)
156					X								4–7 years	Total body fat (%)	SMD=−3.05 (−8.73 to 2.62)
155					X								Infants	Fat mass (kg)	MD=−0.05 (−0.09 to −0.01)
155					X								Infants	Fat-free mass (kg)	MD=−0.46 (−0.64 to −0.27)
156					X								4–7 years	Fat mass index	SMD=−1.31 (−5.42 to 2.81)
156					X								4–7 years	Childhood Trunk Fat Index	SMD=1.03 (−1.64 to 3.71)
157							**						At birth	Cord blood adiponectin concentrations	SMD=−1.14 (−2.15 to −0.12)
157							*						At birth	Cord blood adiponectin concentrations	SMD=−1.93 (−4.093 to −0.022)
157							X						At birth	Cord blood adiponectin concentrations	SMD=−0.383 (−0.744 to −0.022)
158							X						0.5 hours–11 days	Total body water (%)	MD=4.40 (2.83 to 5.96)
158									X				6 hours–7 days	Total body water (%)	β=−1.44 (−0.63 to −2.24) per week
158												X	0.5 hours–11 days	Total body water (%)	MD=−5.23 (−4.54 to −5.91)
														Bone mineralisation	
159								X					10 years	Bone mass content	β=0.02 (0.01 to 0.04)
159								X					10 years	Bone mass density	β=0.01 (−0.01 to 0.03)
														BMI	
84	X												6–32 years	BMI (kg/m^2)	MD=−0.50 (−1.10 to 0.09)
84			X										5–30 years	BMI (kg/m^2)	MD=−0.30 (−0.54 to −0.05)
84					X								4.5–35.7 years	BMI (kg/m^2)	MD=−0.13 (−0.40 to 0.14)
84					X								<10 years	BMI (kg/m^2)	MD=−0.70(−1.13 to −2.28)
84					X								<19 years	BMI (kg/m^2)	MD=5.20 (−3.82 to 14.21)
84					X								10–19 years	BMI (kg/m^2)	MD=−0.25 (−0.76 to 0.26)
91								X_{GA}					16.0–46.9 years	BMI (kg/m^2)	β=0.52 (0.20 to 0.84)/kg increase
91								GA					16.0–46.9 years	BMI (kg/m^2)	β=0.51 (−0.08 to 1.11)/kg increase
91								X					16.0–46.9 years	BMI (kg/m^2)	β=0.52 (0.17 to 0.86)/kg increase
77					T								0–2 years	BMI trajectory: class 2 (rapid growth to 2 years)	aOR=2.02 (1.49 to 2.74)
77					T								0–6 years	BMI trajectory: class 3 (persistent rapid growth to 6 years)	aOR=1.89 (0.42 to 8.49)
77						◊							0–2 years	BMI trajectory: class 2 (rapid growth)	aOR=1.48 (1.05 to 2.10)
77						◊							0–6 years	BMI trajectory: class 3 (persistent rapid growth)	aOR=0.78 (0.10 to 6.45)
77										X			0–2 years	BMI trajectory: class 2 (rapid growth)	aOR=0.81 (0.68 to 0.96)
77										X			0–6 years	BMI trajectory: class 3 (persistent rapid growth)	aOR=0.48 (0.15 to 1.53)
77											T		0–2 years	BMI trajectory: class 2 (rapid growth)	aOR=0.98 (0.86 to 1.12)
77											T		0–6 years	BMI trajectory: class 3 (persistent rapid growth)	aOR=1.62 (0.88 to 2.99)
														Undernutrition	

Continued

Table 2 Continued

Ref	Exposures (size at birth)												Population	Outcomes	Effect size (CI), direction of the association
	Small							Cont		Large					
	EPT (<28 weeks)	ELBW (<1000 g)	VPT (<32 weeks)	VLBW (<1500 g)	PT (<37 weeks)	LBW (<2500 g)	SGA (<10th percentile)	BW (cont.)	GA (cont.)	Post term (>41 weeks)	HBW (>4000 g)	LGA (>90th percentile)			
160					X								12–60 months	Wasting (weight for length/height for age <2 z-scores)	OR=1.55 (1.21 to 1.97)
160						X							12–60 months	Wasting (weight for length/height for age <2 z-scores)	OR=2.68 (2.23 to 3.21)
160							X						12–60 months	Wasting (weight for length/height for age<2 z-scores)	OR=2.36 (2.14 to 2.60)
160					X								12–60 months	Stunting (length/height for age<2 z-scores)	OR=1.69 (1.48 to 1.93)
160						X							12–60 months	Stunting (length/height for age<2 z-scores)	OR=2.92 (2.56 to 3.33)
160							X						12–60 months	Stunting (length/height for age<2 z-scores)	OR=2.32 (2.12 to 2.54)
160					X								12–60 months	Underweight (weight for age less than 2 z-scores)	OR=1.66 (1.42 to 1.95)
160						X							12c60 months	Underweight (weight for age less than 2 z-scores)	OR=3.48 (3.14 to 3.87)
160							X						12–60 months	Underweight (weight for age less than 2 z-scores)	OR=2.96 (2.61 to 3.36)
														Overnutrition	
161						X							0–18 years	Overweight	OR=0.60 (0.54 to 0.67)
161								X					1–75 years	Overweight	β=0.34 (0.28 to 0.40)/kg increase
161											X		0–18 years	Overweight	OR=1.76 (1.65 to 1.87)
156					X								6–14 years	Obesity	OR=1.19 (1.13 to 1.26)
162						◊							3–18 years	Obesity	OR=0.87 (0.69 to 1.08)
162						X							1–17 years	Obesity	OR=0.61 (0.46 to 0.80)
162						X							<6 years	Obesity	OR=0.61 (0.43 to 0.88)
162						X							6–13 years	Obesity	OR=0.54 (0.32 to 0.90)
162						X							13–17 years	Obesity	OR=0.74 (0.37 to 1.49)
163								X					7–11 years	Obesity	β=0.649/kg increase
162											◊		1–16 years	Obesity	OR=2.23 (1.91 to 2.61)
162											X		0–17 years	Obesity	OR=2.07 (1.91 to 2.24)
162											X		<6 years	Obesity	OR=2.10 (1.93 to 2.29)
162											X		6–13 years	Obesity	OR=1.76 (1.36 to 2.20)
162											X		13–17 years	Obesity	OR=2.58 (1.56 to 4.26)

Exposures: EPT (<28 weeks), ELBW (<1000 g), VPT (<32 weeks), VLBW (<1500 g), PT (<37 weeks), LBW (<2500 g), SGA (<10th percentile), post term (>41 weeks), HBW (>4000 g) and LGA (>90th percentile).
Symbols in exposures: X, as defined in exposure; X_{adj}, adjusted and unadjusted for GA; GA, BW adjusted for GA; **, SGA <3rd, 5th and 10th percentile/value×by SD for GA; *, SGA <3rd percentile/value×by SD for GA; ◊, reference category 2500–4000 g; T, reference category GA 37≤term≤41.
Outcomes: , harmful effect; , no effect; , beneficial effect; *italic*, calculation/post review.
aOR, adjusted OR; BMI, body mass index; BW, birth weight; BW (cont.), birth weight continuous; ELBW, extremely low birth weight; EPT, extremely preterm; GA, gestational age; GA (cont.), gestational age continuous; HBW, high birth weight; LBW, low birth weight; LGA, large for gestational age; MD, mean difference; PT, preterm; SGA, small for gestational age; SMD, standardised mean difference; VLBW, very low birth weight; VPT, very preterm.

Table 3 Association between maturity and SGA/IUGR combinations and different outcomes

			Exposures					Reference			Effect size (CI), direction of association
Ref	Outcomes	Population	PT SGA	PT AGA	T IUGR	T SGA	T LBW	T AGA	T NBW	T	
48	Neonatal mortality	≤28 days	<34					X			OR=56.97 (11.1 to 291.7)
48	Neonatal mortality	≤28 days		<34				X			OR=74.9 (32.6 to 171.7)
48	Neonatal mortality	≤28 days	34–36					X			OR=19.88 (8.3 to 47.5)
48	Neonatal mortality	≤28 days		34–36				X			OR=3.18 (1.0 to 10.7)
48	Neonatal mortality	≤28 days				X		X			OR=2.23 (1.2 to 4.10)
46	Neonatal mortality	<28 days	X					X			RR=15.42 (9.11 to 26.1)
46	Neonatal mortality	<28 days		X				X			RR=8.05 (3.88 to 16.72)
46	Neonatal mortality	<28 days				X		X			RR=2.44 (1.67 to 3.57)
46	Early neonatal mortality	<7 days	X					X			RR=17.19 (9.57 to 30.91)
46	Early neonatal mortality	<7 days		X				X			RR=7.59 (3.38 to 17.08)
46	Early neonatal mortality	<7 days				X		X			RR=2.76 (1.82 to 4.18)
46	Late neonatal mortality	8–28 days	X					X			RR=17.37 (10.27 to 29.37)
46	Late neonatal mortality	8–28 days		X				X			RR=5.60 (2.75 to 11.43)
46	Late neonatal mortality	8–28 days				X		X			RR=2.45 (1.7 to 3.51)
46	Postneonatal mortality	29–365 days	X					X			RR=5.22 (2.8 to 9.64)
46	Postneonatal mortality	29–365 days		X				X			RR=2.72 (1.5 to 4.79)
46	Postneonatal mortality	29–365 days				X		X			RR=1.98 (1.39 to 2.81)
46	Infant mortality	<365 days	X					X			RR=9.24 (4.33 to 19.71)
46	Infant mortality	<365 days		X				X			RR=5.30 (2.39 to 11.76)
46	Infant mortality	<365 days				X		X			RR=2.28 (1.52 to 3.41)
160	Wasting	12–60 months	X					X			aOR=4.19 (2.90 to 6.05)
160	Wasting	12–60 months		X				X			aOR=1.96 (1.46 to 2.63)
160	Wasting	12–60 months				X		X			aOR=2.52 (2.27 to 2.80)
160	Stunting	12–60 months	X					X			aOR=4.51 (3.42 to 5.93)
160	Stunting	12–60 months		X				X			aOR=1.93 (1.71 to 2.18)
160	Stunting	12–60 months				X		X			aOR=2.43 (2.22 to 2.66)
160	Undernutrition	12–60 months	X					X			aOR=5.35 (4.39 to 6.53)
160	Undernutrition	12–60 months		X				X			aOR=2.07 (1.76 to 2.44)
160	Undernutrition	12–60 months				X		X			aOR=3.17 (2.78 to 3.62)
174	Motor	<7 years	X					X			aSMD=−0.15 (−0.40 to 0.09)
174	Motor	<7 years		X				X			aSMD=−0.23 (−0.42 to −0.03)
174	Motor	<7 years				X		X			aSMD=−0.007 (−0.08 to 0.06)
174	Cognitive	<7 years	X					X			aSMD=−0.17 (−0.29 to −0.05)
174	Cognitive	<7 years		X				X			aSMD=−0.14 (−0.24 to −0.05)
174	Cognitive	<7 years				X		X			aSMD=−0.02 (−0.10 to 0.06)
174	Language	<7 years		X				X			aSMD=−0.02 (−0.23 to 0.19)
174	Language	<7 years				X		X			aSMD=−0.03 (−0.12 to 0.06)
172	Cerebral palsy	Neonates	X					X			OR=2.34 (1.43 to 3.82)
42	Neonatal mortality	Neonates				X		X			OR=4.11 (3.70 to 4.56)
42	Non-neurological neonatal morbidity	Neonates				X		X			OR=2.98 (1.58 to 5.61)
42	Neonatal morbidity: neurological	Neonates				X		X			OR=2.12 (1.56 to 2.91)
43	Morbidly composite	1–18 years				X		X			OR=1.49 (1.02 to 2.1)
43	Morbidly composite	1–18 years					X		X		OR=0.98 (0.87 to 1.10)
43	Learning difficulties or learning disabilities	12 months–18 years				X		X			OR=2.03 (1.65 to 2.50)
43	Obesity	2–18 years				X		X			OR=0.94 (0.59 to 1.49)
43	Obesity	6–11 years					X		X		OR=0.90 (0.50 to 1.64)
43	Hypertension	3–16 years					X		X		OR=0.98 (0.8 to 1.12)
44	Neurodevelopmental scores (high scores)	40 weeks–10 years				X		X			Largest SMD=−0.32 (−0.38 to −0.25)
44	Neurodevelopmental scores (low scores)	40 weeks–10y ears				X		X			Smallest SMD=−0.31 (−0.38 to −0.25)
45	Cognitive score	0.16–10.0 years			X	XI		X			SMDH=−0.39 (−0.50 to −0.28)

Continued

Table 3 Continued

Ref	Outcomes	Population	Exposures					Reference			Effect size (CI), direction of association
			PT SGA	PT AGA	T IUGR	T SGA	T LBW	T AGA	T NBW	T	
45	Cognitive score	0.16–10.0 years				X		X			SMDH=−0.34 (−0.45 to −0.22)
45	Cognitive score	2.0–9.5 years			X	I		X			SMDH=−0.58 (−0.82 to −0.35)
45	Borderline intellectual impairment	Child				X		X			OR=1.75 (1.50 to 2.04)
84	Systolic blood pressure	Child/adult	X					X			MD=2.00 (0.21 to 3.78)
84	Systolic blood pressure	Child/adult		X				X			MD=1.46 (0.13 to 2.79)
84	Diastolic blood pressure	Child/adult	X					X			MD=1.39 (0.00 to 2.78)
84	Diastolic blood pressure	Child/adult		X				X			MD=1.22 (0.19 to 2.25)
84	High-density lipoprotein	Child/adult	X					X			MD=0.03 (−0.04 to 0.10)
84	High-density lipoprotein	Child/adult		X				X			MD=0.01 (−0.04 to 0.07)
84	Low-density lipoprotein	Child/adult	X					X			MD=0.67 (0.38 to 0.97)
84	Low-density lipoprotein	Child/adult		X				X			MD=0.13 (−0.03 to 0.29)
84	Triglyceride	Child/adult	X					X			MD=0.00 (−0.07 to 0.06)
84	Triglyceride	Child/adult		X				X			MD=−0.04 (−0.09 to 0.02)
84	Insulin	Child/adult	X					X			MD=−1.65 (−3.39 to 0.10)
84	Insulin	Child/adult		X				X			MD=−1.07 (−2.29 to 0.15)
84	BMI	Child/adult	X					X			MD=−0.38 (−0.98 to 0.22)
84	BMI	Child/adult		X				X			MD=0.06 (−0.34 to 0.46)
87	Systolic blood pressure	11.3–41.3 years	X							X	SMD=0.41 (0.12 to 0.70)
87	Systolic blood pressure	11.3–41.3 years		X						X	SMD=0.31 (−0.33 to 0.95)
87	Diastolic blood pressure	11.3–41.3 years	X							X	SMD=0.28 (0.05 to 0.51)
87	Diastolic blood pressure	11.3–41.3 years		X						X	SMD=0.09 (−0.08 to 0.26)
87	Serum creatinine	17.6–22.9 years	X							X	SMD=0.18 (−0.24 to 0.59)
87	Serum creatinine	17.6–22.9 years		X						X	SMD=0.02 (−0.32 to 0.35)

, harmful effect from high to lower risks; , no effect high to lower risk.

Symbols inexposures: X, as defined in exposure; XI, SGA and IUGR (defined in reference 45); I, IUGR (defined in reference 45).

(45) IUGR is defined as antenatal evidence of growth restriction by abnormal middle cerebral artery pulsatility index and umbilical artery pulsatility index, or late onset verified by ultrasound or clinically, or ultrasound and clinical evaluation, or third trimester serial ultrasound.

AGA, appropriate for gestational age; BMI, body mass index; IUGR, intrauterine growth restriction; LBW, low birth weight; MD, mean difference; NBW, normal body weight; PT, preterm; RR, relative risk; SGA, small for gestational age; SMD, standardised mean difference; SMDH, standardized mean difference for heteroscedastic population variances; T, term.

these risk factors and are better able to track intervention impacts.

It was not feasible in this discussion to explore all the potential reasons why mixed or contradictory effects were observed for each of the subthemes. Key reasons for why mixed estimates of effect were seen could include the number of included studies, the search strategy and inclusion/exclusion criteria, the constituent study designs and heterogeneity. Other potential reasons for inconsistent associations include the population used for the exposure (grouping extremely preterm with preterm), the comparator used (grouping normal birth weight with HBW as a comparator for LBW), the age of the child at assessment (allowing more or less time for a disease, such as type 2 diabetes, to develop), measurement practices in older versus newer reviews, and whether or not sex or other variables were adjusted for (female babies are appropriate for GA at a lower birth weights than male babies and could be misclassified if sex was not adjusted for).

By way of example of how the results have varied by review, we unpacked meta-analysis of the association between LBW and type 1 diabetes. The earliest review, by Harder and colleagues, included eight papers and suggested a protective effect (0.82), but had a confidence interval (CI) that overlapped 1 (95% CI 0.54 to 1.23).[109] However, this review compared LBW to babies born at 2500+ g, including HBW infants. The next review, by Cardwell and colleagues, used a more appropriate normal (2500–4000 g) comparator and included many more studies (29 studies of which five were cohorts).[111] They showed no association (OR=0.98, 95% CI 0.84 to 1.13), with high heterogeneity observed, although a meta-analysis of the cohorts showed a protective effect (OR=0.79, 95% CI 0.67 to 0.92).[111] The most recent meta-analysis by Haiyan Wang and colleagues, focused only on six cohort studies and by virtue of having less heterogeneity and a larger sample size, they established that LBW appears to protect against type 1 diabetes compared with normal birth weight (HR 0.78, 95% CI 0.69 to 0.88).[110] By contrast there was only one systematic review of the effects of prematurity (Li and colleagues[108]) which included 18 studies and showed prematurity increased the risk of type 1 diabetes (OR=1.17, 95% CI 1.10 to 1.25) for high-quality studies.

Although we assessed review quality, we aimed to be comprehensive and so extracted data regardless of quality. This meant we included 28 reviews with low critical appraisal scores which might explain some of the mixed direction of effects observed. Thus, when exploring the association presented, it is important to consider the quality of the meta-analysis. For example, low-quality review on extremely preterm and ELBW and mortality showed very small neonates had a reduced prevalence of

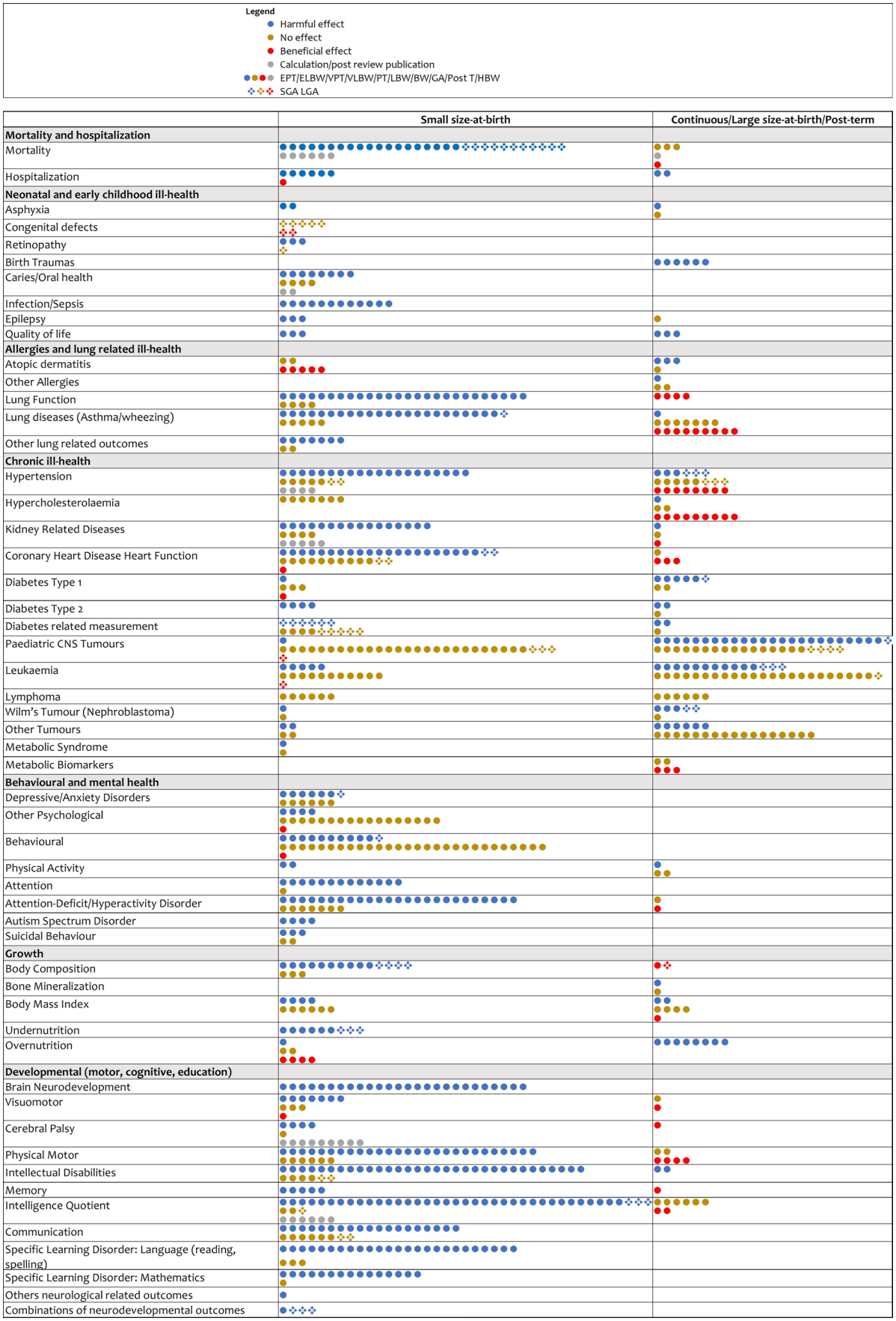

Figure 3 Summary of the associations presented in online supplemental table 1a–g. BW, birth weight; ELBW, extremely low birth weight; EPT, extremely preterm; GA, gestational age; HBW, high birth weight; LBW, low birth weight; LGA, large for gestational age; PT, preterm; SGA, small for gestational age; VLBW, very low birth weight; VPT, very preterm.

mortality compared with larger babies,[47] an anomalous finding which probably stemmed from selection and publication bias favouring reports of very small surviving babies.

The evolution of our understanding of the relationships between size at birth and various outcomes in children is inextricably linked to improvements in measurement and in theory, as well as to disease burden and priority health topics. For example, literature on effects of small size at birth on adult health burgeoned after the 'developmental origins of disease' theory.[1 2] Our review identified several gaps in relation to the risk factors, outcomes and populations studied. Very few meta-analyses examined outcomes linked to the effect of LGA and SGA or of the different combinations of gestation and size for GA at birth. For some subtheme outcomes (cognitive and motor), very small size at birth was the exposure measured rather than LBW or prematurity. Most of the systematic reviews were from high-income countries, reflecting a general bias in research.[202] We also identified 14 subtheme outcomes missing meta-analyses. Older age children are rarely a priority population for studies of mortality or acute ill health, but this neglect may be because they generally have fewer ill-health outcomes and so are more difficult to study.

Strengths and limitations

Our review synthesised an enormous literature and was comprehensive, not restricting on outcome, year or language. It assessed methodological quality using a critical appraisal tool, showed gaps and focused on children up to 18, thereby bridging a gap between studies focused on young children and those focused on adults. Its limitations are its reliance on published systematic reviews, particularly those with meta-analyses. Our approach missed single studies not included in previous reviews and topics without systematic reviews. We did not do additional meta-analyses nor did we recalculate effect sizes, so we include three reviews with inconsistent data presented in abstract, figures and results.[87 124 159] Moreover, while we did not restrict on language, we used English search terms and did not search non-English databases, for example, Chinese literature. As part of the umbrella review, we did not assess methods of the selected papers. In meta-analyses where we did not detect an association, we did not conduct further examination by assessing the confidence intervals.

RECOMMENDATIONS/CONCLUSION

Our umbrella review compiled evidence from 1041 associations and showed the strength of evidence. It also alluded to potential mechanisms, enabling us to identify areas where we can appropriately target or track interventions aimed at improving outcomes in LBW/preterm or HBW children.

To improve future research and evidence on the mechanisms involved, we highlight the need to

- Address gaps in the range of risk factors explored by including the whole spectrum of size and maturity where possible, including (1) splitting preterm into subgroups based on maturity, for example, extremely preterm, very preterm and moderate or late preterm; (2) considering all the combinations of size for GA (adjusted for preterm/term/post-term, specifically focusing on SGA and LGA); and (3) excluding HBW, post-term and LGA from the comparator when examining small size at birth (LBW, preterm and AGA). The latter recommendation is made because when the comparator is 'anyone not SGA', then the relative risk of SGA may be underestimated because the comparator lumps low-risk AGA babies with higher-risk LGA ones.
- Conduct further research on understudied exposures (ie, large size at birth/post-term) or outcomes (eg, current research on LGA is largely limited to outcomes of growth, diabetes or cancer) and on inconclusive areas (for small size these include coronary heart disease and heart function indicators, congenital defects, overweight, leukaemia, paediatric central nervous system tumours, type 1 diabetes, and adverse behavioural and visuomotor outcomes). For large size at birth, there are numerous areas with inconclusive results. There is also a need to conduct meta-analyses on the 14 subthemes without one.
- Address gaps in populations studied by further examining associations by different age groups and by sex, and by conducting additional research in low-income and middle-income countries for specific subtopics, particularly where risks may differ because of differences in access to treatment and preventive measures, or to differing epigenetic and environmental exposures.
- Conduct theme-based meta-analyses starting with subthemes that are inconsistent in the literature and with meta-analysis that have low-quality scores. Considering the different reasons for inconsistency indicated in the discussion, future research would benefit from subanalysis of the associations stratified by age at the occurrence of the outcome and by the sex of the child.

Acknowledging that both small and large size at birth contribute to multiple burdens of diseases, this study gives further evidence on the importance of correctly measuring size at birth in order to be able to intervene properly. Compiling this evidence allows researchers and policymakers to understand potential pathways for child survival and to further explore pathways for children to attain their full thriving potential. This study provides guidance to funders and researchers to help prioritise understanding of inconsistent evidence in the literature and to inform and prioritise points of interventions that contribute the most to disability-adjusted life years.

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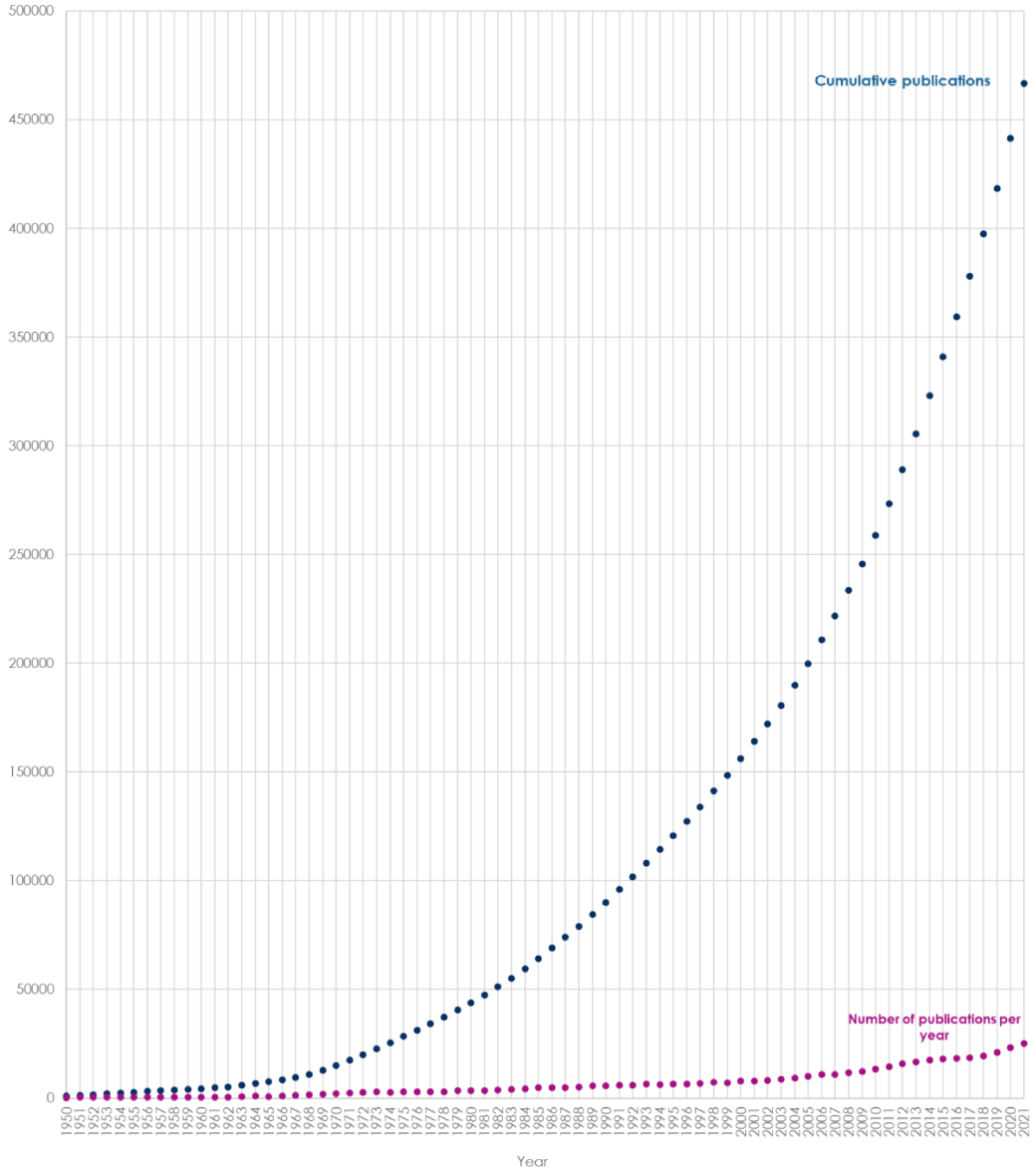
Supplementary Material

Contents

Supplementary material 1- Figure 1. Number of publications on size at birth based on PubMed search



2

Jamaluddine Z, *et al. Arch Dis Child* 2023;0:1–14. doi: 10.1136/archdischild-2022-324884

Supplementary material 2-a Full search terms in all the databases

MEDLINE
Ovid MEDLINE(R) ALL <1946 to July 15, 2021>
1 review.pt.
2 (medline or medlars or embase or pubmed or cochrane).tw,sh.
3 (scisearch or psychinfo or psycinfo).tw,sh.
4 (psychlit or psyclit).tw,sh.
5 cinahl.tw,sh.
6 ((hand adj2 search$) or (manual$ adj2 search$)).tw,sh.
7 (electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw,sh.
8 (pooling or pooled or mantel haenszel).tw,sh.
9 (peto or dersimonian or der simonian or fixed effect).tw,sh.
10 (retraction of publication or retracted publication).pt.
11 or/2-10
12 1 and 11
13 meta-analysis.pt.
14 meta-analysis.sh.
15 (meta-analys$ or meta analys$ or metaanalys$).tw,sh.
16 (systematic$ adj5 review$).tw,sh.
17 (systematic$ adj5 overview$).tw,sh.
18 (quantitativ$ adj5 review$).tw,sh.
19 (quantitativ$ adj5 overview$).tw,sh.
20 (quantitativ$ adj5 synthesis$).tw,sh.
21 (methodologic$ adj5 review$).tw,sh.
22 (methodologic$ adj5 overview$).tw,sh.
23 (integrative research review$ or research integration).tw.
24 or/13-23
25 12 or 24
26 (birth-weight* or birthweight* or gestation* age* or f?etal growth restriction* or f?etal growth retardation* or intra-uterine growth restriction* or intrauterine growth restriction* or IUGR or prematur* or pre-matur* or preterm* or pre-term* or catch-up or catchup* or rapid weight gain).mp.
27 exp infant, low birth weight/ or exp infant, premature/ or exp Birth Weight/ or Fetal Growth Retardation/
28 26 or 27
29 28 and 25

Using https://bestpractice.bmj.com/info/toolkit/learn-ebm/study-design-search-filters/ for systematic review

Embase
1 exp review/
2 (literature adj3 review$).ti,ab.
3 exp meta analysis/
4 exp "Systematic Review"/
5 or/1-4
6 (medline or medlars or embase or pubmed or cinahl or amed or psychlit or psyclit or psychinfo or psycinfo or scisearch or cochrane).ti,ab.
7 Retracted Article/
8 6 or 7
9 5 and 8
10 (systematic$ adj2 (review$ or overview)).ti,ab.
11 (meta?anal$ or meta anal$ or meta-anal$ or metaanal$ or metanal$).ti,ab.

12 9 or 10 or 11
13 (birth-weight* or birthweight* or gestation* age* or f?etal growth restriction* or f?etal growth retardation* or intra-uterine growth restriction* or intrauterine growth restriction* or IUGR or prematur* or pre-matur* or preterm* or pre-term* or catch-up* or catchup* or rapid weight gain).mp.
14 exp infant, low birth weight/ or exp infant, premature/ or exp Birth Weight/ or Fetal Growth Retardation/
15 13 or 14
16 12 and 15

ERIC
(Birthweight or birth weight or gestational age or gestation age or gestational-age or fetal growth restriction or fetal growth retardation or foetal growth restriction or foetal growth retardation or intra-uterine growth restriction or intrauterine growth restriction or IUGR or premature or prematurity or pre-term or preterm or pre-term or catchup or catch-up or catch up or rapid weight gain)

AND
("meta-analysis" or "meta analysis" or "meta-analyses" or "meta analyses" or "metaanalysis" or "metanalyses" or "systematic review" or "systematic reviews")
Peer review ONLY

Cochrane Library searched using MESH and Medline search terms shown above

Supplementary material 2 b-Detailed full Methods

Search strategy and eligibility criteria

We conducted an umbrella review, gathering information from existing systematic reviews and meta-analyses which examined the effects of size-at-birth on health, growth, and developmental outcomes, in children up to 18 years of age.

We systematically searched MEDLINE, Embase, ERIC, and Cochrane Library databases for manuscripts published until 15 July 2021, without restricting on date, language, or location. The search was limited to peer-reviewed systematic reviews or meta-analyses. Key search concepts included ("birthweight" OR "gestational age" OR "intrauterine growth restriction" OR "prematurity") AND ("systematic review" OR "meta-analysis"). To maximize the eligible reviews, we did not limit the outcomes or the study population. The full search strategy is in supplementary 2. We also hand-searched the reference lists of the eight identified umbrella reviews to ensure we did not miss any reviews.

Citations were imported into EndNote and duplicates removed. Titles and abstracts were screened independently by at least two authors (among NEH, GS, ES) in Rayyan, to identify the studies that met the inclusion/exclusion criteria. All articles identified for full-text screening were assessed for inclusion by at least two authors (ES, NER, VH). Discrepancies were resolved through discussion with a third author (ZJ). We excluded umbrella reviews and systematic reviews of interventions and articles with size-at-birth as an outcome, or which did not have a term, normal birthweight, or appropriate-for-gestational-age comparator, or which included birthweight discordance as an exposure in twins or triplets. Reviews that only showed results for adults (age 18+ years) were excluded, while meta-analyses with children alone or which merged children and adults, were included.

Data extraction and analysis

At least two authors (among ES, VH, GS, NEH, ZJ) independently extracted data on the author, year, location, study design, eligibility criteria, sample size (number of papers reviewed and number of meta-analyses), participants' age-group, exposures with corresponding definitions, outcomes, and, where available, meta-analyses of the measures of effect. If no measure of effect was included and data were available, we calculate a relative risk as appropriate. We sought consensus for discrepancies by discussing with a third author (ZJ, OC). We assessed overall quality and risk of bias of the constituent systematic reviews using the 12 elements in the Joanna Briggs Institute Critical Appraisal checklists (NER, ES); we did not examine the quality of individual studies within each included systematic review. Publication bias assessment of each meta-analysis was a component of the quality assessment (supplementary material 4 b)

In Tables 1 a-g (detailed in supplementary 3), we mapped the evidence examining size-at-birth risk factors on a wide range of outcomes, in seven themes: (a) mortality and hospitalization (b) neonatal and early childhood acute ill-health (c) allergies and lung-related ill-health (d) chronic ill-health (e) behavioural and mental health (f) growth and nutrition (g) developmental (motor, cognitive and educational). The seven themes had 67 sub-themes. The sub-themes in the behavioural, and mental health theme (theme g) were grouped based on DSM5 classifications12. Correlates of size-at-birth measured contemporaneously with birthweight, e.g., head circumference, were not considered to be outcomes. Cost of hospitalization and genetic factors outcomes were not included as they reflected proxies of outcomes included. In Table 2 we did the same as Table 1 for the effects of size-for-gestational-age stratified by gestation.

In Tables 1 a-g meta-analyses of measures of effect were collected for each risk factor and outcome and reported with confidence intervals. The direction of the association was indicated using different colours in Tables 1 a-g– with dark blue denoting a harmful effect, yellow no statistically significant effect, and green, a beneficial effect. The different risk factors examined in Tables a-g are as defined in Box 1; non-standard definitions were indicated by different symbols. A narrative summary of each of the different sub-themes was synthesized, focusing separately on associations between small exposures and continuous/large exposures. Narrative synthesis highlights the magnitude, direction, and consistency of the associations. In Table 3, the results of Tables 1 a-g are summarized with each meta-analysis marked by a symbol indicating the direction of the association.

Age groups studied are shown in Table 1 a-g and Table 2. Occasionally, reviews had sub-themes with only one study and hence no meta-analysis, we did not report effect estimates for these sub-themes.

Country maps were generated using Datawrapper.

We registered our umbrella review (PROSPERO CRD42021268843) and followed PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).

Supplementary material 3- Detailed results by table.

ASSOCIATIONS BETWEEN SIZE-AT-BIRTH AND DIFFERENT OUTCOMES

Mortality and hospitalization- Table 1 a

Thirty-six meta-analyses (4 reviews)[46-49] measured the association between very preterm, preterm, late preterm, very LBW, LBW, SGA, and mortality. All but three meta-analyses (from one low-quality review where we calculated prevalence ratios [47]) showed those with small size-at birth had higher risks of mortality. Very preterm had the greatest increase in early and late neonatal morality. HBW was not associated with higher mortality (3/3 meta-analyses)[50,51]. Nearly all reviews assessed mortality risks in children under 5 years -- only one included mortality in older children[51].

Nearly all meta-analyses showed that being early or late preterm (6/7)[52] or HBW (2/2)[49] increased the risk of hospitalization among neonates.

Neonatal and early childhood ill-health - Table 1 b

Most meta-analyses (5/7)[53] showed that SGA and IUGR were not associated with patent ductus arteriosus, while 2/7 [53] showed that they decreased the risk. Preterm and LBW neonates had a higher risk of having poor Apgar scores or neonatal asphyxia (2/2)[54], while one meta-analysis showed that HBW (>4000g) was associated with a higher risk of asphyxia [49], but no effect when HBW was defined as >4260 g [49]. As physiologically expected, extremely preterm, and other markers of preterm, including extremely LBW and very LBW, were associated with higher risks of retinopathy of prematurity (3/3)[55], while SGA was not (1/1)[55] HBW increased the risk of birth trauma, including shoulder dystocia, Erb's palsy and other trauma (6/6)[49].

LBW and preterm neonates had an increased risk of poor oral health, including more dental carries, opacity, hypoplasia, and molar incisor hypo-mineralisation in nearly all (10/14) meta-analyses (four reviews) [56-59]. Seven reviews (12/12 meta-analyses) [50,52,60-63] all showed that small size-at-birth (very preterm, preterm, late preterm, very LBW, LBW) babies had an increased risk of sepsis and infection, including methicillin-resistant staphylococcus aureus (MRSA) infection, respiratory syncytial virus (RSV) infection, and pneumonia in the first five years of life. The risk of infection at older ages were not studied in meta-analyses. Preterm births had higher risks of epilepsy (3/3) while post-term (1/1) (defined as >41 weeks) did not (1/1)[64]. Extremely LBW, very LBW, preterm (3/3)[65] and increased gestational age per week (3/3)[66] were associated with poorer quality of life, assessed via health utility and sleep duration.

Allergy and lung-related ill-health- Table 1 c

Meta-analyses of small size-at-birth (very preterm, preterm, late term, LBW) neonates showed reduced risks of dermatitis (5/7 meta-analyses; two reviews)[67,68] while continuous measures of birthweight and gestation showed larger and more mature babies had increased risks of dermatitis (2/3)[69]. One review found no relationship between higher birthweight and other allergies (2/3 meta-analyses)[69].

Most meta-analyses of lung-related diseases (57/68 meta-analyses in 14 reviews)[52,70-80,82,83] showed that very preterm, preterm, very LBW, and LBW neonates had an increased risk of asthma, wheezing, or other measures of poor lung function. Only one meta-analysis examined SGA and asthma and found that SGA was associated with a higher risk[73]. Continuous measures of birthweight and gestational age showed children with higher values had a reduced risk of lung-related disease (13/14 meta-analyses in three reviews)[70,73,74]. Post-term and HBW were not associated with asthma or wheezing (6/7 meta-analysis in four reviews)[77,78,80,81].

Chronic ill-health- Table 1 d

Chronic ill-health sub-themes included cardiovascular-related outcomes (hypertension, hypercholesterolaemia and measurements of heart related function, chronic heart disease), chronic kidney diseases, diabetes, cancer and metabolic syndrome.

Extremely preterm, extremely LBW, very preterm, very LBW, preterm and LBW babies generally had increased risks of hypertension, including higher systolic or diastolic blood pressure (SBP/DBP) (24/32 meta-analyses in six reviews)[84-88,94], although 2 metanalyses found IUGR (measured as a combination of fetal growth restriction and SGA) did not. The effects of HBW or LGA on hypertension were mixed, with 6/13 meta-analyses showing increased risk, 2/13 decreased risk, and 5/13 no association (in a total of three reviews)[88,92,93]. In all meta-analyses (7/7)[84] preterm was not associated with total cholesterol, HDL, LDL, triglyceride. The majority of metanalyses showed that for every kg increase in birthweight, cholesterol levels were reduced (9/12 meta-analyses in six reviews)[91,96-100]. Many meta-analyses showed that very preterm, preterm, SGA were associated with an increased risk of coronary heart function indicators (23/36 meta-analyses in two reviews)[101,102], but none examined the effect of large size-at-birth.

Extremely LBW, very preterm, preterm and LBW children had an increased the risk of kidney-related disease markers (21/25 meta-analyses including 5 with a calculated prevalence ratio in five reviews)[85,87,105-107]. One metanalysis examined HBW and chronic kidney disease; it showed no effect [106].

Meta-analyses of the effect of size-at-birth on the development of type 1 diabetes were mixed: 1/5 showed lower risk (LBW) (in one review)[110], 3/5 no risk (LBW) (in two reviews[109,111], and 1/5 higher risk (preterm) (in one review)[108]. By contrast, HBW was consistently associated with a higher risk of type 1 diabetes (4/5 meta-analyses in four reviews)[109-112]. LBW (4/4) and HBW (2/3) were both associated with higher risks of developing type 2 diabetes (in two reviews)[113,114].

Many (178) meta-analyses looked at whether size-at-birth was associated with cancer, including central nervous system tumours, leukaemia, lymphoma, and Wilms' tumour, among others. Among meta-analyses examining preterm, LBW, or SGA (in 13 reviews)[116-122,124,126-130], most (49/60) found no association. Among metanalysis of post-term, HBW, LGA, and continuous measurement of birthweight (in 15 reviews)[112,117-120,122-131], nearly half (50/118) of meta-analyses found an association. Evidence of the association between SGA or LGA and cancer outcomes[112,120,126,129] was mixed.

Meta-analyses of the effect of prematurity or LBW on metabolic syndrome, measured as a combination of chronic diseases outcomes, was also mixed [132].

Behavioural and mental health- Table 1 e

Very preterm, very LBW, preterm, LBW, and SGA neonates had an increased risk of anxiety and depression disorders in some meta-analyses (7/13 in six reviews) [133-137 138]. This was not observed for other psychological disorders (with 17/22 observing no association in three reviews) [134,135,139]. In some cases, extremely LBW was associated with harmful behavioural outcomes (7/18)[140], however, this association did not persist for very LBW or preterm neonates (18/21 no association in three reviews) [138,139,141]. IUGR neonates had a higher risk of adverse behavioural outcomes (1/1) [142]. Extremely preterm, very LBW, LBW and preterm had higher risks of low attention scores (13/14 meta-analyses in five reviews) [138,139,146-148], ADHD (25/32 meta-analyses in six review)) [140-142,149-151] , and autism (4/4 meta-analyses in three reviews) [140,152,153]. Two of the latter reviews examined IUGR and SGA as risk factors and showed no association for ADHD (1/1)[142] but an increased risk for autism (1/1) [153]. The association between preterm, LBW and SGA, and the risk of suicide and suicide attempt was inconsistent (3/5) [154]. Preterm and LBW were associated with lower physical activity among early childhood and older age populations (including adults) (2/2 in two reviews) [143,144]. Large size-at-birth/ post term was rarely examined as a risk factor for either behavioural or developmental themes.

Nutrition and growth- Table 1 f

Sixty-two meta-analyses (13 reviews) examined the effect of size-at-birth on body composition, namely height, weight, head circumference, body fat, body water, bone mineralization, body mass index (BMI), overweight and underweight[77,84,85,91,155-157,159-163 158]. The association between size-at-birth and BMI was mixed, with some meta-analyses showing small size increased the risk of high BMI among children aged under 10 years old (4/10), while others showed no effect among children aged 10-19 years (6/10) in two reviews[77,84]. Small size-at-birth (LBW, preterm and SGA) was consistently associated with higher risk of childhood stunting, wasting, and underweight (9/9)[160]. Evidence on the association between small size-at-birth and overweight/obesity was also mixed, with (2/7) meta-analyses showing no effect (in three reviews), (1/7) increased, and (4/7) decreased effect in three reviews[156,161,162]. LBW was associated with a decreased risk of obesity in children below age 13 years, but not in older children.

In 6 meta-analyses (two reviews), HBW babies had nearly twice the long-term risk of becoming overweight compared to normal birthweight children, irrespective of the age at assessment[161,162]. No meta-analyses examined this association for LGA.

Developmental (neurodevelopment, motor, cognitive and educational)- Table 1 g

Infants born with a small size-at-birth were at increased risk of neurological impairment, and thus of motor and cognitive developmental delays. Evidence on the association between small size-at-birth and brain structure was very consistent; all 26 meta-analyses (4 reviews) indicated that very LBW, very preterm and preterm were more likely to have brain-structure abnormalities, specifically smaller brain volume, reduced cerebral cortex surface area, regional cortical thinning, and brain white-matter injury [164-167].

The association between size-at-birth, specifically very LBW, very preterm and preterm, and poor visuomotor outcomes, was mixed in three reviews [146,147,168], with some meta-analyses showing no effect (3/11) or decreased visuomotor outcomes (7/11), and one meta-analysis showing preterm births had better visuomotor outcomes in neonates (1/11), though the same review showed no improvement in infants.

Small size-at-birth risk factors (extremely preterm, very preterm, preterm, late term extremely LBW, LBW, SGA)) were associated with an increased risk of cerebral palsy (13/14 meta-analyses including 9 with calculated prevalence ratio in four reviews) [170-173], with increasing gestational age being associated with a decreasing cerebral palsy risk (1/1) [170] . Thirty-three meta-analyses (eight reviews)[139,141,174-179], compared small-sized at birth (very LBW, very preterm, preterm, LBW, SGA) to normal birthweight neonates, and showed small-sized babies had increased motor impairment and developmental coordination disorders and decreased muscle strength (27/33). SGA was not associated with motor development (2/2) [174].

Meta-analyses also indicated that poor neurodevelopment led to cognitive deficits that persisted into adolescence and early adulthood. Small size-at-birth (extremely preterm, very preterm, preterm, extremely LBW, very LBW, LBW, SGA) was consistently associated with an increased risk of intellectual disability including of lower cognitive scores, processing speed, mental function, and shifting (cognitive flexibility), planning, and executive functions (32/38 meta-analyses in 13 reviews) [138,139,141,146,148,151,174,177,179,181-184], and of reduced working memory (5/5 meta-analyses in four reviews) [138,141,146,182]. Small size-at-birth babies (extremely preterm, extremely LBW, very preterm, very LBW, preterm, late term, LBW) had lower intelligence quotient (IQ) scores than normal size babies (42/44 meta-analyses in ten reviews)[141,146,177,181,183,185-189]; we noted that the association persisted among SGA and IUGR babies (3/4 meta-analyses in two reviews)[142,188]. However, continuous exposures of gestation age or birthweight did not appear to have an effect in 6/8meta-analyses (with no effect) in two reviews [142 188]. Small size-at-birth babies (extremely preterm, very preterm, very LBW, preterm, LBW, SGA) had lower language development (19/27 meta-analysis in seven reviews)[138,148,174,183,190-192], reading performance (decoding, word identification, comprehension) (25/28 meta-analyses in seven reviews) [138,141,184,190,191,193,194], and applied

mathematics school performance (knowledge, calculation, fluency, applied problem solving) (15/16 meta-analyses in five reviews) [138,141,173,184,193] compared to other babies.

UNDERSTANDING THE RELATIVE EFFECTS OF MATURITY (PRETERM) AND IUGR (SMALL FOR GESTATIONAL AGE) COMBINATIONS- Table 2

Only 11 reviews, and 73 meta-analyses within these, compared risks by size-for-gestational-age stratified by gestation (Table 2). Four reviews[46,48,160,174] (37 meta-analyses) compared term-SGA, preterm- SGA, and preterm-AGA to term-AGA babies. These ideal comparisons elucidated the relative magnitude of the effect of SGA matching on preterm/term status, and the relative magnitude of the effect of gestational age, matching on AGA status. For example, we see that when compared to term-AGA, the preterm-SGA group had the highest risk of neonatal mortality, RR=15.4, followed by preterm-AGA, RR=8.1, and term-SGA, RR=2.4 [46]. This pattern was also observed for cognitive outcomes (Table 2). By contrast for undernutrition (wasting, stunting), the preterm-SGA group had the highest increased risk. For example, when compared to term-AGA, the preterm-SGA risk for stunting was aOR=4.5, followed by term-SGA, aOR=2.4, and preterm-AGA aOR=1.9 (Table 2)[160]. The remaining seven studies (36 meta-analyses) either compared preterm-SGA, preterm-AGA to term-AGA only, or term-SGA to term-AGA or looked at term LBW compared to term normal body weight [42-45,84,87,172]. Table 2 also shows that binarizing gestational age may mask a u-shaped variation in risk and join a higher risk group (HBW) with a lower risk one (normal birthweight), inflating risk in the comparator. For example, very preterm (<34 weeks)-SGA neonates had very high mortality risks (OR=57.0) when compared to term-AGA, while for 34-36 week preterm-SGA births, the risks were lower (OR=19.9)[48].

EXPOSURES

EPT(<28wks)	Extremely preterm
ELBW(<1000g)	Extremely low birthweight
VPT(<32wks)	Very preterm
VLBW(<1500g)	Very low birthweight
PT (<37wks)	Preterm
LBW(<2500g)	Low birthweight
SGA(<10th percentile)	Small for gestational age
BW (cont.)	Birthweight continuous
GA (cont.)	Gestational age continuous
Post Term(>42 wks)	Post term
HBW(>4000g)	High birthweight
LGA(>90th percentile)	Large for gestational age

SYMBOLS in EXPOSURES

X	As defined in exposure

GA

26	GA<26 wks
v	GA- 28/29-31/32 wks
^	GA<34 wks
LLT	GA- 32-36 wks
LT	GA- 34/33 - 36 wks
ET	GA- 37-38 wks
41	GA≥41 wks

BW

X	1500<BW<2500g
o	1000<BW<1500g
^	BW<2000g
X_{GA}	Adjusted and unadjusted for GA
GA	BW adjusted for GA
~	BW 4260-4750g
~~	BW 4760-5250g

SGA

()	SGA<3rd, 5th, and 10th percentile/value x by SD for GA
(	SGA<3rd percentile/value x by SD for GA
BT	SGA between 3 to 10th percentile
P3	SGA< 3 percentile
P5	SGA< 5 percentile
XI	SGA with IUGR defined as per footnote
I	IUGR defined as per footnote

REFERENCE

◊	Reference category (2500-4000 g)
◊	Reference category (3260–3750g)
T	Reference category (37≤term≤41)

OUTCOMES

	Harmful effect
	No effect
	Beneficial effect
italic	Calculation/post review publication

aβ	Adjusted β Correlation
aHR	Adjusted Hazard Ratio
aOR	Adjusted Odds Ratio
aRR	Adjusted Relative Risk
aSMD	Adjusted Standardized Mean Difference
HR	Hazard Ratio
MD	Mean Difference
OR	Odds Ratio
RR	Relative Risk
SD	Standard Deviation
SMD	Standardized Mean Difference
SMDH	Standardized Mean Difference for Heteroscedastic Population Variances
WMD	Weighted Mean Difference

ABBREVIATIONS

ABPM	Ambulatory Blood Pressure Monitoring
ADHD	Attention Deficit Hyperactivity Disorder
AGTE	Ankara-Gelisim-Tarama-Envanteri (Ankara Developmental Screening Inventory)
APGAR	Appearance, Pulse, Grimace, Activity and Respiration
ASQ	Ages and Stages Questionnaire
BMI	Body Mass Index
BOTMP	Bruininks-Oseretsky Test of Motor Proficiency
BPD	Bronchopulmonary dysplasia
BSID	Bayley Scales of Infant Development
CELF	Clinical Evaluation of Language Fundamentals
CLD	Chronic Lung Disease
CNS	Central Nervous System
d	Day
DLCO	Diffusion Capacity of the Lung for Carbon Monoxide
EBP	Externalizing Behavioural Problems
eGFR	Estimated Glomerular Filtration Rate
ESRD	End-Stage Renal Disease
$FEF_{25-75\%}$	Forced Expiratory Flow between 25%-75% of Forced Vital Capacity
FEF_{75}	Forced Expiratory Flow at 75% of Forced Vital Capacity
FeNO	Fractional Exhaled Nitric Oxide
FEV_1	Forced Expiratory Volume in 1 second
FGR	Fetal Growth Retardation
FTFQ	Five to Fifteen Questionnaire
FVC	Forced Vital Capacity
GDS-II	Griffiths Developmental Scales Second Edition Motor Subscale
GFR	Glomerular Filtration Rate
h	Hour
HDL	High Density Lipoprotein
HOMA-IR	Homeostasis Model Assessmentof Insulin Resistance
HSCS	Health Status Classification System
hsPDA	Hemodynamically Significant Patent Ductus Arteriosus
HSU	Health Service Use
HUI2/HUI3	Health Utilities Index Mark 2, HUI3 Health Utilities Index Mark 3
IU	International Units
JLO	Judgment of Line Orientation
K-ABC	Kaufman Assessment Battery for Children
KTK	Körperkoordinationstest Für Kinder
LDL	Low Density Lipoprotein
m	Month
MABC	Movement Assessment Battery for Children
MEF_{50}	Maximum Expiratory Flow at 50% of Forced Vital Capacity
min	Minutes
mmHg	Millimeters of Mercury
MRSA	Methicillin-Resistant Staphylococcus Aureus
ms	Millisecond
MSCA	McCarthy Scales of Children's Ability
MVPT	Motor-Free Visual Perception Test Revised
NEPSY	Developmental NEuroPSYchological Assessment
NICU	Neonatal Intensive Care Unit
OGTT	Oral Glucose Tolerance Test
pc	Percentile
PDA	Patent Ductus Arteriosus
PDMS	Peabody Developmental Motor Scales
PEDI	Paediatric Evaluation of Disability Inventory
RSV	Respiratory Syncytial Virus
SDM	Seed-based d Mapping
Touwen	Touwen Neurological Examination
TVPS-R	Test of Visual Perceptual Skills Revised
VMI	Beery-Buktenica Developmental Test of Visual Motor Integration
VO_2	Volume of oxygen
Wee-FIM	Functional Independence Measure for Children
wks	Weeks
y	Year

Table 1 a- Associations between size-at-birth and mortality and hospitalization outcomes

Ref	Exposures (size at birth)												Population	Outcomes	Effect size [confidence interval], direction of association
	Small							Cont		Large					
	EPT (<28wks)	ELBW (<1000g)	VPT (<32wks)	VLBW (<1500g)	PT (<37wks)	LBW (<2500g)	SGA(<10th percentile)	BW (cont.)	GA (cont.)	Post Term (>42 wks)	HBW (>4000g)	LGA(>90th percentile)			
														Mortality	
46			X										<7d	Early Neonatal Mortality	RR= 34.77 [18.10, 66.79]
46					X								<7d	Early Neonatal Mortality	RR= 7.07 [3.50, 14.28]
46					LT								<7d	Early Neonatal Mortality	RR= 2.86 [1.75, 4.67]
46							X						<7d	Early Neonatal Mortality	RR= 1.98 [1.45, 2.70]
46							P3						<7d	Early Neonatal Mortality	RR= 2.81 [1.93, 4.11]
46			X										8-28d	Late Neonatal Mortality	RR= 24.68 [12.60, 48.36]
46					X								8-28d	Late Neonatal Mortality	RR= 5.53 [3.01, 10.17]
46					LT								8-28d	Late Neonatal Mortality	RR= 3.38 [2.37, 4.82]
46							X						8-28d	Late Neonatal Mortality	RR= 2.08 [1.41, 3.06]
46							P3						8-28d	Late Neonatal Mortality	RR= 2.84 [1.84, 4.38]
47	X												Neonates	Neonatal Mortality	*Prevalence ratio= 0.25*
47		X											Neonates	Neonatal Mortality	*Prevalence ratio= 0.5*
47			v										Neonates	Neonatal Mortality	*Prevalence ratio= 1.5*
46			X										<28d	Neonatal Mortality	RR= 28.82 [15.51, 53.56]
48			^										≤28d	Neonatal Mortality	OR= 58.74 [28.41, 121.45]
47				o									Neonates	Neonatal Mortality	*Prevalence ratio= 1.5*
46					X								<28d	Neonatal Mortality	RR= 6.82 [3.56, 13.07]
47					LT								Neonates	Neonatal Mortality	*Prevalence ratio= 0.75*
48					LT								≤28d	Neonatal Mortality	OR= 6.25 [3.03, 12.87]
46					LT								<28d	Neonatal Mortality	RR= 3.05 [2.02, 4.60]
47						X							Neonates	Neonatal Mortality	*Prevalence ratio= 1.5*
48						X							≤28d	Neonatal Mortality	OR= 7.64 [4.8, 12.15]
46							P3						<28d	Neonatal Mortality	RR= 2.41 [1.66, 3.50]
46							X						<28d	Neonatal Mortality	RR= 1.83 [1.34, 2.50]
48							X						≤28d	Neonatal Mortality	OR= 2.14 [1.33, 3.45]
47										X			Neonates	Neonatal Mortality	*Prevalence ratio= 0.25*
49											X		Neonates	Perinatal Death	OR= 1.77 [0.30, 10.34]
49											~		Neonates	Perinatal Death	OR= 0.73 [0.28, 1.90]
46			X										29-365d	Post Neonatal Mortality	RR= 5.71 [2.70, 12.06]
46					X								29-365d	Post Neonatal Mortality	RR= 2.50 [1.48, 4.22]
46					LT								29-365d	Post Neonatal Mortality	RR= 2.28 [1.62, 3.19]
46							X						29-365d	Post Neonatal Mortality	RR= 1.90 [1.32, 2.73]
46							P3						29-365d	Post Neonatal Mortality	RR= 2.15 [1.48, 4.22]
46			X										<365d	Infant Mortality	RR= 18.42 [8.93, 38.01]
46					X								<365d	Infant Mortality	RR= 4.65 [2.32, 9.33]
46					LT								<365d	Infant Mortality	RR= 2.49 [1.64, 3.78]
46							X						<365d	Infant Mortality	RR= 1.85 [1.28, 2.67]
46							P3						<365d	Infant Mortality	RR= 2.44 [1.53, 3.89]
50					X								<5y	Mortality	OR= 3.81 [1.68, 8.63]
51								X					13-100y	All-cause Mortality	HR= 0.94 [0.92, 0.97] per kg increase
51											◊		13-100y	All-cause Mortality	HR= 1.02 [0.99, 1.05]
														Hospitalization	
52					LT								<14d	Jaundice/Hyperbilirubinemia Admission	OR= 3.87 [2.63, 5.69]
52					LT								<28d	Nonjaundice Admission	OR= 1.35 [0.84, 2.18]
52					LT								≤1m	All-cause Health Service Use (HSU)	OR= 2.24 [1.17, 4.30]
52					LT								≤1y	All-cause Health Service Use (HSU)	OR= 1.73 [1.44, 2.07]
52					LT								1-6y	All-cause Health Service Use (HSU)	OR= 1.37 [1.28, 1.47]
52					ET								<28d	All-cause Health Service Use (HSU)	OR= 2.13 [1.90, 2.40]
52					ET								≤1y	All-cause Health Service Use (HSU)	OR= 1.12 [1.02, 1.23]
49											X		Neonates	Neonatal Intensive Care Unit (NICU) Admission	OR= 1.79 [1.41, 2.26]
49											~		Neonates	Neonatal Intensive Care Unit (NICU) Admission	OR= 2.02 [1.54, 2.63]

Jamaluddine Z, *et al. Arch Dis Child* 2023;0:1–14. doi: 10.1136/archdischild-2022-324884

Table 1 b- Associations between size-at-birth and neonatal and early childhood ill-health outcomes

Ref	Exposures (size at birth)												Population	Outcomes	Effect size [confidence interval], direction of association
	Small							Cont		Large					
	EPT (<28wks)	ELBW (<1000g)	VPT (<32wks)	VLBW (<1500g)	PT (<37wks)	LBW (<2500g)	SGA(<10th percentile)	BW (cont.)	GA (cont.)	Post Term (>42 wks)	HBW (>4000g)	LGA(>90th percentile)			
														Primarily neonatal outcomes	
														Congenital defects	
53							XI						<10d	Patent Ductus Arteriosus (PDA)	OR= 0.82 [0.70, 0.96]
53							X						<10d	Patent Ductus Arteriosus (PDA)	OR= 0.81 [0.66, 0.98]
53							P5						<10d	Patent Ductus Arteriosus (PDA)	OR= 0.63 [0.26, 1.52]
53							P3						<10d	Patent Ductus Arteriosus (PDA)	OR= 1.09 [0.70, 1.71]
53							XI						<10d	Hemodynamically Significant PDA and PDA Treatment	OR= 0.87 [0.72, 1.04]
53							XI						<10d	Hemodynamically Significant PDA	OR= 0.92 [0.71, 1.20]
53							XI						<10d	PDA Requiring Treatment	OR= 0.82 [0.64, 1.06]
														Asphyxia	
54					X								1-5min life	Low APGAR Score, Neonatal Asphyxia	aOR= 3.98 [3.00, 5.29]
54						X							1-5min life	Low APGAR Score, Neonatal Asphyxia	aOR= 5.17 [2.62, 10.22]
49											X		Neonates	Neonatal Asphyxia	OR= 2.88 [1.34, 6.22]
49											~		Neonates	Neonatal Asphyxia	OR= 2.45 [0.24, 25.59]
														Retinopathy	
55	X												<28d	Retinopathy of Prematurity	OR= 6.26 [4.86, 8.06]
55		X											<28d	Retinopathy of Prematurity	OR= 5.8 [4.8, 6.8]
55				X									<28d	Retinopathy of Prematurity	OR= 4.81 [3.77, 6.13]
55							X						<28d	Retinopathy of Prematurity	OR= 1.2 [0.9, 1.80]
														Birth Traumas	
49											X		Neonates	Shoulder Dystocia	OR= 7.18 [2.06, 25.00]
49											~		Neonates	Shoulder Dystocia	OR= 7.33 [5.13, 10.48]
49											~~		Neonates	Shoulder Dystocia	OR= 16.16 [7.62, 34.26]
49											X		Neonates	Other Birth Trauma	OR= 2.99 [1.28, 7.02]
49											~		Neonates	Other Birth Trauma	OR= 25.69 [3.26, 32.13]
49											X		Neonates	Erb's Palsy	OR= 3.45 [1.56, 7.61]
														Primarily children outcomes	
														Caries/Oral Health	
56					X								2–72m	Dental Caries	*Prevalence Ratio= 1.30*
57					X								1-6y	Dental Caries	OR= 1.59 [1.36, 1.87]
57					X								≤3y	Dental Caries	OR= 0.90 [0.59, 1.37]
56						X							2-72m	Dental Caries	*Prevalence Ratio= 1.21*
57						X							≤3y	Dental Caries	OR= 0.78 [0.24, 2.51]
57						X							6m-6y	Dental Caries	OR= 1.12 [0.94, 1.33]
58					X								9-10y	Molar Incisor Hypomineralisation	OR= 1.57 [1.07, 2.31]
59					X								72-336m	Molar Incisor Hypomineralisation	OR= 1.65 [1.14, 2.38]
58						X							8.4-12y	Molar Incisor Hypomineralisation	OR= 3.25 [2.28, 4.62]
59					X								9-156m	Enamel Hypoplasia	OR= 6.63 [3.61, 12.18]
59					X								9-156m	Enamel Opacity	OR= 1.98 [1.21, 3.25]
59					X								9-156m	Developmental Defects of Enamel	OR= 3.27 [2.02, 5.30]
59					X								9-156m	Developmental Defects of Enamel Primary Dentition	OR= 4.07 [2.49, 6.65]
59					X								9-156m	Developmental Defects of Enamel Permanent Dentition	OR= 1.57 [0.88, 2.77]
														Infection/Sepsis	
60					X								<28d	Neonatal Sepsis	OR= 3.36 [2.50, 4.54]
60						X							<28d	Neonatal Sepsis	OR= 1.42 [1.07, 1.88]
61			X										Neonates	Methicillin-Resistant Staphylococcus Aureus (MRSA) Infection	OR= 2.67 [1.35, 5.27]
61				X									Neonates	Methicillin-Resistant Staphylococcus Aureus (MRSA) Infection	OR= 2.63 [1.25, 5.55]
62			X										0-5y	Respiratory Syncytial Virus Acute Lower Respiratory Infection	OR= 2.79 [2.19, 3.55]
50			X										<5y	Respiratory Syncytial Virus Acute Lower Respiratory Infection	OR= 5.90 [2.35, 14.83]
50					X								<5y	Respiratory Syncytial Virus Acute Lower Respiratory Infection	OR= 2.73 [1.92, 3.87]
62					X								0-5y	Respiratory Syncytial Virus Acute Lower Respiratory Infection	OR= 1.96 [1.44, 2.67]
62						X							0-5y	Respiratory Syncytial Virus Acute Lower Respiratory Infection	OR= 1.91 [1.45, 2.53]
63					X								0-5y	Pneumonia Acute Lower Respiratory Infection	OR= 1.9 [1.3, 2.8]
63						X							0-5y	Pneumonia Acute Lower Respiratory Infection	OR= 3.18 [1.02, 9.90]
52					LT								<1y	Infection Admission	OR= 1.44 [1.03, 2.00]

Jamaluddine Z, *et al. Arch Dis Child* 2023;0:1–14. doi: 10.1136/archdischild-2022-324884

Ref	Exposures (size at birth)												Population	Outcomes	Effect size [confidence interval], direction of association
	Small							Cont		Large					
	EPT (<28wks)	ELBW (<1000g)	VPT (<32wks)	VLBW (<1500g)	PT (<37wks)	LBW (<2500g)	SGA(<10th percentile)	BW (cont.)	GA (cont.)	Post Term (>42 wks)	HBW (>4000g)	LGA(>90th percentile)			
														Epilepsy	
64					X								0-85y	Epilepsy	OR= 2.16 [1.80, 2.58]
64					X								<5y	Epilepsy	OR= 3.01 [1.95, 4.66]
64					X								≥5y	Epilepsy	OR= 2.01 [1.73, 2.34]
64										41			0-85y	Epilepsy	OR= 1.05 [0.98, 1.12]
														Quality of life	
65		X											8-28y	Health Utility (HUI2, HUI3)	β= -0.068 [-0.098, -0.038]
65				X									8-28y	Health Utility (HUI2, HUI3)	β= -0.030 [-0.030, -0.030]
65					X								5-28y	Health Utility (HUI2, HUI3)	β= -0.066 [-0.098, -0.035]
66									X				3-36m	Total Sleep Duration	β= -0.11 [-0.15, -0.06] per wk increase
66									X				3-36m	Night Sleep Duration	β= -0.05 [-0.08, -0.02] per wk increase
66									X				3-36m	Nap Duration	β= -0.04 [-0.06, -0.01] per wk increase

(53) symbol (XI) IUGR is defined as BW<10th percentile or BW<5th percentile or BW<3rd percentile (or -2 standard deviations); or the combination of BW percentile; or as ultrasound fetal weight

Table 1 c-Associations between size-at-birth and allergies and lung related ill-health outcomes

Ref	Exposures (size at birth)											Population	Outcomes	Effect size [confidence interval], direction of association
	Small							Cont		Large				
	EPT (<28wks)	ELBW (<1000g)	VPT (<32wks)	VLBW (<1500g)	PT (<37wks)	LBW (<2500g)	SGA(<10th percentile)	BW (cont.)	GA (cont.)	Post Term (>42 wks)	HBW (>4000g)	LGA(>90th			
													Atopic dermatitis	
67			X									1-27y	Atopic dermatitis (Eczema)	RR= 0.78 [0.72, 0.85]
67					X							1-27y	Atopic dermatitis (Eczema)	RR= 0.87 [0.83, 0.91]
67					X							≤2y	Atopic dermatitis (Eczema)	RR= 0.92 [0.59, 1.41]
67					X							>2-5y	Atopic dermatitis (Eczema)	RR= 0.88 [0.84, 0.91]
67					X							>5y	Atopic dermatitis (Eczema)	RR= 0.87 [0.83, 0.90]
67					LT							1-27y	Atopic dermatitis (Eczema)	RR= 0.88 [0.77, 1.00]
68						◊						1-8y	Atopic dermatitis (Eczema)	OR= 0.68 [0.63, 0.75]
69								X				≤6-16y	Atopic dermatitis (ever)	OR= 1.17 [1.04, 1.32] per kg increase
69								X				6m-11y	Atopic dermatitis (current)	OR= 1.03 [0.87, 1.22] per kg increase
69								X				≤2y	Atopic dermatitis (ever or current)	OR= 1.34 [1.08, 1.68] per kg increase
68											◊	1-8y	Atopic dermatitis (Eczema)	OR= 1.09 [1.02, 1.17]
													Other Allergies	
69								X				18m-10y	Food Allergy	OR= 1.44 [1.04, 1.99]
69								X				≤16y	Allergic Rhinitis (ever)	OR= 1.02 [0.91, 1.14]
69								X				4-10y	Allergic Rhinitis (current)	OR= 0.92 [0.69, 1.23]
													Lung Function	
70			X	X								16-33y	FEV_1	MD= -0.78 [-0.96, -0.61]
70			X	X								16-33y	FVC	MD= -0.25 [-0.40, -0.10]
70			X	X								16-33y	FEV_1/FVC	MD= -0.74 [-0.85, -0.64]
70			X	X								16-33y	FEF_{25-75}	MD= -0.88 [-1.12, -0.65]
71			X									6-14y	%FEV_1 (without BPD)	MD= -7.41 [-9.46, -5.37]
71			X									6-14y	%FEV_1 (mild to severe BPD)	MD= -10.54 [-12.90, -8.19]
71			X									6-14y	%FEV_1 (moderate to severe BPD)	MD= -17.76 [-20.04, -15.47]
71			X									6-14y	FVC (without BPD)	MD= -3.0 [-7.8, 1.7]
71			X									6-14y	FVC (mild BPD)	MD= -4.2 [-9.4, 1.0]
71			X									6-14y	FVC (moderate to severe BPD)	MD= -6.3 [-12.6, -0.1]
71			X									6-14y	FEV_1 (without BPD)	MD= -5.6 [-10.6, -0.7]
71			X									6-14y	FEV_1 (mild BPD)	MD= -9.9 [-15.3, -4.4]
71			X									6-14y	FEV_1 (moderate to severe BPD)	MD= -12.1 [-18.6, -5.6]
71			X									6-14y	FEV_1/FVC (without BPD)	MD= -2.8 [-6.2, 0.7]
71			X									6-14y	FEV_1/FVC (mild BPD)	MD= -5.5 [-9.3, -1.7]
71			X									6-14y	FEV_1/FVC (moderate to severe BPD)	MD= -6.8 [-11.3, -2.2]
71			X									6-14y	MEF_{50} (without BPD)	MD= -13.5 [-23.3, -3.7]
71			X									6-14y	MEF_{50} (mild BPD)	MD= -22.0 [-32.7, -11.2]
71			X									6-14y	MEF_{50} (moderate to severe BPD)	MD= -26.6 [-39.5, -13.8]
71			X									6-14y	DLCO (without BPD)	MD= -1.8 [-7.7, 4.1]
71			X									6-14y	DLCO (mild BPD)	MD= -8.0 [-14.7, -1.4]
71			X									6-14y	DLCO (moderate to severe BPD)	MD= -9.9 [-17.6, -2.2]
72					X							7-19y	%FEV_1 (without BPD cases)	MD= -7.15 [-8.73, -5.58]
72					X							7-19y	%FEV_1 (including BPD cases)	MD= -8.70 [-10.98, -6.42]
73					X							3.9-19.1y	FEV_1	β= -0.20 [-0.26, -0.14]
73					X							3.9-19.1y	FEV_1/FVC	β= -0.15 [-0.21, -0.09]
73					X							3.9-19.1y	FEF_{75}	β= -0.19 [-0.27, -0.11]
73						X						3.9-19.1y	FEV_1	β= -0.29 [-0.38, -0.21]
73						X						3.9-19.1y	FEV_1/FVC	β= -0.16 [-0.25, -0.08]
73						X						3.9-19.1y	FEF_{75}	β= -0.17 [-0.26, -0.08]
70									X			16-33y	FEV_1	MD= 0.08 [0.04, 0.12] per wk increase
70									X			16-33y	FVC	MD= 0.04 [0.004, 0.07] per wk increase
70									X			16-33y	FEV_1/FVC	MD= 0.06 [0.03, 0.09] per wk increase
70									X			16-33y	$FEF_{25-75\%}$	MD= 0.06 [0.03, 0.10] per wk increase
													Lung Diseases (Asthma/wheezing)	
74			X									9m-12y	Wheezing Disorders	OR= 3.00 [2.61, 3.44]
74					X							0-14y	Wheezing Disorders	OR= 1.71 [1.57, 1.87]
74					X							<5y	Wheezing Disorders	OR= 1.70 [1.49, 1.94]
74					X							≥5y	Wheezing Disorders	OR= 1.71 [1.44, 2.03]
74					X							0.5-11y	Wheezing	OR= 1.63 [1.40, 1.90]

Ref	Exposures (size at birth)											Population	Outcomes	Effect size [confidence interval], direction of association
	Small							Cont		Large				
	EPT (<28wks)	ELBW (<1000g)	VPT (<32wks)	VLBW (<1500g)	PT (<37wks)	LBW (<2500g)	SGA(<10th percentile)	BW (cont.)	GA (cont.)	Post Term (>42 wks)	HBW (>4000g)	LGA(>90th			
74					X								0-14y	Asthma	OR= 1.76 [1.57, 1.96]
75					X								1-4y	Wheezing	OR= 1.34 [1.25, 1.43]
76					X								1-31y	Asthma	aOR= 1.36 [1.30, 1.43]
76					X								<10y	Asthma	OR= 1.40 [1.11, 1.90]
76					X								≥10y	Asthma	OR= 1.19 [0.93, 1.51]
73					X								3.9-19.1y	Asthma	aOR= 1.34 [1.15, 1.57]
77					X								0-6y	Asthma	HR= 1.29 [0.74, 2.23]
75					X								5-10y	Asthma	OR= 1.40 [1.18,1.67]
74					LT								9m-11y	Wheezing Disorders	OR= 1.49 [1.34, 1.66]
78						X							6m-16y	Wheezing Disorders	OR= 1.60 [1.39, 1.85]
78						X							1-16y	Asthma	OR= 1.60 [1.36, 1.89]
78						X							6m-16y	Wheezing	OR= 1.50 [0.95, 2.39]
75						X							1-4y	Wheezing	OR= 1.10 [1.00, 1.21]
79						X							<3-16y	Asthma	Risk ratio= 1.15 [1.08, 1.22]
79						X							≤10y	Asthma	Risk ratio= 1.17 [1.06, 1.28]
79						X							>10y	Asthma	Risk ratio= 1.15 [1.07, 1.23]
73						X							3.9-19.1y	Asthma	aOR= 1.32 [1.07,1.62]
77						X							0-6y	Asthma	HR= 1.43 [0.76, 2.70]
80						X							Children	Asthma	OR= 1.28 [1.09, 1.50]
75						X							5-10y	Asthma	OR= 1.13 [1.01, 1.27]
80						◊							Children	Asthma	OR= 1.34 [1.13, 1.60]
78						◊							1-18y	Wheezing Disorders	OR= 1.37 [1.05, 1.79]
73							X						3.9-19.1y	Asthma	aOR= 1.18 [1.01 , 1.37]
73								X					3.9-19.1y	Asthma	aOR= 0.94 [0.90,0.97] per 500g increase
73								X					3.9-19.1y	Asthma	aOR= 0.98 [0.94, 1.03] per SDS increase
74									X				0.5-14y	Wheezing Disorders	aOR= 0.94 [0.92, 0.96] per wk increase
74									X				<5y	Wheezing Disorders	aOR= 0.96 [0.94, 0.97] per wk increase
74									X				≥5y	Wheezing Disorders	aOR= 0.93 [0.92, 0.95] per wk increase
74									X				9m-14y	Wheezing Disorders (parental reported)	aOR= 0.95 [0.92, 0.97] per wk increase
74									X				0.5-11y	Wheezing Disorders (doctor diagnosed)	aOR= 0.93 [0.91, 0.96] per wk increase
74									X				0.5-6y	Wheezing	aOR= 0.95 [0.93, 0.96] per wk increase
74									X				1-14y	Asthma	aOR= 0.93 [0.90, 0.96] per wk increase
73									X				3.9-19.1y	Asthma	aOR= 0.94 [0.92, 0.97] per wk increase
77										X			0-6y	Asthma	HR= 1.02 [0.71, 1.47]
78											X		1-18y	Wheezing Disorders	OR= 1.02 [0.99, 1.04]
78											X		1-18y	Asthma	OR= 1.33 [0.95, 1.85]
81											X		6m-31y	Asthma	RR= 1.2 [1.1, 1.3]
77											X		0-6y	Asthma	HR= 0.93 [0.72, 1.21]
80											X		Children	Asthma	OR= 1.06 [0.93, 1.21]
80											◊		Children	Asthma	OR= 1.04 [0.92, 1.19]
52					LT								2-6y	Asthma Admission	HR= 1.22 [1.13, 1.32]
														Other lung related outcomes	
52					LT								<1y	Respiratory Problem Admission	OR= 2.02 [1.26, 3.23]
82					X								6-33y	Fractional Exhaled Nitric Oxide (FeNO) (ppb)	MD= -0.74 [-1.88, 0.41]
82					X								6-33y	Fractional Exhaled Nitric Oxide (FeNO) with CLD (ppb)	MD= -2.82 [-5.87, 0.22]
83					X								5-22y	Bronchial Hyper-Responsiveness	OR= 1.88 [1.32, 2.66]
83					X								7-22y	Bronchial Hyper-Responsiveness (after methacholine challenge)	OR= 1.89 [1.12, 3.19]
83					X								6-14y	Bronchial Hyper-Responsiveness (after an exercise test)	OR= 2.59 [1.50, 4.50]
83					X								5-22y	Bronchial Hyper-Responsiveness had CLD	OR= 4.54 [2.68, 7.69]
83					X								7-22y	Bronchial Hyper-Responsiveness had CLD (after methacholine ch	OR= 4.35 [2.36, 8.03]
83					X								6-14y	Bronchial Hyper-Responsiveness had CLD(after an exercise test)	OR= 5.13 [1.82, 14.47]

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Table 1 d-Associations between size-at-birth and chronic ill-health outcomes

Ref	Exposures (size at birth)													Population	Outcomes	Effect size [confidence interval], direction of association
	Small							Cont		Large						
	EPT (<28wks)	ELBW (<1000g)	VPT (<32wks)	VLBW (<1500g)	PT (<37wks)	LBW (<2500g)	SGA(<10th percentile)	BW (cont.)	GA (cont.)	Post Term (>42 wks)	HBW (>4000g)	LGA(>90th				
															Hypertension	
84	X													Child/Adult	Systolic Blood Pressure (mmHg)	MD= 2.31 [0.27, 4.36]
84	X													Child/Adult	Diastolic Blood Pressure (mmHg)	MD= 0.61 [-0.28, 1.50]
85		X	^											11y	Systolic Blood Pressure (mmHg)	*MD= 4.6 (0.73)*
85		X	^											11y	Systolic Blood Pressure (pc)	*MD= 9.8 (1.2)*
85		X	^											11y	Diastolic Blood Pressure (pc)	*MD= 9.3 (5.9)*
85		X	^											11y	Diastolic Blood Pressure (mmHg)	*MD= 2.3 (0.9)*
85		X	^											11y	Blood Pressure >95 pc	OR= 1.37, *p*= 0.049
84			X											Child/Adult	Systolic Blood Pressure (mmHg)	MD= 2.12 [1.25, 3.00]
84			X											Child/Adult	Diastolic Blood Pressure (mmHg)	MD= 0.45 [-0.22, 1.12]
86			X	X										7-20.7y	Systolic Blood Pressure (mmHg)	MD= 3.30 [2.43, 4.18]
86				X	X									5-30y	Systolic Blood Pressure (mmHg)	MD= 2.50 [1.67, 3.32]
84					X									5-45y	Systolic Blood Pressure (mmHg)	MD= 3.26 [2.08, 4.44]
84					X									<10y	Systolic Blood Pressure (mmHg)	MD= 1.03 [-1.13, 3.18]
84					X									<10-19y	Systolic Blood Pressure (mmHg)	MD= 2.00 [1.17, 2.83]
84					X									10-19y	Systolic Blood Pressure (mmHg)	MD= 3.24 [0.90, 5.57]
87					X									6.6-49y	Systolic Blood Pressure (mmHg)	SMD= 0.35 [0.22, 0.48]
87					X									10.6-26y	ABPM-Systolic Blood Pressure	SMD= 0.33 [0.18, 0.49]
87					X									10.6-35.8y	ABPM-Systolic Blood Pressure Daytime	SMD= 0.35 [0.20, 0.49]
87					X									10.6-35.8y	ABPM-Systolic Blood Pressure Night-time	SMD= 0.22 [0.07, 0.37]
84					X									5-45y	Diastolic Blood Pressure (mmHg)	MD= 1.32 [0.61, 2.04]
84					X									<10y	Diastolic Blood Pressure (mmHg)	MD= 1.46 [0.33, 2.60]
84					X									<10-19y	Diastolic Blood Pressure (mmHg)	MD= -0.98 [-0.41, 1.45]
84					X									10-19y	Diastolic Blood Pressure (mmHg)	MD= 1.14 [-0.36, 2.63]
87					X									6.6-49y	Diastolic Blood Pressure	SMD= 0.33 [0.20, 0.47]
87					X									10.6-26y	ABPM-Diastolic Blood Pressure	SMD= 0.23 [0.07, 0.39]
87					X									10.6-35.8y	ABPM-Diastolic Blood Pressure Daytime	SMD= 0.19 [0.05, 0.33]
87					X									10.6-35.8y	ABPM-Diastolic Blood Pressure Night-time	SMD= 0.19 [-0.01, 0.38]
88						X								4-84y	Systolic Blood Pressure (mmHg)	MD= 2.58 [1.51, 3.64]
88						X								5-84y	Diastolic Blood Pressure (mmHg)	MD= 1.01 [0.19, 1.83]
89								X						Child/Adult	Systolic Blood Pressure (mmHg)	aβ= -2.00 [-2.49, -1.50] per kg increase
89								X						<18y	Systolic Blood Pressure (mmHg)	aβ= -1.64 [-2.16, -1.12] per kg increase
90								X						0-71y	Systolic Blood Pressure (mmHg)	β= -1.38 [-1.66, -1.10] per kg increase
91								X_{GA}						8.1-38.1y	Systolic Blood Pressure (mmHg)	β= -2.02 [-3.07, -0.97]
91								GA						8.1-38.1y	Systolic Blood Pressure (mmHg)	β= -0.84 [-3.55, 1.87]
91								X						8.1-38.1y	Systolic Blood Pressure (mmHg)	β= -2.30 [-3.53, -1.07]
91								X						14.5-32.8y	Diastolic Blood Pressure (mmHg)	β= -0.74 [-1.64, 0.10]
92											X			16-70y	Systolic Blood Pressure (Females) (mmHg/kg)	β= 3.27 [1.39, 5.16]
92											X			16-70y	Systolic Blood Pressure (Males) (mmHg/kg)	β= 0.42 [0.02, 0.83]
92											◊			16-70y	Systolic Blood Pressure (Females) (mmHg/kg)	β= 2.96 [0.85, 5.07]
92											◊			16-70y	Systolic Blood Pressure (Males) (mmHg/kg)	β= 0.44 [-0.02, 0.89]
88											X			5-84y	Systolic Blood Pressure (mmHg)	MD= -2.08 [-2.98, -1.17]
88											X			5-84y	Diastolic Blood Pressure (mmHg)	MD= -0.37 [-1.19, 0.45]
93											◊	X		6-59y	Systolic Blood Pressure (mmHg)	WMD= -0.25 [-0.92, 0.42]
93											◊	X		6-11y	Systolic Blood Pressure (mmHg)	WMD= 1.40 [0.20, 2.61]
93											◊	X		6-60y	Diastolic Blood Pressure (mmHg)	WMD= 0.20 [-0.23, 0.62]
93											◊	X		6-12y	Diastolic Blood Pressure (mmHg)	WMD= 0.96 [0.57, 1.35]
94							XI							0.04-48.6y	Blood Pressure (mmHg)	MD= -0.56 [-1.72, 0.60]
94							XI							<18y	Blood Pressure (mmHg)	MD= -0.54 [-1.88, 0.81]
95								X						7-50y	Blood pressure (mmHg): Unpaired twins	aβ= -2.0 [-3.2, -0.8] per kg increase
95								X						7-50y	Blood pressure (mmHg): Paired twins	aβ= -0.4 [-1.5, 0.7] per kg increase
88						X								6-84y	Hypertension	OR= 1.21 [1.13, 1.30]
88											X			12-84y	Hypertension	OR= 0.78 [0.71, 0.86]
93											◊	X		4-80y	Hypertension	RR= 1.00 [0.93, 1.06]
93											◊	X		4-12y	Hypertension	RR= 1.18 [1.05, 1.32]
															Hypercholesterolaemia	
84					X									8-35.7y	Total Cholesterol (mmol/L)	SMD= 0.12 [-0.05, 0.30]
84					X									10-19y	Total Cholesterol (mmol/L)	SMD= -0.02 [-0.10, 0.07]

Ref	Exposures (size at birth)												Population	Outcomes	Effect size [confidence interval], direction of association
	Small							Cont		Large					
	EPT (<28wks)	ELBW (<1000g)	VPT (<32wks)	VLBW (<1500g)	PT (<37wks)	LBW (<2500g)	SGA(<10th percentile)	BW (cont.)	GA (cont.)	Post Term (>42 wks)	HBW (>4000g)	LGA(>90th			
91								X_{GA}					16.5-50.4y	Cholesterol (mmol/L)	β= -0.07 [-0.11, -0.04]
96								X					0-84y	Cholesterol (mmol/L)	aWMD= -0.036 [-0.047, -0.025]
97								X					13-16y	Total Cholesterol (mmol/L)	β= -0.061 [-0.131, 0.008]per kg increase
97								X					0-70y	Total Cholesterol (mmol/L)	β= -0.048 [-0.078, -0.018]per kg increase
98								X					6-70y	Total Cholesterol: Males (mmol/L)	aβ= -0.04 [-0.07, -0.02] per kg increase
98								X					6-70y	Total Cholesterol: Females (mmol/L)	aβ= -0.01 [-0.04, 0.02]] per kg increase
99								X					16-75y	Total Cholesterol (mmol/L)	aβ= 0.038 [0.00984, 0.0661] per kg lower
84					X								8-35.7y	High Density Lipoprotein (HDL) (mmol/L)	SMD= -0.00 [-0.12, 0.11]
84					X								10-19y	High Density Lipoprotein (mmol/L)	SMD= 0.00 [-0.08, 0.08]
84					X								9-35.7y	Low Density Lipoprotein (LDL) (mmol/L)	SMD= 0.02 [-0.10, 0.14]
84					X								8-45y	Triglycerides (mmol/L)	SMD= 0.03 [-0.06, 0.12]
84					X								10-19y	Triglycerides (mmol/L)	SMD= 0.02 [-0.11, 0.07]
99								X					16-75y	Total Triglycerides (mmol/L)	aβ= 0.043 [0.0301, 0.0563] per kg lower
99								X					16-75y	Total Phospholipids (mmol/L)	aβ= 0.015 [0.000414, 0.0298] per kg lower
99								X					16-75y	Total Fatty acids (mmol/L)	aβ= 0.197 [0.122, 0.272] per kg lower
100								X					0.9-75.8y	Circulating Cortisol Levels (nmol/L)	β= 25.3 [5.9, 44.8] (per 1 kg lowe)
99								X					16-75y	Saturated Fatty Acids (mmol/L)	aβ= 0.082 [0.0521, 0.112] per kg lower
														Coronary Heart Disease and Heart Function	
101			X										>1-35y	Left Ventricular Ejection Fraction (%)	WMD= 1.15 [0.35 , 1.95]
101			X										<28d	Left Ventricular Ejection Fraction (%)	WMD= -2.48 [-5.78 , 0.82]
101			X										≥28d-1y	Left Ventricular Ejection Fraction (%)	WMD= -1.97 [-4.38, 0.44]
101			X										>1-≤14y	Left Ventricular Ejection Fraction (%)	WMD= 1.67 [-0.48, 3.82]
101			X										>1-35y	Left Ventricular Peak Systolic Tissue Velocity (cm/s)	WMD= -0.61 [-0.88, -0.34]
101			X										<28d	Left Ventricular Peak Systolic Tissue Velocity (cm/s)	WMD= -0.93 [-1.15, -0.71]
101			X										≥28d-1y	Left Ventricular Peak Systolic Tissue Velocity (cm/s)	WMD= -0.10 [-0.60, 0.40]
101			X										>1-≤14y	Left Ventricular Peak Systolic Tissue Velocity (cm/s)	WMD= -0.73 [-1.05, -0.41]
101			X										>1-35y	Right Ventricular Strain (%)	WMD= 3.02 [2.23, 3.82]
101			X										<28d	Right Ventricular Strain (%)	WMD= 3.87 [1.54, 6.20]
101			X										≥28d-1y	Right Ventricular Strain (%)	WMD= 3.01 [0.81, 5.22]
101			X										>1-35y	Left Ventricular Peak Early Diastolic Tissue velocity(cm/s)	WMD= -1.12 [-1.54, -0.70]
101			X										<28d	Left Ventricular Peak Early Diastolic Tissue velocity(cm/s)	WMD= -1.93 [-2.46, -1.39]
101			X										≥28d-1y	Left Ventricular Peak Early DiastolicTissue velocity(cm/s)	WMD= -1.48 [-2.63, -0.32]
101			X										>1-≤14y	Left Ventricular Peak Early Diastolic Tissue velocity(cm/s)	WMD= -1.28 [-1.82, -0.74]
102					X								3m-16y	Carotid Intima-Media Thickness (cm)	SMD= 0.03 [-0.17, 0.22]
102					X								2-16y	Carotid Intima-Media Thickness (cm)	SMD= 0.02 [-0.20, 0.25]
101					X								>1-35y	Left Ventricular Ejection Fraction (%)	WMD= 0.79 [0.02, 1.55]
101					X								<28d	Left Ventricular Ejection Fraction (%)	WMD= -2.89 [-5.18, -0.61]
101					X								≥28d-1y	Left Ventricular Ejection Fraction (%)	WMD= -1.58 [-3.60, 0.44]
101					X								>1-≤14y	Left Ventricular Ejection Fraction (%)	WMD= 1.67 [-0.48, 3.82]
101					X								>1-35y	Left Ventricular Peak Systolic Tissue Velocity (cm/s)	WMD= -0.34 [-0.83, 0.14]
101					X								<28d	Left Ventricular Peak Systolic Tissue Velocity (cm/s)	WMD= -0.81 [-1.13, -0.49]
101					X								≥28d-1y	Left Ventricular Peak Systolic Tissue Velocity (cm/s)	WMD= 0.13 [-0.52, 0.78]
101					X								>1-≤14y	Left Ventricular Peak Systolic Tissue Velocity (cm/s)	WMD= -0.73 [-1.05, -0.41]
101					X								<28d	Right Ventricular Strain (%)	WMD= 2.94 (0.54, 5.35)
101					X								≥28d-1y	Right Ventricular Strain (%)	WMD= 2.73 [0.89, 4.57]
101					X								>1-35y	Right Ventricular Strain (%)	WMD= 3.02 [2.23, 3.82]
101					X								>1-35y	Left Ventricular Peak Early Diastolic Tissue velocity(cm/s)	WMD= -1.05 [-1.46, -0.65]
101					X								<28d	Left Ventricular Peak Early Diastolic Tissue velocity (cm/s)	WMD= -1.19 [-1.76, -0.62]
101					X								≥28d-1y	Left Ventricular Peak Early Diastolic Tissue velocity(cm/s)	WMD= -0.87 [-1.50, -0.23]
101					X								>1-≤14y	Left Ventricular Peak Early Diastolic Tissue velocity(cm/s)	WMD= -1.28 [-1.82, -0.74]
102							X						0-16y	Left Ventricular Peak Early Diastolic Tissue velocity (cm/s)	SMD= 0.40 [0.15, 0.64]
102							X						0-1y	Left Ventricular Peak Early Diastolic Tissue velocity	SMD= 0.63 [-0.02, 1.27]
102							X						2-16y	Left Ventricular Peak Early Diastolic Tissue velocity(cm/s)	SMD= 0.31 [0.06, 0.55]
102							XI						0-16y	Carotid Intima-Media Thickness (cm)	SMD= 0.35 [-0.06, 0.77]
102								X					0-16y	Carotid Intima-Media Thickness (cm)	β= -0.06 [-0.19, 0.08]
103								X					11-85y	Non-fatal and Fatal Ischemic Heart Disease	aRR= 0.84 [0.81, 0.88] per 1kg increase
103								X					15-85y	Fatal Ischemic Heart Disease	aRR= 0.84 [0.80, 0.88] per kg increase
104								X					11-85y	Combined for Non-Fatal And Fatal CHD	RR= 0.83 [0.80, 0.86] per kg increase
101													11-85y	Additional data on paper 101 in appendix	Additional data on paper 101 in appendix

Ref	Exposures (size at birth)												Population	Outcomes	Effect size [confidence interval], direction of association
	Small							Cont		Large					
	EPT (<28wks)	ELBW (<1000g)	VPT (<32wks)	VLBW (<1500g)	PT (<37wks)	LBW (<2500g)	SGA(<10th percentile)	BW (cont.)	GA (cont.)	Post Term (>42 wks)	HBW (>4000g)	LGA(>90th			
														Kidney Related Diseases	
105		X											5.3-20.7y	Glomerular Filtration Rate (mL/min/1.73m^2) (%)	MD= -13 [-8, -25]
85		X	^										11y	Estimated Glomerular Filtration Rate (mL/min/1.73m^2)	*MD= -11.27 (1.27)*
85		X	^										11y	Glomerular Filtration Rate <90 (mL/min/1.73m^2)	*Prevalence ratio= 3.08 , p<0.001*
87					X								8-14y	Glomerular Filtration Rate	SMD= -0.54 [-0.85, -0.22]
106						X							6.1-41y	Glomerular Filtration Rate (mL/min/1.73m^2)	WMD= -4.55 [-9.08, -0.23]
106								X					6-64y	Estimated Glomerular Filtration Rate (mL/min/1.73m^2)	OR= 2.09 [1.33, 2.85] per kg increase
85		X	^										11y	Cystatin (mg/L)	*MD= 0.085 (0.031)*
85		X	^										11y	High Serum Cystatin C Level >0.95 mg/L	*Prevalence ratio= 3.13 , p<0.001*
87					X								10.7-23.2y	Cystatin-C	SMD= 0.36 [-0.12, 0.85]
85		X	^										11y	Absolute Left Kidney Length (cm)	*MD= -0.449 (0.02)*
85		X	^										11y	Relative Left Kidney Length	*MD= -0.03 (0.001)*
85		X	^										11y	Absolute Right Kidney Length (cm)	*MD= -0.447 (0.07)*
85		X	^										11y	Relative Right Kidney Length	*MD= -0.02 (0.007)*
87					X								10.7-20.7y	Kidney Length (cm)	SMD= -0.73 [-1.04, -0.41]
87					X								10.7-23.2y	Kidney Volume (cm^3)	SMD= -0.82 [-1.05, -0.60]
87					X								10.7-23.2y	Relative Kidney Volume (cm^3/m^2)	SMD= -0.57 [-0.79, -0.35]
85									X				11y	Low Relative Kidney Length	OR= 0.712 per week increase
87					X								10.7-14y	Blood Urea Nitrogen	SMD= 0.13 [-0.27, 0.52]
87					X								20.7-23.2y	Serum Renin	SMD= -0.07 [-0.49, 0.34]
87					X								8-26y	Effective Renal Plasma Flow	SMD= -0.39 [-0.74, -0.04]
87					X								6.7-23.2y	Urine Albumin To Creatinine Ratio	SMD= 0.25 [0.07, 0.43]
87					X								8.6-23.2y	Serum Creatinine (mg/dL)	SMD= -0.03 [-0.21, 0.16]
106						X							5.8-38y	Albumin Creatinine Ratio	WMD= -1.09 [-2.32, 0.14]
107						X							8.8-61y	Albuminuria	OR= 1.81 [1.19, 2.77]
107						X							8.8-61y	Risk of Chronic Kidney Disease(Albuminuria, ESRD, EGFR,Other)	OR= 1.73 [1.44, 2.08]
106						X							<1-75y	Chronic Kidney Disease (assessed by blood)	OR= 1.77 [1.42, 2.20]
106						X							8.8-61y	Chronic Kidney Disease (assessed by urine)	OR= 1.68 [1.27, 2.33]
106											X		<1-75y	Chronic Kidney Disease	OR= 1.09 [0.91, 1.32]
														Diabetes	
														Type 1 Diabetes	
108					X								<6-37y	Type 1 Diabetes	OR= 1.18 [1.11, 1.25]
109						X							≤20y	Type 1 Diabetes	OR= 0.82 [0.54, 1.23]
110						◊							Children	Type 1 Diabetes	HR= 0.78 [0.69, 0.88]
111						◊							0-19y	Type 1 Diabetes	OR= 0.98 [0.84, 1.13]
109						◊							≤20y	Type 1 Diabetes	OR= 1.02 [0.71, 1.46]
110								X					Children	Type 1 Diabetes	β= -0.00032, p= 0.001
109								X					≤20y	Type 1 Diabetes	OR= 1.07 [0.99, 1.15] per kg increase
112											X		<18y	Type 1 Diabetes	OR= 1.15 [1.05, 1.26]
109											X		≤20y	Type 1 Diabetes	OR= 1.17 [1.09, 1.26]
109											◊		≤20y	Type 1 Diabetes	OR= 1.19 [1.02, 1.38]
110											◊		Children	Type 1 Diabetes	HR= 1.08 [1.00, 1.17]
111											◊		0-19y	Type 1 Diabetes	OR= 1.10 [1.03, 1.18]
112												X	<18y	Type 1 Diabetes	OR= 1.10 [1.03, 1.21]
														Type 2 Diabetes	
113						X							6-84y	Type 2 Diabetes	OR= 1.51 [1.43, 1.58]
114						X							6-75y	Type 2 Diabetes	OR= 1.32 [1.06, 1.64]
113						◊							6-76y	Type 2 Diabetes	OR= 1.41 [1.26, 1.58]
114						◊							6-75y	Type 2 Diabetes	OR= 1.47 [1.26, 1.72]
114											X		6-75y	Type 2 Diabetes	OR= 1.27 [1.01, 1.59]
114											◊		6-75y	Type 2 Diabetes	OR= 1.36 [1.07, 1.73]
113											◊		6-76y	Type 2 Diabetes	OR= 1.1 [1.00,1.24]
														Diabetes related measurement	
84					X								3-45y	Fasting Blood Glucose (mg/dl)	SMD= -0.32 [-0.70, 0.07]
84					X								10-19y	Fasting Blood Glucose (mg/dl)	SMD= -0.12 [-0.35, 0.12]
115						X	X						6.5-41y	Fasting Blood Glucose (mmol/L)	MD= 0.05 [-0.03, 0.14]
115						X	X						≤10y	Fasting Blood Glucose (mmol/L)	MD= 0.08 [-0.04, 0.20]

Jamaluddine Z, *et al. Arch Dis Child* 2023;0:1–14. doi: 10.1136/archdischild-2022-324884

Ref	Exposures (size at birth)												Population	Outcomes	Effect size [confidence interval], direction of association
	Small							Cont		Large					
	EPT (<28wks)	ELBW (<1000g)	VPT (<32wks)	VLBW (<1500g)	PT (<37wks)	LBW (<2500g)	SGA(<10th percentile)	BW (cont.)	GA (cont.)	Post Term (>42 wks)	HBW (>4000g)	LGA(>90th			
115						X	X						>10-20y	Fasting Blood Glucose (mmol/L)	MD= 0.14 [0.04, 0.24]
115						X	X						8.6-41y	OGTT 2-h Glucose (mmol/L)	MD= 0.32 [0.13, 0.52]
115						X	X						>10-20y	OGTT 2-h Glucose (mmol/L)	MD= 0.40 [0.08, 0.71]
84					X								3-35.7y	Fasting Insulin (mIU/mL)	SMD= 0.06 [-0.34, 0.45]
84					X								<10y	Fasting Insulin (mIU/mL)	SMD= -0.54 [-1.13, 0.04]
115						X	X						6.5-26y	Fasting Insulin (pmol/L)	MD= 7.47 [1.77, 13.17]
115						X	X						≤10y	Fasting Insulin (pmol/L)	MD= 5.15 [-4.49, 14.79]
115						X	X						>10-20y	Fasting Insulin (pmol/L)	MD= 6.56 [-4.54, 17.65]
115						X	X						8.6-23.9y	OGTT 2-h Insulin (pmol/L)	MD= 105.55 [65.43, 145.66]
115						X	X						≤10y	OGTT 2-h Insulin (pmol/L)	MD= 118.51 [56.8, 180.22]
115						X	X						>10-20y	OGTT 2-h Insulin (pmol/L)	MD= 65.89 [-50, 181.78]
99								X					16-75y	Insulin (IU/L)	aβ= 0.0426 [0.0282, 0.0569] per kg lower
99								X					16-75y	Glycolysis and Gluconeogenesis: Glucose (mmol/L)	aβ= 0.00367 [-0.000407, 0.00775] per kg lower
99								X					16-75y	Glycolysis and Gluconeogenesis: Pyruvate (µmol/L)	aβ= 2.12 [1.29, 2.95] per kg lower
														Cancer	
														Paediatric CNS Tumour	
116					X								28d-≤21y	Neuroblastoma	OR= 1.09 [0.90, 1.32]
117						X							0-18y	Neuroblastoma	OR= 1.24 [1.00, 1.55]
117						◊							0-18y	Neuroblastoma	OR= 1.23 [0.98, 1.55]
117								X					0-18y	Neuroblastoma	β= 0.52 [0.28, 0.96]
117											X		0-18y	Neuroblastoma	OR= 1.19 [1.04, 1.36]
117											◊		0-18y	Neuroblastoma	OR= 1.21 [1.05, 1.39]
118						X							<19y	Astrocytoma	OR= 0.85 [0.58, 1.25]
119						X							<19y	Astrocytoma	OR= 0.96 [0.79, 1.16]
120						X							0-19y	Astrocytoma	OR= 0.98 [0.86, 1.11]
120						X							0-14y	Astrocytoma	OR= 0.99 [0.82, 1.19]
120						X							0-19y	Low-grade Astrocytoma	OR= 0.75 [0.60, 0.95]
120						X							0-19y	High-grade Astrocytoma	OR= 1.18 [0.78, 1.79]
120							X						0-15y	Astrocytoma	OR= 0.70 [0.51, 0.97]
120								X					0-19y	Astrocytoma	OR= 1.04 [1.02, 1.05] per 500g increase
120								X					0-19y	Low-grade Astrocytoma	OR= 1.02 [0.99, 1.05] per 500g increase
120								X					0-19y	High-grade Astrocytoma	OR= 1.05 [1.02, 1.08] per 500g increase
118								X					<19y	Astrocytoma	linear trend= 19% [4, 36] increase per 1000g
119											X		<19y	Astrocytoma	OR= 1.60 [1.23, 2.09]
118											X		<19y	Astrocytoma	OR= 1.38 [1.07, 1.79]
120											X		0-19y	Astrocytoma	OR= 1.22 [1.13, 1.31]
120											X		0-5y	Astrocytoma	OR= 1.34 [0.93, 1.93]
120											X		0-14y	Astrocytoma	OR= 1.25 [1.14, 1.37]
120											X		0-19y	Low-grade Astrocytoma	OR= 1.15 [1.02, 1.29]
120											X		0-19y	High-grade Astrocytoma	OR= 1.60 [1.21, 2.11]
120												X	0-15y	Astrocytoma	OR= 0.96 [0.75, 1.21]
118						X							<15y	Ependymoma	OR= 1.65 [0.60, 4.53]
119						X							≤15y	Ependymoma	OR= 0.87 [0.54, 1.39]
120						X							0-38y	Ependymoma	OR= 1.10 [0.76, 1.61]
120						X							0-14y	Ependymoma	OR= 0.98 [0.53, 1.79]
120							X						0-15y	Ependymoma	OR= 1.89 [1.00, 3.58]
120								X					0-17y	Ependymoma	OR= 1.01 [0.98, 1.05] per 500g increase
120											X		0-38y	Ependymoma	OR= 1.12 [0.94, 1.34]
120											X		0-14y	Ependymoma	OR= 1.27 [1.05, 1.55]
118											X		<15y	Ependymoma	OR= 1.15 [0.65, 2.04]
119											X		≤15y	Ependymoma	OR= 1.18 [0.97, 1.43]
120												X	0-15y	Ependymoma	OR= 1.52 [0.95, 2.54]
116					X								≤15y	Primary Central Nervous System Tumour	OR= 1.05 [0.93, 1.17]
120						X							0-19y	Central Nervous System Tumour	OR= 1.03 [0.93, 1.13]
120						X							0-5y	Central Nervous System Tumour	OR= 1.02 [0.75, 1.39]
120						X							0-14y	Central Nervous System Tumour	OR= 1.04 [0.95, 1.14]
120							X						0-14y	Central Nervous System Tumour	OR= 0.93 [0.84, 1.02]
120								X					0-19y	Central Nervous System Tumour	OR= 1.03 [1.01, 1.04] per 500g increase

Jamaluddine Z, *et al. Arch Dis Child* 2023;0:1–14. doi: 10.1136/archdischild-2022-324884

Ref	Exposures (size at birth)												Population	Outcomes	Effect size [confidence interval], direction of association
	Small							Cont		Large					
	EPT (<28wks)	ELBW (<1000g)	VPT (<32wks)	VLBW (<1500g)	PT (<37wks)	LBW (<2500g)	SGA(<10th percentile)	BW (cont.)	GA (cont.)	Post Term (>42 wks)	HBW (>4000g)	LGA(>90th			
120											X		0-24y	Central Nervous System Tumour	OR= 1.14 [1.08, 1.20]
120											X		0-5y	Central Nervous System Tumour	OR= 1.20 [1.07, 1.36]
120											X		0-14y	Central Nervous System Tumour	OR= 1.14 [1.09, 1.20]
112											X		Children	Central Nervous System Tumour	aOR= 1.15 [1.05, 1.27]
120												X	0-14y	Central Nervous System Tumour	OR= 1.12 [1.03, 1.22]
112												X	Children	Central Nervous System Tumour	aOR= 1.09 [0.95, 1.23]
120						X							0-19y	Embryonal Tumour	OR= 1.06 [0.88, 1.26]
120						X							0-14y	Embryonal Tumour	OR= 1.14 [0.94, 1.38]
120						X							0-19y	Medulloblastoma	OR= 0.98 [0.62, 1.56]
120							X						0-15y	Embryonal Tumour	OR= 1.18 [0.57, 2.44]
120								X					0-19y	Embryonal Tumour	OR= 1.02 [1.01, 1.04] per 500g increase
120								X					0-19y	Medulloblastoma	OR= 1.03 [0.94, 1.13] per 500g increase
120											X		0-19y	Embryonal Tumour	OR= 1.16 [1.04, 1.29]
120											X		0-5y	Embryonal Tumour	OR= 1.15 [0.79, 1.67]
120											X		0-14y	Embryonal Tumour	OR= 1.18 [1.05,1.32]
120												X	0-15y	Embryonal Tumour	OR= 1.10 [0.68, 1.77]
118						X							<19y	Medulloblastoma and Primitive Neuroectodermal Tumours	OR= 1.64 [0.42, 6.48]
119						X							<19y	Medulloblastoma and Primitive Neuroectodermal Tumours	OR= 1.19 [1.02, 1.39]
119						X							≤15y	Medulloblastoma	OR= 1.15 [0.92, 1.43]
118											X		<19y	Medulloblastoma and Primitive Neuroectodermal Tumours	OR= 1.27 [1.02, 1.60]
119											X		<19y	Medulloblastoma and Primitive Neuroectodermal Tumours	OR= 1.20 [1.07, 1.35]
119											X		<16y	Medulloblastoma	OR= 1.31 [1.08, 1.58]
120											X		0-19y	Medulloblastoma	OR= 0.91 [0.69, 1.21]
119						X							<19y	Primitive Neuroectodermal Tumours	OR= 1.24 [0.96, 1.60]
119											X		<19y	Primitive Neuroectodermal Tumours	OR= 1.16 [0.92, 1.46]
120						X							0-21y	Other Gliomas	OR= 0.99 [0.59, 1.66]
120								X					0-21y	Other Gliomas	OR= 1.02 [0.99, 1.06] per 500g increase
120											X		0-21y	Other Gliomas	OR= 1.21 [0.93, 1.56]
120						X							0-21y	Other Specified Tumours	OR= 0.75 [0.48, 1.19]
120								X					0-21y	Other Specified Tumours	OR= 1.03 [0.96, 1.10] per 500g increase
120											X		0-21y	Other Specified Tumours	OR= 1.14 [0.90, 1.45]
120						X							0-21y	Unspecified Tumours	OR= 1.26 [0.68, 2.32]
120								X					0-21y	Unspecified Tumours	OR= 1.01 [0.95, 1.06] per 500g increase
120											X		0-21y	Unspecified Tumours	OR= 1.19 [0.84, 1.67]
														Leukaemia	
121					X								<20y	Acute Leukaemia	OR= 1.09 [1.02, 1.17]
121					X								<5y	Acute Leukaemia	OR= 1.05 [0.97, 1.15]
122					X								<38y	Leukaemia	OR= 1.06 [0.98, 1.13]
123								X					<15y	Leukaemia	HR= 1.25 [0.89, 1.75]
123								X					<3y	Leukaemia	HR= 1.29 [0.79, 2.11]
123								X					≥3y	Leukaemia	HR= 1.57 [0.96, 2.57]
122										X			<38y	Leukaemia	OR= 1.01 [0.90, 1.13]
122										X			≤9y	Leukaemia	OR= 0.91 [0.79, 1.04]
122										X			9-16y	Leukaemia	OR= 1.03 [0.92, 1.15]
123											X		<15y	Leukaemia	HR= 1.25 [0.80, 1.96]
123											X		<3y	Leukaemia	HR= 1.08 [0.55, 2.13]
123											X		≥3y	Leukaemia	HR= 1.56 [0.84, 2.88]
112											X		Children	Leukaemia	aOR= 1.29 [1.20, 1.39]
124						X							<20y	Leukaemia	OR= 1.03 [0.87, 1.23]
124						X							<20y	Acute Lymphoblastic Leukaemia	OR= 0.97 [0.81, 1.16]
124						X							<20y	Acute Myeloid Leukaemia	OR= 1.50 [1.05,2.13]
124								X					<20y	Leukaemia	OR= 1.18 [1.12, 1.23] per kg increase
124								X					<20y	Acute Lymphoblastic Leukaemia	OR= 1.18 [1.12,1.23] per kg increase
125								X					0-29y	Acute Lymphoblastic Leukaemia and Leukaemia Combined	OR= 1.14 [1.08, 1.20]
125											X		0-29y	Acute Lymphoblastic Leukaemia and Leukaemia Combined	OR= 1.26 [1.17, 1.37]
124											X		<20y	Leukaemia	OR= 1.35 [1.24, 1.48]
124											X		<20y	Acute Lymphoblastic Leukaemia	OR= 1.24 [1.16, 1.33]
124											X		<20y	Acute Myeloid Leukaemia	OR= 1.40 [1.11, 1.76]
122					X								<38y	Acute Lymphoblastic Leukaemia	OR= 1.04 [0.97, 1.11]

Ref	Exposures (size at birth)												Population	Outcomes	Effect size [confidence interval], direction of association
	Small							Cont		Large					
	EPT (<28wks)	ELBW (<1000g)	VPT (<32wks)	VLBW (<1500g)	PT (<37wks)	LBW (<2500g)	SGA(<10th percentile)	BW (cont.)	GA (cont.)	Post Term (>42 wks)	HBW (>4000g)	LGA(>90th			
121					X								<15y	Acute Lymphoblastic Leukaemia	OR= 1.04 [0.96, 1.13]
121					X								<5y	Acute Lymphoblastic Leukaemia	OR= 1.04 [0.93, 1.16]
126							X						0-15y	Acute Lymphoblastic Leukaemia	OR= 0.83 [0.75, 0.92]
126								X					0-15y	Acute Lymphoblastic Leukaemia	OR= 1.16 [1.09, 1.24] (per 1SD increase)
126								X					0-1y	Acute Lymphoblastic Leukaemia	aOR= 1.09 [0.87, 1.37]
126								X					>1-5y	Acute Lymphoblastic Leukaemia	aOR= 1.17 [1.08, 1.27]
126								X					>5y	Acute Lymphoblastic Leukaemia	aOR= 1.18 [1.06, 1.31]
123								X					<15y	Acute Lymphoblastic Leukaemia	HR= 1.16 [0.81, 1.67]
123								X					<3y	Acute Lymphoblastic Leukaemia	HR= 1.23 [0.72, 2.11]
123								X					≥3y	Acute Lymphoblastic Leukaemia	HR= 1.34 [0.78, 2.30]
122										X			<38y	Acute Lymphoblastic Leukaemia	OR= 1.03 [0.95, 1.12]
122										X			≤9y	Acute Lymphoblastic Leukaemia	OR= 0.91 [0.78, 1.05]
122										X			9-16y	Acute Lymphoblastic Leukaemia	OR= 1.03 [0.94, 1.13]
123											X		<15y	Acute Lymphoblastic Leukaemia	HR= 1.21 [0.74, 1.96]
123											X		<3y	Acute Lymphoblastic Leukaemia	HR= 1.02 [0.48, 2.15]
123											X		≥3y	Acute Lymphoblastic Leukaemia	HR= 1.49 [0.77, 2.88]
126												X	0-15y	Acute Lymphoblastic Leukaemia	OR= 1.24 [1.13, 1.36]
126												X	0-1y	Acute Lymphoblastic Leukaemia	aOR= 1.04 [0.75, 1.44]
126												X	>1-5y	Acute Lymphoblastic Leukaemia	aOR= 1.20 [1.06, 1.35]
126												X	>5y	Acute Lymphoblastic Leukaemia	aOR= 1.26 [1.08, 1.46]
122					X								<38y	Acute Myeloid Leukaemia	OR= 1.20 [1.00, 1.44]
127					X								<1y	Acute Myeloid Leukaemia	*OR= 0.92 [0.60, 1.41]*
127					X								1-14y	Acute Myeloid Leukaemia	*OR= 0.98 [0.81, 1.19]*
121					X								<15y	Acute Myeloid Leukaemia	OR= 1.42 [1.21, 1.67]
121					X								<5y	Acute Myeloid Leukaemia	OR= 1.35 [1.07, 1.70]
127						X							<1y	Acute Myeloid Leukaemia	*OR= 1.51 [1.04, 2.19]*
127						X							1-14y	Acute Myeloid Leukaemia	*OR= 1.13 [0.99, 1.29]*
122										X			<38y	Acute Myeloid Leukaemia	OR= 1.20 [1.00, 1.43]
127											X		<1y	Acute Myeloid Leukaemia	*OR= 0.96 [0.68, 1.35]*
127											X		1-14y	Acute Myeloid Leukaemia	*OR= 1.31 [0.99, 1.29]*
125											X		0-29y	Acute Myeloid Leukaemia	OR= 1.27 [0.73, 2.20]
														Lymphoma	
128						X							0-17y	Lymphoma	OR= 1.03 [0.79, 1.33]
128						◊							0-17y	Lymphoma	OR= 1.02 [0.79, 1.33]
128											X		0-17y	Lymphoma	OR= 0.95 [0.79, 1.14]
128											◊		0-17y	Lymphoma	OR= 1.09 [0.76, 1.56]
128						X							0-17y	Non-Hodgkin Lymphoma	OR= 1.03 [0.70, 1.51]
128						◊							0-17y	Non-Hodgkin Lymphoma	OR= 1.07 [0.71, 1.62]
128											X		0-17y	Non-Hodgkin Lymphoma	OR= 1.18 [0.84, 1.67]
128											◊		<18y	Non-Hodgkin Lymphoma	OR= 1.17 [0.76, 1.80]
128						X							0-17y	Hodgkin Lymphoma	OR= 0.94 [0.54, 1.64]
128						◊							0-17y	Hodgkin Lymphoma	OR= 0.94 [0.54, 1.65]
128											X		0-17y	Hodgkin Lymphoma	OR= 0.92 [0.66, 1.24]
128											◊		<18y	Hodgkin Lymphoma	OR= 0.94 [0.64, 1.38]
														Wilm's Tumour (Nephroblastoma)	
129					X								0-15y	Wilms' Tumour	OR= 1.42 [1.14, 1.79]
129						◊							0-15y	Wilms' Tumour	OR= 0.90 [0.67, 1.22]
129											X		0-15y	Wilms' Tumour	OR= 1.36 [1.12, 1.65]
129											X		<24m	Wilms' Tumour	OR= 1.27 [0.97, 1.65]
129											X		24m-15y	Wilms' Tumour	OR= 1.66 [1.28, 2.16]
112											X		Children	Wilms' Tumour	aOR= 1.68 [1.38, 2.06]
129												X	0-15y	Wilms' Tumour	OR= 1.51 [1.25, 1.83]
112												X	Children	Wilms' Tumour	aOR= 1.77 [1.31, 2.39]
														Other tumours	
130						◊							1-59y	Testicular Cancer	OR= 1.18 [1.01, 1.38]
130						◊							1-55y	Testicular Cancer: Seminoma and Non-seminoma	OR= 1.18 [0.98, 1.41]
130						◊							1-55y	Seminoma	OR= 1.44 [1.11, 1.88]
130						◊							1-55y	Non-seminoma	OR= 0.98 [0.81, 1.17]
130											◊		1-59y	Testicular Cancer	OR= 1.12 [1.02, 1.22]

Ref	Exposures (size at birth)													Population	Outcomes	Effect size [confidence interval], direction of association
	Small							Cont		Large						
	EPT (<28wks)	ELBW (<1000g)	VPT (<32wks)	VLBW (<1500g)	PT (<37wks)	LBW (<2500g)	SGA(<10th percentile)	BW (cont.)	GA (cont.)	Post Term (>42 wks)	HBW (>4000g)	LGA(>90th				
130											◊			1-55y	Testicular Cancer: Seminoma and Non-seminoma	OR= 1.05 [0.95, 1.15]
130											◊			1-55y	Seminoma	OR= 1.04 [0.89, 1.22]
130											◊			1-55y	Non-seminoma	OR= 1.05 [0.93, 1.19]
123								X						<15y	Non-Leukaemia	HR= 1.04 [0.83,1.28] per kg increase
123								X						<3y	Non-Leukaemia	HR= 0.99 [0.71,1.38] per kg increase
123								X						≥3y	Non-Leukaemia	HR= 1.39 [1.02,1.91] per kg increase
123											X			<15y	Non-Leukaemia	HR= 1.09 [0.79, 1.50]
123											X			<3y	Non-Leukaemia	HR= 0.75 [0.45,1.24]
123											X			≥3y	Non-Leukaemia	HR= 1.62 [1.06, 2.46]
131								X						<45y	Bone Tumour	OR= 1.01 [1.00, 1.02] (per 500g increase)
131											X			<45y	Bone Tumour	OR= 1.13 [0.96, 1.33]
131											X			<18y	Bone Tumour	OR= 1.17 [0.96, 1.42]
131											X			<18y	Osteosarcoma	OR= 1.25 [0.91, 1.72]
131											X			<18y	Ewing Sarcoma	OR= 0.81 [0.54, 1.21]
131											X			<18y	Chondrosarcoma	OR= 1.39 [0.55, 3.54]
123								X						<15y	Cancer	aHR= 1.26 [1.02, 1.54] per kg increase
123								X						<15y	Cancer	HR= 1.10 [0.91, 1.31] per kg increase
123								X						<3y	Cancer	HR= 1.08 [0.82,1.42] per kg increase
123								X						≥3y	Cancer	HR= 1.44 [1.11,1.88] per kg increase
123											X			<15y	Cancer	HR= 1.14 [0.88, 1.48]
123											X			<3y	Cancer	HR= 0.84 [0.56, 1.27]
123											X			≥3y	Cancer	HR= 1.60 [1.13, 2.26]
															Metabolic Syndrome	
132					X									9-29y	Metabolic Syndrome (overweight, insulin resistance)	OR= 1.48 [1.00, 2.21]
132						X								7-74y	Metabolic Syndrome (overweight, insulin resistance)	OR= 1.37 [1.17, 1.61]
															Metabolic Biomarkers	
99								X						16-75y	Amino acid: Alanine (µmol/L)	aβ= 5.26 [3.14, 7.38] per kg lower
99								X						16-75y	Ketone bodies: Acetoacetate (µmol/L)	aβ= 0.0177 [-0.00279, 0.0381] per kg lower
99								X						16-75y	Miscellaneous: Albumin	aβ= 0.219 cu [-0.0485, 0.487] per kg lower
99								X						16-75y	Liver function markers: Alanine aminotransferase (cu)	aβ= 0.00282 [0.000213, 0.00542] per kg lower
99								X						16-75y	Inflammatory markers: C-reactive protein (mg/L)	aβ= 0.0518 [0.00349, 0.1] per kg lower
99															Additional data on paper 99 in appendix	Additional data on paper 99 in appendix

(94) IUGR is defined as BW<10th percentile or BW<5th percentile or BW<3rd percentile (or -2 standard deviations); or the combination of BW and length <-2 standard deviations; or BW<2500g and <-2 standard deviations; or BW<1500g and <-2 standard deviations; or ELBW with BW<10th percentile; or BW<10th percentile and BW ratio<0.85; or BW<-2 standard deviations and estimated fetal weight<-15%; or BW ratio<0.8; or estimated fetal weight<10th percentile or abdominal circumference<5th percentile and placental insufficiency>2SD; or VLBW with BW<-2 standard deviations

(102) IUGR is defined based on fetal biometry or Doppler velocimetry

Table 1 e- Associations between size-at-birth and behavioural and mental health outcomes

Ref	Exposures (size at birth)												Population	Outcomes	Effect size [confidence interval], direction of association
	Small							Cont		Large					
	EPT (<28wks)	ELBW (<1000g)	VPT (<32wks)	VLBW (<1500g)	PT (<37wks)	LBW (<2500g)	SGA(<10th percentile)	BW (cont.)	GA (cont.)	Post Term (>42 wks)	HBW (>4000g)	LGA(>90th percentile)			
														Depressive/ Anxiety Disorders	
133			X	X									11-20y	Anxiety	OR= 2.27 [1.15, 4.47]
134					X	X							3-19y	Clinically Unspecified Anxiety	OR= 2.17 [1.43, 3.29]
134					X	X							5-18y	Generalized Anxiety Disorder	OR= 2.20 [1.26, 3.84]
134					X	X							5-11y	Separation Anxiety Disorder	OR= 1.56 [0.90, 2.71]
134					X	X							7-14y	Clinically Unspecified Depression	OR= 1.55 [0.45, 5.33]
134					X	X							9.7-18y	Major Depressive Disorder	OR= 1.14 [0.71, 1.82]
135					X	X							11-25y	Anxiety and Depressive Disorder Diagnosis	OR= 2.92 [1.82, 4.67]
136					X								7-31y	Depression	OR= 1.38 [1.00, 1.90]
137						X							11-68y	Depression	OR= 1.15 [1.00, 1.32]
136						X							6-45y	Depression	OR= 1.44 [1.17, 1.76]
136							X						11-33y	Depression	OR= 1.46 [1.11, 1.94]
138			^	X									7-17.8y	Anxiety or Depression: Child Behaviour Checklist	Cohen's d= -0.20 [-0.48, 0.08]
138			^	X									7-11.6y	Anxiety or Depression: Teachers Report Form	Cohen's d= -0.28 [-0.45, -0.12]
														Other Psychological	
134					X	X							5-18y	Specific Phobia	OR= 1.93 [1.05, 3.52]
134					X	X							5-18y	Social Phobia	OR= 2.63 [0.87, 7.95]
135					X	X							11-25y	Any Psychiatric Diagnosis	OR= 3.66 [2.57, 5.21]
139					X								1-60m	Negative Affect	Cohen's d= -0.17 [-0.42, 0.08]
139					X								1-60m	Falling Reactivity	Cohen's d= -0.92 [-2.59, 0.75]
139					X								1-60m	Fear	Cohen's d= 0.14 [-0.05, 0.33]
139					X								1-60m	Frustration/Distress to Limitations	Cohen's d= -0.03 [-0.25, 0.20]
139					X								1-60m	Sadness	Cohen's d= 0.10 [-0.07, 0.28]
139					X								1-60m	Discomfort	Cohen's d= -0.07 [-0.54, 0.51]
139					X								1-60m	Perceptual Sensitivity	Cohen's d= -0.05 [-0.29, 0.19]
139					X								1-60m	Shyness	Cohen's d= 0.06 [-0.18, 0.30]
139					X								3-60m	Surgency: Activity level	Cohen's d= -0.20 [-0.38, -0.02]
139					X								1-60m	Surgency: High-intensity Pleasure	Cohen's d= -0.28 [-0.72, 0.16]
139					X								1-60m	Surgency: Impulsivity	dCohen's d= -0.04 [-0.28, 0.20]
139					X								1-60m	Surgency: Vocal Reactivity	Cohen's d= -0.58 [-1.62, 0.46]
139					X								1-60m	Surgency: Smiling and Laughter	Cohen's d= -0.09 [-0.27, 0.09]
139					X								1-60m	Surgency: Approach	Cohen's d= -0.09 [-0.27, 0.09]
139					X								1-60m	Effortful Control	Cohen's d= 0.26 [0.007, 0.52]
139					X								1-60m	Cuddliness	Cohen's d= 0.13 [-0.38, 0.65]
139					X								1-60m	Duration of Orientation	Cohen's d= -0.18 [-0.56, 0.20]
139					X								1-60m	Low-intensity Pleasure	Cohen's d= -0.15 [-0.33, -0.03]
139					X								1-60m	Soothability	Cohen's d= -0.13 [-0.40, 0.14]
														Behavioural	
140		X											6-12y	Internalizing: Parent-Reported	SMD= 0.42 [0.26, 0.58]
140		X											6-12y	Internalizing: Teacher-Reported	SMD= 0.32 [0.12, 0.52]
140		X											15.6-19.7y	Internalizing: Parent-Reported	SMD= 0.51 [0.26, 0.76]
140		X											15.6-18.4y	Internalizing: Self-Reported	SMD= 0.31 [-0.44, 1.06]
140		X											5-36y	Externalizing: Parent-Reported	SMD= 0.15 [0.02, 0.28]
140		X											16.3-19.7y	Externalizing: Parent-Reported	SMD= 0.29 [-0.26, 0.84]
140		X											5-36y	Externalizing: Teacher-Reported	SMD= 0.14 [0.00, 0.29]
140		X											5-36y	Oppositional Defiant Disorder: Parent-Reported	SMD= 0.14 [-0.01, 0.28]
140		X											5-36y	Oppositional Defiant Disorder: Teacher-Reported	SMD= 0.79 [0.40, 1.17]
140		X											14.1-14.7y	Oppositional Defiant Disorder: Parent-Reported	SMD= -0.03 [-0.21, 0.14]
140		X											14.1-14.7y	Oppositional Defiant Disorder: Self-Reported	SMD= -0.34 [-0.54, -0.13]
140		X											5-10y	Social Problems: Parent-Reported	SMD= 0.46 [0.31, 0.61]
140		X											15.6-19.7y	Social Problems: Parent-Reported	SMD= 0.52 [0.00, 1.03]
140		X											15.6-18.4y	Social Problems: Self-Reported	SMD= 0.21 [-0.16, 0.57]
140		X											6-12y	Conduct Disorder: Parent-Reported	SMD= 0.23 [0.09, 0.37]
140		X											6-12y	Conduct Disorder: Teacher-Reported	SMD= 0.19 [-0.01, 0.38]
140		X											14.1-19.7y	Conduct Disorder: Parent-Reported	SMD= -0.30 [-1.58, 0.98]

Ref	Exposures (size at birth)												Population	Outcomes	Effect size [confidence interval], direction of association
	Small							Cont		Large					
	EPT (<28wks)	ELBW (<1000g)	VPT (<32wks)	VLBW (<1500g)	PT (<37wks)	LBW (<2500g)	SGA(<10th percentile)	BW (cont.)	GA (cont.)	Post Term (>42 wks)	HBW (>4000g)	LGA(>90th percentile)			
140		X											14.1-18.4y	Conduct Disorder: Self-Reported	SMD= -0.17 [-0.38, 0.05]
138			^	X									7-17.8y	Externalizing Behavioural Problem: Child Behaviour Checklist	Cohen's d= -0.09 [-0.05, 0.22]
138			^	X									7-11.6y	Externalizing Behaviour Problem: Teachers Report Form	Cohen's d= -0.08 [-0.24, 0.07]
139					X								1-60m	Adaptability (Behaviour)	Cohen's d= -0.08 [-0.68, 0.51]
139					X								1-60m	Approach (Behaviour)	Cohen's d= -0.07 [-0.27, 0.13]
139					X								1-60m	Difficult (category) (Behaviour)	OR= 0.78 [0.41, 1.50]
139					X								1-60m	Difficult (mean) (Behaviour)	Cohen's d= -0.02 [-0.15, 0.10]
139					X								1-60m	Easy (category) (Behaviour)	OR= 1.67 [0.90, 3.01]
139					X								1-60m	Intensity (Behaviour)	Cohen's d= 0.25 [-0.46, 0.96]
139					X								1-60m	Negativity (Behaviour)	Cohen's d= -0.16 [-0.68, 0.36]
139					X								1-60m	Persistence (Behaviour)	Cohen's d= 0.15 [-0.11, 0.41]
139					X								1-60m	Rhythmicity (Behaviour)	Cohen's d= -0.12 [-0.38, 0.13]
139					X								1-60m	Social Orientation (Behaviour)	Cohen's d= 0.09 [-0.16, 0.34]
139					X								1-60m	Threshold (Behaviour)	Cohen's d= -0.19 [-0.75, 0.38]
139					X								1-60m	Unadaptable (Behaviour)	Cohen's d= -0.22 [-0.63, 0.20]
139					X								1-60m	Unpredictable (Behaviour)	Cohen's d= -0.004 [-0.15, 0.14]
139					X								1-60m	Mood (Behaviour)	Cohen's d= -0.12 [-1.26, 1.03]
139					X								1-60m	Positive emotions (Behaviour)	Cohen's d= -0.16 [-0.61, 0.29]
139					X								1-60m	Activity (Behaviour)	Cohen's d= 0.26 [-0.06, 0.59]
141					X								2-18y	Behaviour Test Score	SMD= -0.32 [-0.41, -0.24]
141					X								4-11y	Behaviour Test Score	SMD= -0.34 [-0.45, -0.23]
141					X								11-18y	Behaviour Test Score	SMD= -0.72 [-0.97, -0.47]
142							X						5-14y	Behavioural Problems	SMD= 0.31 [0.13, 0.48]
														Physical Activity	
143					X								5.8-19y	Exercise Capacity VO_2 max (mL/kg/min)	SMD= -0.33 [-0.58, -0.09]
144						X							14-69y	Leisure Time Physical Activity	OR= 0.72 [0.59, 0.88]
144											◊		14-69y	Leisure Time Physical Activity	OR= 0.92 [0.81 - 1.03]
144											◊		14-69y	Leisure Time Physical Activity	OR= 0.65 [0.50, 0.86]
145								X					0-18y	Physical Activity (counts per minute)	β= -3.08 [-10.20, 4.04] per kg increase
														Attention	
146			X	X									4-5y	Selective Visual Attention (per correct answer)	Cohen's d= -0.36 [-0.53, -0.19]
138			^	X									7-17.8y	Attention Problems using Child Behaviour Checklist	Cohen's d= -0.59 [-0.74, - 0.44]
138			^	X									7-11.6y	Attention Problems using Teachers Report Form	Cohen's d= -0.43 [-0.61, - 0.25]
147					X								0-14m	Latency to Fixate	Cohen's d= -0.18 [-0.33, -0.02]
147					X								0-14m	Habituation	Cohen's d= -0.10 [-0.22, 0.03]
147					X								0-14m	Novelty Preference	Cohen's d= -0.20 [-0.32, -0.08]
147					X								6-24m	Focused Attention	Cohen's d= -0.28 [-0.45, -0.11]
139					X								10-60m	Attention Span (Behaviour)	Cohen's d= 0.26 [0.005, 0.51]
139					X								28-60m	Attentional Focusing (Psychological)	Cohen's d= 0.48 [0.24, 0.73]
139					X								1-60m	Attentional Shifting (Psychological)	Cohen's d= -0.22 [-0.46, -0.02]
148					X								2-17y	Selective Attention	Cohen's d= 0.38 [0.21, 0.54]
148	26												2-17y	Selective Attention	Cohen's d= 0.58 [0.43, 0.74]
148					X								2-17y	Sustained Attention	Cohen's d= 0.45 [0.23, 0.66]
148	26												2-17y	Sustained Attention	Cohen's d= 0.67 [0.31, 1.03]
														Attention-Deficit/Hyperactivity Disorder (ADHD)	
141	X												6-11y	ADHD	OR= 3.3 [2.0, 5.6]
149	X												3-22.5y	ADHD	R= -0.15 [-0.43, 0.13]
140		X											6-12y	Combined ADHD: Teacher-Reported	SMD= 0.54 [0.29, 0.79]
140		X											6-12y	Inattentive ADHD: Teacher-Reported	SMD= 0.54 [0.27, 0.82]
140		X											6-12y	Hyperactive ADHD: Teacher-Reported	SMD= 0.35 [0.19, 0.50]
140		X											6-12y	Combined ADHD: Parent-Reported	SMD= 0.68 [0.56, 0.80]
140		X											6-12y	Inattentive ADHD: Parent-Reported	SMD= 0.58 [0.39, 0.77]
140		X											6-12y	Hyperactive ADHD: Parent-Reported	SMD= 0.46 [0.37, 0.55]
140		X											14.1-18.4y	ADHD: Self-Reported	SMD= -0.03 [-0.28, 0.23]
140		X											14.1-19.7y	Combined ADHD: Parent-Reported	SMD= 0.52 [0.19, 0.85]
140		X											14.7-17.4y	Inattentive ADHD: Parent-Reported	SMD= 0.40 [0.24, 0.56]
140		X											14.7-17.4y	Hyperactive ADHD: Parent-Reported	SMD= 0.26 [0.10, 0.43]

Jamaluddine Z, *et al. Arch Dis Child* 2023;0:1–14. doi: 10.1136/archdischild-2022-324884

Ref	Exposures (size at birth)												Population	Outcomes	Effect size [confidence interval], direction of association
	Small							Cont		Large					
	EPT (<28wks)	ELBW (<1000g)	VPT (<32wks)	VLBW (<1500g)	PT (<37wks)	LBW (<2500g)	SGA(<10th percentile)	BW (cont.)	GA (cont.)	Post Term (>42 wks)	HBW (>4000g)	LGA(>90th percentile)			
150			X	X									2-23.2y	ADHD: Combined Symptoms	SMD= 0.55 [0.42, 0.68]
150	X	X											2.5-23.2y	ADHD: Combined Symptoms	SMD= 0.66 [0.39, 0.92]
150			X	X									2-20y	ADHD: Combined Symptoms	SMD= 0.50 [0.38, 0.61]
150			X	X									3-32y	ADHD: Categorically Defined	OR= 3.04 [2.19, 4.21]
150	X	X											5.96-32y	ADHD: Categorically Defined	OR= 4.05 [2.38, 6.87]
150			X	X									3-14y	ADHD: Categorically Defined	OR= 2.25 [1.56, 3.26]
150			X	X									2-23.2y	ADHD: Hyperactivity or Impulsivity Symptoms	SMD= 0.74 [0.35, 1.13]
150	X	X											6.2-23.2y	ADHD: Hyperactivity or Impulsivity Symptoms	SMD= 0.73 [-0.27, 1.18]
150			X	X									2-20y	ADHD: Hyperactivity or Impulsivity Symptoms	SMD= 0.70 [0.00, 1.41]
150			X	X									2-20y	ADHD: Inattentive Symptoms	SMD= 1.31 [0.66,1.96]
150	X	X											8-17.3y	ADHD: Inattentive Symptoms	SMD= 1.23 [0.50, 1.96]
150			X	X									2-20y	ADHD: Inattentive Symptoms	SMD= 1.34 [0.00, 2.69]
149				X									3-22.5y	ADHD	R= -0.09 [-0.30, 0.11]
149					X								3-22.5y	ADHD	r= -0.16 [-0.24, -0.08]
151					X								5-14y	ADHD	RR= 2.64 [1.85, 3.78]
141					X								5-19y	ADHD	OR= 1.6 [1.3, 1.8]
141			v										7-14y	ADHD	OR= 3.7 [1.8, 7.7]
141					LT								5-19y	ADHD	OR= 1.3 [1.1, 1.5]
149						X							3-22.5y	ADHD	R= -0.20 [-0.28, -0.13]
142							X						5-14y	ADHD	OR= 2.36 [0.78, 7.11]
149								X					3-22.5y	ADHD	R= -0.15 [-0.16, -0.13]
149									X				3-22.5y	ADHD	Intercept= -0.12/ SE (0.0089)
														Autism Spectrum Disorder	
140		X											8-11y	Autistic Symptoms Parent-Reported	SMD= 0.56 [0.29, 0.83]
152					X								Children	Autism Spectrum Disorder	Risk ratio= 1.31 [1.16, 1.48]
152						X							Children	Autism Spectrum Disorder	Risk ratio= 1.26 [1.20, 1.34]
153							X						<2-15y	Autism Spectrum Disorder	OR= 1.17 [1.09, 1.24]
														Suicidal Behaviour	
154					X								10-76y	Suicide Attempt	OR= 1.18 [1.12, 1.25]
154						X							10-49y	Suicide Attempt	OR= 1.39 [1.23, 1.56]
154					X								10-87y	Suicide	OR= 1.11 [0.98, 1.25]
154						X							1-51y	Suicide	OR= 1.30 [1.09, 1.55]
154							X						10-87y	Suicide	OR= 1.18 [1.00, 1.40]

Jamaluddine Z, *et al. Arch Dis Child* 2023;0:1–14. doi: 10.1136/archdischild-2022-324884

Table 1 f- Associations between size-at-birth and nutrition and growth outcomes

Ref	Exposures (size at birth)												Population	Outcomes	Effect size [confidence interval], direction of association
	Small							Cont		Large					
	EPT (<28wks)	ELBW (<1000g)	VPT (<32wks)	VLBW (<1500g)	PT (<37wks)	LBW (<2500g)	SGA(<10th percentile)	BW (cont.)	GA (cont.)	Post Term (>42 wks)	HBW (>4000g)	LGA(>90th percentile)			
														Body Composition	
155					X								Infants	Length (cm)	MD= -3.71 [-4.60, -2.81]
85		X											11y	Height (cm)	*z-score difference= -0.92 (-0.03), p <0.001*
155					X								Infants	Weight (kg)	MD= -0.59 [-0.75, -0.44]
85		X											11y	Weight (kg)	*z-score difference= -0.61 (0.18), p <0.001*
155					X								Infants	Head Circumference (cm)	MD= -1.03 [-1.52, -0.54]
85		X											11y	Head Circumference (cm)	*z-score difference= -1.52 (0.44), p <0.001*
85		X											11y	Body Surface Area	*z-score difference= -0.10 (-0.01), p <0.001*
155					X								Infants	Total Body Fat (%)	MD= 3.06 [0.25, 5.88]
156					X								4-7y	Total Body Fat (%)	SMD= -3.05 [-8.73, 2.62]
155					X								Infants	Fat Mass (kg)	MD= -0.05 [-0.09, -0.01]
155					X								Infants	Fat Free Mass (kg)	MD= -0.46 [-0.64, -0.27]
156					X								4-7y	Fat Mass Index	SMD= -1.31 [-5.42, 2.81]
156					X								4-7y	Childhood Trunk Fat Index	SMD= 1.03 [-1.64, 3.71]
157							()						At birth	Cord Blood Adiponectin Concentrations	SMD= -1.14 [-2.15, -0.12]
157							(						At birth	Cord Blood Adiponectin Concentrations	SMD= -1.93 [-4.093, -0.022]
157							X						At birth	Cord Blood Adiponectin Concentrations	SMD= -0.383 [-0.744, -0.022]
158							X						0.5h-11d	Total Body Water (%)	*MD= 4.40 [2.83, 5.96]*
158									X				6h-7d	Total Body Water (%)	β= -1.44 [-0.63, -2.24] per week
158												X	0.5h-11d	Total Body Water (%)	*MD= -5.23 [-4.54, -5.91]*
														Bone Mineralization	
159								X					10y	Bone Mass Content	β= 0.02 [0.01, 0.04]
159								X					10y	Bone Mass Density	β= 0.01 [-0.01, 0.03]
														BMI	
84	X												6-32y	Body Mass Index (BMI) (kg/m^2)	MD= -0.50 [-1.10 ,0.09]
84		X											5-30y	Body Mass Index (BMI) (kg/m^2)	MD= -0.30 [-0.54, -0.05]
84					X								4.5-35.7y	Body Mass Index (BMI) (kg/m^2)	MD= -0.13 [-0.40, 0.14]
84					X								<10y	Body Mass Index (BMI) (kg/m^2)	MD= -0.70 [-1.13, -2.28]
84					X								<19y	Body Mass Index (BMI) (kg/m^2)	MD= 5.20 [-3.82, 14.21]
84					X								10-19y	Body Mass Index (BMI) (kg/m^2)	MD= -0.25 [-0.76, 0.26]
91								X_{GA}					16-46.9y	Body Mass Index (BMI) (kg/m^2)	β= 0.52 [0.20, 0.84] per kg increase
91								GA					16-46.9y	Body Mass Index (BMI) (kg/m^2)	β= 0.51 [-0.08, 1.11] per kg increase
91								X					16-46.9y	Body Mass Index (BMI) (kg/m^2)	β= 0.52 [0.17, 0.86] per kg increase
77					T								0-2y	BMI Trajectory: Class 2 (Rapid Growth up to 2 years)	aOR= 2.02 [1.49, 2.74]
77					T								0-6y	BMI Trajectory: Class 3 (Persistent Rapid Growth up to 6 years)	aOR= 1.89 [0.42, 8.49]
77						◊							0-2y	BMI Trajectory: Class 2 (Rapid Growth)	aOR= 1.48 [1.05, 2.10]
77						◊							0-6y	BMI Trajectory: Class 3 (Persistent Rapid Growth)	aOR= 0.78 [0.10, 6.45]
77										X			0-2y	BMI Trajectory: Class 2 (Rapid Growth)	aOR= 0.81 [0.68,0.96]
77										X			0-6y	BMI Trajectory: Class 3 (Persistent Rapid Growth)	aOR= 0.48 [0.15, 1.53]
77											T		0-2y	BMI Trajectory: Class 2 (Rapid Growth)	aOR= 0.98 [0.86, 1.12]
77											T		0-6y	BMI Trajectory: Class 3 (Persistent Rapid Growth)	aOR= 1.62 [0.88, 2.99]
														Undernutrition	
160					X								12-60m	Wasting (weight for length/height for age <2 z-scores)	OR= 1.55 [1.21, 1.97]
160						X							12-60m	Wasting (weight for length/height for age <2 z-scores)	OR= 2.68 [2.23, 3.21]
160							X						12-60m	Wasting (weight for length/height for age <2 z-scores)	OR= 2.36 [2.14, 2.60]
160					X								12-60m	Stunting (length/height for age <2 z-scores)	OR= 1.69 [1.48, 1.93]
160						X							12-60m	Stunting (length/height for age <2 z-scores)	OR= 2.92 [2.56, 3.33]
160							X						12-60m	Stunting (length/height for age <2 z-scores)	OR= 2.32 [2.12, 2.54]
160					X								12-60m	Underweight (weight for age less than 2 z-scores)	OR= 1.66 [1.42, 1.95]
160						X							12-60m	Underweight (weight for age less than 2 z-scores)	OR= 3.48 [3.14, 3.87]
160							X						12-60m	Underweight (weight for age less than 2 z-scores)	OR= 2.96 [2.61, 3.36]
														Overnutrition	
161						X							0-18y	Overweight	OR= 0.60 [0.54, 0.67]
161								X					1-75y	Overweight	β= 0.34 [(0.28, 0.40)] per kg increase
161											X		0-18y	Overweight	OR= 1.76 [1.65, 1.87]

Ref	Exposures (size at birth)												Population	Outcomes	Effect size [confidence interval], direction of association
	Small							Cont		Large					
	EPT (<28wks)	ELBW (<1000g)	VPT (<32wks)	VLBW (<1500g)	PT (<37wks)	LBW (<2500g)	SGA(<10th percentile)	BW (cont.)	GA (cont.)	Post Term (>42 wks)	HBW (>4000g)	LGA(>90th percentile)			
156					X								6-14y	Obesity	OR= 1.19 [1.13, 1.26]
162						◊							3-18y	Obesity	OR= 0.87 [0.69, 1.08]
162						X							1-17y	Obesity	OR= 0.61 [0.46, 0.80]
162						X							<6y	Obesity	OR= 0.61 [0.43, 0.88]
162						X							6-13y	Obesity	OR= 0.54 [0.32, 0.90]
162						X							13-17y	Obesity	OR= 0.74 [0.37, 1.49]
163								X					7-11y	Obesity	β= 0.649 per kg increase
162											◊		1-16y	Obesity	OR= 2.23 [1.91, 2.61]
162											X		0-17y	Obesity	OR= 2.07 [1.91, 2.24]
162											X		<6y	Obesity	OR= 2.10 [1.93, 2.29]
162											X		6-13y	Obesity	OR= 1.76 [1.36, 2.20]
162											X		13-17y	Obesity	OR= 2.58 [1.56, 4.26]

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Table 1 g- Associations between size-at-birth and developmental (neurodevelopmental, motor, cognitive and educational) outcomes

Ref	Exposures (size at birth)												Population	Outcomes	Effect size [confidence interval], direction of association
	Small							Cont		Large					
	EPT (<28wks)	ELBW (<1000g)	VPT (<32wks)	VLBW (<1500g)	PT (<37wks)	LBW (<2500g)	SGA(<10th percentile)	BW (cont.)	GA (cont.)	Post Term (>42 wks)	HBW (>4000g)	LGA(>90th percentile)			
														Brain neurodevelopment	
164			X	X									8-18y	Total Brain Volume	Cohen's d= -0.58 [-0.43, -0.73]
164			X	X									8-18y	White Matter Volume	Cohen's d= -0.53 [-0.40, -0.67]
164			X	X									8-18y	Grey Matter Volume	Cohen's d= -0.62 [-0.48, -0.76]
164			X	X									14-18y	Cerebellar Volume	Cohen's d= -0.74 [-0.56, -0.92]
164			X	X									14-17y	Hippocampus Volume	Cohen's d= -0.47 [-0.26, -0.69]
164			X	X									14-19y	Size of Corpus Callosum	Cohen's d= -0.71 [-0.34, -1.07]
165					X								3d-20y	Fractional Anisotropy Splenium of Corpus Callosum	SMD= -0.75 [-0.93, -0.57]
165					X								3d-20y	Fractional Anisotropy Genu of Corpus Callosum	SMD= -0.65 [-0.97, -0.33]
165					X								3d-20y	Fractional Anisotropy Body of Corpus Callosum	SMD= -0.73 [-1.13, -0.32]
166					X								Newborn	Auditory Brainstem Response Interval Between Peaks III &V (ms)	MD= 0.081 [0.055, 0.110]
166					X								Newborn	Auditory Brainstem Response: Interval Between Peaks I-V (ms)	MD= 0.073 [0.036, 0.122]
166					X								Newborn	Auditory Brainstem Response: Latency of Peak V (ms)	MD= 0.112 [0.058, 0.165]
166					X								Newborn	Auditory Brainstem Response: Latency of Peak I (ms)	MD= 0.048 [0.008, 0.087]
167					X								9.3-26.5y	Grey matter Left Cuneus Cortex, Brodmann Area 18	SDM= 1343, p<0.05
167					X								9.3-26.5y	Grey Matter Left Superior Frontal Gyrus, Medial Area 8	SDM= 1.554, p<0.05
167					X								9.3-26.5y	Grey Matter Right Anterior Cingulate, Brodmann Area 32	SDM= 1.363, p<0.05
167					X								9.3-26.5y	Grey Matter Right Inferior Temporal Gyrus, Brodmann Area 20	SDM= -4.061, p<0.05
167					X								9.3-26.5y	Grey Matter Left Inferior Temporal Gyrus, Brodmann Area 20	SDM= -3.967, p<0.05
167					X								9.3-26.5y	Grey Matter Left Superior Frontal Gyrus, Orbital Area 11	SDM= -2.198, p<0.05
167					X								9.3-26.5y	Grey Matter Right Caudate Nucleus	SDM= -2.197, p<0.05
167					X								9.3-20.2y	White Matter Right Fusiform Gyrus, Brodmann Area 37	SDM= 2.934, p<0.05
167					X								9.3-20.2y	White Matter Right praecuneus, Brodmann Area 30	SDM= 2.920, p<0.05
167					X								9.3-20.2y	White Matter Left Inferior Temporal Gyrus, Brodmann Area 19	SDM= -5.404, p<0.05
167					X								9.3-20.2y	White Matter Right Inferior Temporal Gyrus, BrodmannArea 20	SDM= -4.278, p<0.05
167					X								9.3-20.2y	White Matter Left Cortico-Spinal Projections	SDM= -2.960, p<0.05
167					X								9.3-20.2y	White Matter Right Inferior Frontal Gyrus	SDM= -3.599, p<0.05
														Motor	
														Visuomotor	
147					X								0-14m	Visual Following	Cohen's d= -0.13 [-0.49, 0.23]
147					X								Neonates	Visual Following (animate stimuli)	Cohen's d= -0.45 [-0.86, -0.04]
147					X								Neonates	Visual Following	Cohen's d= 0.22 [0.03, 0.04]
147					X								Infants	Visual Following	Cohen's d= -0.77 [-1.23, -0.31]
168			X	X									5.1-7y	Visual Perception Abilities (K-ABC)	Cohen's d= -0.10 [-0.22, 0.03]
168			X	X									5.2-11.5y	Visual Perception Abilities (MVPT)	Cohen's d= -0.10 [-0.31, 0.11]
168			X	X									8-16.8y	Visual Perception Abilities (JLO)	Cohen's d= -0.60 [-0.87, -0.32]
168			X	X									6.0-8.7y	Visual Perception Abilities (NEPSY)	Cohen's d= -0.92 [-1.44, -0.40]
168			X	X									5.5-8.0y	Visual Perception Abilities (TVPS-R)	Cohen's d= -0.72 [-1.2, -0.23]
168			X	X									3.5-16.8y	Visual Motor Integration (VMI)	Cohen's d= -0.69 [-0.80, -0.58]
146			X	X									3-5y	Visuomotor Integration Skill: Graphomotor Skill	Cohen's d= -0.57 [-0.72, - 0.43]
169								X					10-11y	Unaided Distance Vision of 6/12 or Worse (indicative of myopia)	aOR= 0.85 [0.76, 0.95] per kg increase
169								X					15-16y	Unaided Distance Vision of 6/12 or Worse (indicative of myopia)	aOR= 1.00 [0.90, 1.11] per kg increase
														Cerebral Palsy	
170	X												1-10y	Cerebral Palsy	*Prevalence Ratio= 129.20*
171	X												2-8y	Cerebral Palsy	*Prevalence Ratio= 60.92*
171		X											2-8y	Cerebral Palsy	*Prevalence Ratio= 42.58*
170			v										1-10y	Cerebral Palsy	*Prevalence Ratio= 54.80*
171			v										2-8y	Cerebral Palsy	*Prevalence Ratio= 31.96*
171				o									2-8y	Cerebral Palsy	*Prevalence Ratio= 44.49*
170					LLT								1-10y	Cerebral Palsy	*Prevalence Ratio= 4.42*
172					LLT								Infants	Cerebral Palsy	RR= 1.89 [1.04–3.43]
171					LT								2-8y	Cerebral Palsy	*Prevalence Ratio= 5.00*
172					LT								Infants	Cerebral Palsy	RR= 3.47 [1.29, 9.31]
173					ET								4-19y	Cerebral Palsy	Risk Ratio= 1.75 [1.32, 2.31]
171						X							2-8y	Cerebral Palsy	*Prevalence Ratio= 7.64*
172							X						Infants	Cerebral Palsy	RR= 3.48 [1.86, 6.49]
172							X						Infants	Cerebral Palsy	RR= 1.39 [0.95, 2.03]

Ref	Exposures (size at birth)												Population	Outcomes	Effect size [confidence interval], direction of association
	Small							Cont		Large					
	EPT (<28wks)	ELBW (<1000g)	VPT (<32wks)	VLBW (<1500g)	PT (<37wks)	LBW (<2500g)	SGA(<10th percentile)	BW (cont.)	GA (cont.)	Post Term (>42 wks)	HBW (>4000g)	LGA(>90th percentile)			
170									X				1-10y	Cerebral Palsy	logit= -0.4x+8.6 [8.4, 8.8] per GA category
														Physical Motor	
174			^										<7y	Motor Development	aSMD= -0.26 [-0.53, 0.006]
174					LT								<7y	Motor Development	aSMD= -0.14 [-0.33, 0.04]
174						X							<7y	Motor Development	aSMD= -0.14 [-0.23, -0.06]
174						X							<7y	Motor Development	aSMD= -0.11 [-0.20, -0.02]
174						^							<7y	Motor Development	aSMD= -0.26 [-0.40,-0.12]
174							BT						<7y	Motor Development	aSMD= -0.01 [-0.10, 0.07]
174							P3						<7y	Motor Development	aSMD= 0.02 [-0.09,0.12]
175			X	X									6-36m	Motor Skills (BSID-II)	Cohen's d= -0.88 [-0.96, -0.80]
175			X	X									5-15y	Motor Skills (MABC)	Cohen's d= -0.65 [-0.70, -0.60]
175			X	X									6-9y	Fine Motor Skills (BOTMP)	Cohen's d= -0.86 [-0.99, -0.73]
175			X	X									8-9y	Gross Motor Skills (BOTMP)	Cohen's d= -0.53 [-0.60, -0.46]
141					X								2-4y	Standardised Score for Motor Skills	SMD= -0.44 [-0.50, -0.37]
141					X								4-11y	Standardised Score for Motor Skills	SMD= -0.59 [-0.89, -0.28]
176			X	X									3-6y	Motor Performance(VMI, MSCA, MABC-2, PDMS BSID-II, PEDI, GD	SMD= -0.71 [-0.80, -0.62]
176			X	X									3.7-5y	Visual Motor Integration (VMI)	SMD= -0.70 [-0.87, -0.54]
176			X	X									4y	Motor (MSCA)	SMD= -0.92 [-1.16, -0.68]
176			X	X									3-6y	Movement Assessment (MABC-2)	SMD= -0.71 [-0.92, -0.50]
176			X	X									5.1-6y	Motor Skills (PDMS)	SMD= -0.71 [-0.98, -0.44]
176			X	X									3-6.2y	Activity Limitation (BSID-II,MABC-1, ASQ, HSCS, AGTE, FTFQ)	RR= 3.39 [2.68, 4.27]
176			X	X									3y	Motor Skills (BSID-II)	RR= 13.94 [3.45, 56.42]
176			X	X									5.5-6.2y	Movement Assessment (MABC-1)	RR= 2.69 [1.72, 4.22]
175			X	X									8-15y	General Motor Proficiency: Battery Composite (BOTMP)	Cohen's d= -0.57 [-0.68, -0.46]
177						^							<10y	Motor Scores	WMD= -6.45 [-9.64, -3.27]
177						^							<10y	Motor Scores	RR= 3.72 [1.32, 10.54]
177						X							10m-5y	Motor Scores	WMD= -4.16 [-5.42, - 2.89]
177						X							<10y	Motor Impairment	RR= 3.32 [1.56, 7.06]
176			X	X									3-6y	Motor Coordination (KTK and VMI)	SMD= -0.47 [-0.76, -0.17]
176			X	X									3-6y	Upper and Lower Limb Coordination (MSCA)	SMD= -0.98 [-1.38, -0.58]
178			X	X									7.5-14.2y	Developmental Coordination Disorder(<5th percentile MABC)	OR= 6.29 [4.37, 9.05]
178			X	X									8-13y	Developmental Coordination Disorder(<5-15th percentile MABC)	OR= 8.66 [3.40, 22.07]
139					X								1-60m	Motor activity (Behaviour)	Cohen's d= -0.07 [-0.25, 0.39]
179					X								0-21y	Neuromusculoskeletal and Movement-Related Functions	Cohen's d= 0.068, p<0.358
179						X							0-21y	Neuromusculoskeletal and Movement-Related Functions	Cohen's d= -0.391, p<0.000
180								X					5-67y	Grip muscle Strength	aβ= 0.86 [0.58, 1.15] per kg increase
180								X					<21	Grip muscle Strength	aβ= 0.48 [0.05, 0.92] per kg increase
175								X					6-36m	Psychomotor Development Outcomes (BSID-II)	R= 0.54, p= 0.008
175									X				6-36m	Psychomotor Development Outcomes (BSID-II)	R= 0.42, p= 0.05
175								X					5-15y	Overall Motor Impairment (MABC)	R= 0.25, p= 0.53
175									X				5-15y	Overall Motor Impairment (MABC)	R= 0.21, p= 0.58
														Cognitive	
														Intellectual Disabilities	
181			X										4-17y	Executive Functioning	Hedge's g= -0.51 [-0.58, -0.44]
181			X										4-10y	Executive Functioning	Hedge's g= -0.51 [-0.60, -0.42]
181			X										11-17y	Executive Functioning	Hedge's g= -0.52 [-0.62, -0.42]
181			X										4-17y	Processing Speed	Hedge's g= -0.49 [-0.60, -0.39]
181			X										4-10y	Processing Speed	Hedge's g= -0.53 [-0.65, -0.41]
181			X										11-17y	Processing Speed	Hedge's g= -0.30 [-0.52, -0.08]
141					X								4-11y	Processing Speed	SMD= -0.53 [-0.66, -0.41]
148					X								2-17y	Inhibition	Cohen's d= 0.25 [0.03, 0.47]
148	26												2-17y	Inhibition	Cohen's d= 0.50 [0.10, 0.89]
182					X	X							4y-11y	Inhibition	SMD= 0.39 [0.55, 0.23]
148					X								2-17y	Planning	Cohen's d= 0.38 [0.08, 0.68]
148	26												2-17y	Planning	Cohen's d= 0.69 [0.50, 0.88]
177						X							≤3y	Developmental Delay (visual, hearing and speech difficulties)	RR= 1.97 [1.41, 2.73]
146			X	X									3-5y	Executive Functions: Global Executive Composite Score	Cohen's d= 0.49 [0.32, 0.66]
148					X								2-17y	Shifting (measured by Trail Making Test)	Cohen's d= 0.50 [0.36, 0.64]

Ref	Exposures (size at birth)												Population	Outcomes	Effect size [confidence interval], direction of association
	Small							Cont		Large					
	EPT (<28wks)	ELBW (<1000g)	VPT (<32wks)	VLBW (<1500g)	PT (<37wks)	LBW (<2500g)	SGA(<10th percentile)	BW (cont.)	GA (cont.)	Post Term (>42 wks)	HBW (>4000g)	LGA(>90th percentile)			
148					X								2-17y	Shifting (measured by Sorting Tasks)	Cohen's d= 0.10 [-0.06, 0.27]
139					X								1-60m	Inhibition (Behaviour)	Cohen's d= -0.02 [-0.37, 0.32]
139					X								1-60m	Inhibitory Control (Psychological)	Cohen's d= 0.13 [-0.11, 0.37]
139					X								1-60m	Distractibility (Behaviour)	Cohen's d= 0.004 [-0.25, 0.26]
183					ET								3-6y	Cognitive: General	SMD= 0.05 [0.02, 0.08]
182					X	X							5.11-11.2y	Cognitive Flexibility	SMD= 0.51 [0.72, 0.31]
138			^	X									8.2-22.3y	Cognitive Flexibility	Cohen's d= -0.49 [-0.66, -0.33]
151					X								5-14y	Cognitive Test Scores	WMD= 10.85 [9.23, 12.47]
177						^							<10y	Cognitive Score	WMD= -7.23 [-9.20, -5.26]
177						^							<10y	Cognitive Score	RR= 3.59 [1.55, 8.32]
177						X							2m-18y	Cognitive Score	WMD= -6.14 [-8.70, -3.57]
177						X							2m-9y	Cognitive Score	WMD= -4.56 [-6.38, -2.74]
177						X							10-18y	Cognitive Score	WMD= -15.45 [-24.08, -6.83]
151								X					5-14y	Cognitive Test Scores	R^2= 0.51, p<0.001 per g increase
151									X				5-14y	Cognitive Test Scores	R^2= 0.49, p<0.001 per week increase
174			^										<7y	Cognitive Development	aSMD= -0.16 [-0.34, 0.31]
174					LT								<7y	Cognitive Development	aSMD= -0.21 [-0.39, -0.04]
174						^							<7y	Cognitive Development	aSMD= -0.27 [-0.49, -0.07]
174						X							<7y	Cognitive Development	aSMD= -0.13 [-0.20, -0.07]
174						X							<7y	Cognitive Development	aSMD= -0.07 [-0.12, -0.03]
174							BT						<7y	Cognitive Development	aSMD= -0.05 [-0.11, 0.12]
174							P3						<7y	Cognitive Development	aSMD= -0.09 [-0.24, 0.07]
179					X								0-21y	Mental Function	Cohen's d= -0.263, p<0.001
179						X							0-21y	Mental Function	Cohen's d= -0.655, p<0.001
184					X								6-18y	Special Educational Needs	RR= 2.85 [2.12, 3.84]
														Memory	
138			^	X									8-14.9y	Working Memory	Cohen's d= -0.36 [-0.47, -0.20]
141					X								4-11y	Working Memory	SMD= -0.61 [-0.72, -0.50]
141					X								11-18y	Working Memory	SMD= -0.53 [-0.72, -0.34]
182					X	X							4-14y	Working Memory	SMD= 0.52 [0.65, 0.38]
182									X				4.5-12y	Working Memory	β= 0.07 [0.01, 0.13] per wk increase
146			X	X									3-5y	Short-term Verbal Memory (per number of digits recalled)	Cohen's d= -0.49 [-0.75, -0.22]
														Intelligence Quotient (IQ)	
185	X												3-16y	Intelligence Quotient	WMD= -13.9 [-11.5, -16.2]
186		X											4-18y	Intelligence Quotient	WMD= -13.95 [-11.71, -16.20]
187		X											<10y	Intelligence Quotient/Development Quotient	*MD= -6.18*
188			X										5-20.1y	Intelligence Quotient Score	SMD= -0.86 [-0.94, -0.78]
181			X										4-17y	Intelligence Test	Hedge's g= -0.82 [-0.90, -0.74]
181			X										4-10y	Intelligence Test	Hedge's g= -0.86 [-0.99, -0.73]
181			X										11-17y	Intelligence Test	Hedge's g= -0.76 [-0.91, -0.60]
185			v										3-16y	Intelligence Quotient	WMD= -11.4 [-9.7, -13.2]
186				o									5-26y	Intelligence Quotient	WMD= -9.85 [-8.43, -11.28]
187				X									<10y	Intelligence Quotient/Development Quotient	*MD= -7.94*
185					X								3-16y	Intelligence Quotient	WMD= -11.94 [-10.47, -13.42]
141					X								2-31y	Full-Scale Intelligence Quotient	SMD= -0.70 [-0.73, -0.66]
141	X												2-18y	Full-Scale Intelligence Quotient	SMD= -0.78 [-0.85, -0.72]
141			v										2-24y	Full-Scale Intelligence Quotient	SMD= -0.73 [-0.78, -0.67]
141					LT								3-31y	Full-Scale Intelligence Quotient	SMD= -0.24 [-0.35, -0.12]
141					X								2-4y	Full-Scale Intelligence Quotient	SMD= -0.72 [-0.80, -0.65]
141					X								4-11y	Full-Scale Intelligence Quotient	SMD= -0.73 [-0.78, -0.67]
141					X								11-18y	Full-Scale Intelligence Quotient	SMD= -0.73 [-0.85, -0.62]
141					X								5-31y	Performance Intelligence Quotient	SMD= -0.67 [-0.73, -0.60]
141	X												8-18y	Performance Intelligence Quotient	SMD= -0.89 [-1.05, -0.72]
141			v										5-24y	Performance Intelligence Quotient	SMD= -0.65 [-0.73, -0.57]
141					X								4-11y	Performance Intelligence Quotient	SMD= -0.70 [-0.78, -0.61]
141					X								11-18y	Performance Intelligence Quotient	SMD= -0.90 [-1.09, -0.70]
141					X								5-31y	Verbal Intelligence Quotient	SMD= -0.53 [-0.60, -0.47]
141	X												8-18y	Verbal Intelligence Quotient	SMD= -0.67 [-0.83, -0.51]
141			v										5-24y	Verbal Intelligence Quotient	SMD= -0.55 [-0.63, -0.48]

Ref	Exposures (size at birth)												Population	Outcomes	Effect size [confidence interval], direction of association
	Small							Cont		Large					
	EPT (<28wks)	ELBW (<1000g)	VPT (<32wks)	VLBW (<1500g)	PT (<37wks)	LBW (<2500g)	SGA(<10th percentile)	BW (cont.)	GA (cont.)	Post Term (>42 wks)	HBW (>4000g)	LGA(>90th percentile)			
141					LT								12-31y	Verbal Intelligence Quotient	SMD= -0.14 [-0.35, 0.07]
141					X								4-11y	Verbal Intelligence Quotient	SMD= -0.57 [-0.65, -0.48]
141					X								11-18y	Verbal Intelligence Quotient	SMD= -0.49 [-0.65, -0.33]
146			X	X									3-5y	Total Intelligence Quotient Score (per IQ score)	Cohen's d= -0.77 [-0.88, -0.66]
146			X	X									3-5y	Intelligence Quotient Vulnerability	Risk ratio= 3.61 [2.58, 5.06]
183					LT								2-6y	Cognitive: General	aRisk ratio= 1.38 [1.06, 1.79]
183					LT								3-6y	Cognitive: Verbal Intelligence Quotient	aRisk Ratio= 1.34 [0.83, 2.17]
186						X							5-14y	Intelligence Quotient	WMD= -6.83 [-4.76, -8.89]
177						X							<10y	Low Cognitive Score: IQ<25th Percentile or Mental Quotient <85	RR= 2.69 [1.34, 5.39]
177						X							10-18y	Low Cognitive Score: IQ<25th Percentile or Mental Quotient <86	RR= 1.28 [1.02, 1.61]
189						X							14-22.2y	Full-scale Intelligence Quotient Score	MD= -7.63 [-5.95, -9.31]
186						X							4-27y	Intelligence Quotient	WMD= -10.47 [-9.26, -11.68]
186						X							<10y	Intelligence Quotient	WMD= -10.58 [-8.87, -12.30]
186						X							10-18y	Intelligence Quotient	WMD= -9.82 [-7.88, -11.75]
187						X							0-10y	Intelligence Quotient/Development Quotient Score	*MD= -4.14*
187						X							≤2y	Intelligence Quotient/Development Quotient Score	*MD= -0.01 (1.77)*
187						X							2-5y	Intelligence Quotient/Development Quotient Score	*MD= -8.08 (0.86)*
187						X							5-10y	Intelligence Quotient/Development Quotient Score	*MD= -6.9 (2.33)*
142							X						5-19y	Verbal Intelligence Quotient	SMD= -0.26 [-0.36, -0.16]
142							X						5-19y	Performance Intelligence Quotient	SMD= -0.36 [-0.46, -0.25]
188							X						5-20.1y	Intelligence Quotient Score	MD= -0.04 [-0.15, 0.07]
142							X						5-18.1y	Intelligence Quotient	SMD= -0.38 [+T156:T203-0.51, -0.25]
188								X					5-20.1y	Intelligence Quotient Score	MD= 0.02 [0.003, 0.02] per g increase
142								X					5-19y	Total Intelligence Quotient	R= 0.546, p= 0.103
142								X					5-19y	Verbal Intelligence Quotient	R= 0.406, p= 0.497
142								X					5-19y	Performance Intelligence Quotient	R= 0.771, p= 0.127
188									X				5-20.1y	Intelligence Quotient Score	MD= 1.26 [0.52, 2.00] per wk increase
142									X				5-19y	Total Intelligence Quotient	R= 0.509, p= 0.133
142									X				5-19y	Verbal Intelligence Quotient	R= 0.334, p= 0.517
142									X				5-19y	Performance Intelligence Quotient	R= 0.673, p= 0.143
														Communication	
190			X	X									4-12.2y	Expressive Language: Production of Speech	Hedges' g= -0.63 [-0.80, -0.45]
190			X	X									4-6.3y	Expressive Language: Production of Speech	Hedges' g= -0.71 [-0.86, -0.55]
190			X	X									4-12.2y	Receptive Language: Comprehension of Language	Hedges' g= -0.77 [-0.94, -0.60]
190			X	X									4-6.3y	Receptive Language: Comprehension of Language	Hedges' g= -0.83 [-0.97, -0.69]
138			^	X									13.4-23.2y	Verbal Fluency	Cohen's d= -0.57 [-0.82, -0.32]
174			^										<7y	Language Development	aSMD= -0.20 [-0.55, 0.15]
191			X	X									6-8y	Total Language Score	MD= -13.20 [-15.88, -10.51]
191			X	X									5-8y	Receptive Language Score	MD= -6.10 [-8.47, -3.73]
191			X	X									5-8y	Expressive Language Score	MD= -6.16 [-8.49, -3.84]
191			X	X									4-7y	Pragmatics	MD= -8.30 [-20.76, 4.15]
191			X	X									5-8y	Phonological Awareness	MD= -1.46[-1.91, -1.01]
148					X								2-17y	Semantic Fluency	Cohen's d= 0.43 [0.28, 0.59]
148					X								2-17y	Phonemic Fluency	Cohen's d= 0.45 [0.30, 0.60]
148	26												2-17y	Phonemic Fluency	Cohen's d= 0.58 [0. 30, 0.86]
192					X								3-12y	Simple Language Function	Cohen's d= -0.45 [-0.59, -0.30]
192					X								3-12y	Total Complex Language Function	Cohen's d= -0.62 [–0.82, –0.43]
192					X								3-12y	Total Complex Language Function (measured by CELF)	Cohen's d= -0.71 [-0.85, -0.57]
192					X								3-12y	Total Complex Language Function excluding major disabilities	Cohen's d= -0.54 [-1.01, -0.07]
192					X								4-12y	Receptive Language	Cohen's d= -0.69 [-0.82, -0.55]
192					X								4-12y	Expressive Language	Cohen's d= -0.61 [-0.74, -0.47]
183					LT								2-3y	Cognitive: Language	aRR= 1.39 [1.21, 1.60]
174					LT								<7y	Language Development	aSMD= -0.05 [-0.23, 0.13]
174						^							<7y	Language Development	aSMD= -0.28 [-0.60, 0.05]
174						X							<7y	Language Development	aSMD= -0.11 [-0.22,0.00]
174						X							<7y	Language Development	aSMD= -0.05 [-0.10, 0.01]
174							BT						<7y	Language Development	aSMD= -0.06 [-0.18, 0.06]
174							P3						<7y	Language Development	aSMD= 0.03 [-0.13, 0.19]

Ref	Exposures (size at birth)												Population	Outcomes	Effect size [confidence interval], direction of association
	Small							Cont		Large					
	EPT (<28wks)	ELBW (<1000g)	VPT (<32wks)	VLBW (<1500g)	PT (<37wks)	LBW (<2500g)	SGA(<10th percentile)	BW (cont.)	GA (cont.)	Post Term (>42 wks)	HBW (>4000g)	LGA(>90th percentile)			
														Specific Learning Disorder: Language (reading, spelling)	
193	X												5-18y	Reading	MD= -8.54 [-10.52, -6.55]
193			v										5-18y	Reading	MD= -1.42 [-4.58, 1.75]
194			X										6-12.8y	Reading comprehension	Cohen's d= -0.57 [-0.68, -0.46]
194			X										6-12.8y	Reading excluding children with major disabilities	Cohen's d= -0.59 [-1.01, -0.17]
138			^	X									5-20y	Reading	Cohen's d= -0.48 [-0.60, -0.34]
193					X	X							5-18y	Reading: Aggregate Measure of Reading	MD= -7.98 [-13.05, -2.91]
193					X	X							5-18y	Reading: Decoding	MD= -10.18 [-16.83, -3.53]
193					X	X							5-18y	Reading: Word Identification	MD= -7.44 [-9.08, -5.80]
193					X	X							5-18y	Reading: Pseudoword Decoding	MD= -5.37 [-27.41, 16.67]
193					X	X							5-18y	Reading: Reading Comprehension	MD= -7.96 [-12.15, -3.76]
193					X	X							5-8y	Reading	MD= -7.38 [-9.69, -5.07]
193					X	X							9-11y	Reading	MD= -8.93 [-14.42, -3.43]
193					X	X							12-18y	Reading	MD= -3.35 [-6.70, 0.01]
141					X								4-11y	Reading	SMD= -0.67 [-0.87, -0.47]
141					X								11-18y	Reading	SMD= -0.51 [-0.67, -0.35]
193					LT								5-18y	Reading	MD= -8.07 [-14.29, -1.84]
184					X								6-18y	Reading (SD)	SMD= -0.44 (SE 0.10), p<0.001
194			X										6-10.11y	Decoding	Cohen's d Effect= -0.42 [-0.57, -0.27]
194			X										6-10.11y	Decoding (excluding children with intellectual disabilities)	Cohen's d Effect= -0.41 [-0.56, -0.24]
194			X										6-10.11y	Decoding (excluding children with major disabilities)	Cohen's d Effect= -0.43 [-0.54, -0.32]
190			X	X									2-12.2y	Expressive: Semantics	Hedges' g= -0.38 [-0.48, -0.29]
190			X	X									2-8.7y	Expressive: Semantics	Hedges' g= -0.40 [-0.50, -0.31]
190			X	X									5.17-12.2y	Receptive: Semantics	Hedges' g= -0.59 [-0.79, -0.40]
138			^	X									5-17.8y	Spelling	Cohen's d= -0.76 [-1.13, -0.40]
141					X								4-11y	Spelling	SMD= -0.56 [-0.74, -0.38]
141					X								11-18y	Spelling	SMD= -0.51 [-0.92, -0.09]
184					X								6-18y	Spelling (SD)	SMD= -0.52 (SE 0.06), p<0.001
191			X	X									5-8y	Grammar	MD= -4.55 [-8.75, -0.34]
														Specific Learning Disorder: Mathematics	
193	X												5-18y	Mathematics	MD= -11.92 [-14.60, -9.24]
193			v										5-18y	Mathematics	MD= -7.60 [-9.25, -5.96]
138			^	X									5-20y	Mathematics	Cohen's d= -0.60 [-0.74, -0.46]
193					X	X							5-18y	Mathematics: Aggregate Measure of Mathematics	MD= -12.90 [-23.38, -2.43]
193					X	X							5-18y	Mathematics: Mathematical Knowledge	MD= -9.88 [-11.68, -8.08]
193					X	X							5-18y	Mathematics: Calculation	MD= -10.57 [-15.62, -5.52]
193					X	X							5-18y	Mathematics: Mathematical Fluency	MD= -6.89 [-13.54, -0.23]
193					X	X							5-18y	Mathematics: Applied Problems	MD= -11.41 [-17.57, -5.26]
193					X	X							5-8y	Mathematics	MD= -10.42 [-11.83, -9.01]
193					X	X							9-11y	Mathematics	MD= -10.76 [-17.12, -4.41]
193					X	X							12-18y	Mathematics	MD= -8.77 [-11.18, -6.37]
141					X								4-11y	Mathematics	SMD= -0.78 [-1.10, -0.46]
141					X								11-18y	Mathematics	SMD= -0.42 [-0.90, 0.06]
184					X								6-18y	Mathematics: Arithmetic (SD)	SMD= -0.71 (SE 0.09), p<0.001
193					LT								5-18y	Mathematics	MD= -7.98 [-12.81, -3.16]
173					ET								5-10y	Mathematical Difficulties	Risk Ratio= 1.13 [1.05,1.22]
														Others neurological related outcomes	
195					X								3-19y	Non-right Handedness	OR= 2.12 [1.59,2.78]
														Combinations of neurodevelopmental outcomes	
176			X	X									5.1-6.1y	Neurological Dysfunction (Touwen)	RR= 4.55 [1.20, 17.17]

Supplementary material 4 a- Quality of systematic reviews with meta-analyses

Johanna Briggs critical appraisal scores for systematic reviews; additive score of meeting criteria (11 questions)						
5 (low)	6	7	8	9	10	11 (high)
100	124	93	132	193	184	162
89	191	63	97	113	120	86
	107	115	78	117	133	43
	112	167	161	88	145	140
	96	83	80	118	180	150
	148	185	119	114	51	116
	70	187	130	109	181	101
	174	155	128	177	141	188
	137	76	189	178	131	72
	90	98	138	105	159	182
	95	163	149	183	175	87
	127	135	160	108	56	54
		49	64	69	57	52
		71	153	62	58	154
			68	156	67	74
			111	134	166	121
			143	45	164	42
			186	104	91	102
			103	125	122	172
			139	142	192	
			165	151	176	
			82	106	94	
			157	79	195	
			81	190	53	
			44	64	170	
			147	173	59	
			194	47	60	
			146	152	110	
			65	50	136	
			55		61	
			158		171	
			129		168	
					84	

 Chapter 3- Establishment of a birth-to-education cohort of 1 million Palestinian refugees using electronic medical records and electronic education records

To explore the association between birth size and child outcomes, particularly in an understudied region, I required a cohort. UNRWA shifted from collecting health records in a paper format to using an e-health format (in 2010 and then updated the system in 2013 and 2017), this offered me an opportunity to build a cohort and to explore these questions without collecting further data. UNRWA had electronic health data on obstetrics and children's growth and health, though these datasets were not linked. I travelled to UNRWA headquarters in Jordan and collaborated with teams in both Jordan and Gaza to extract and generate a cohesive cohort from these data. I successfully linked all the data, enabling us to utilize different sections of the cohort for our analysis. I explored different methods of linkage including probabilistic and deterministic linkages. I ultimately opted to include only the deterministic linkage method due to its high levels of linkage. Ethical approval letters are included in the Thesis Appendix 2.

RESEARCH PAPER COVER SHEET

SECTION A – Student Details

Student ID Number	2004086	**Title**	Ms
First Name(s)	Zeina		
Surname/Family Name	Jamaluddine		
Thesis Title	Establishing a Palestinian Refugee Birth Cohort Using Electronic Health Records to Investigate the Effects of Size at Birth on Child Wellbeing		
Primary Supervisor	Oona Campbell		

SECTION B – Paper already published.

Where was the work published?	International Journal of Population Data Science		
When was the work published?	24/10/2023		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	Not applicable		
Have you retained the copyright for the work? *	Yes	Was the work subject to academic peer review?	Yes

* Attach evidence of permission from the copyright holder (publisher or other author) to include this work.

SECTION C – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper.	OC conceived the use of UNRWA electronic records for linkage; ZJ, HG, AS, and OC designed the study approach; AS, GB, HA, SA, GP and RI guided the understanding of the dataset structure, GB, HA, SA and RI supported in the extraction of the data; GP encrypted the data; MS, HG, and OC supervised the data analysis; ZJ and OC analysed the data. ZJ wrote the first draft. All authors contributed to the writing of the paper. All authors read and approved the final version.

SECTION D

Student Signature	
Date	27/05/2024
Supervisor Signature	
Date	16/06/2024

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Establishment of a birth-to-education cohort of 1 million Palestinian refugees using electronic medical records and electronic education records

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Abstract

Introduction

By linking datasets, electronic records can be used to build large birth-cohorts, enabling researchers to cost-effectively answer questions relevant to populations over the life-course. Currently, around 5.8 million Palestinian refugees live in five settings: Jordan, Lebanon, Syria, West Bank, and Gaza Strip. The United Nations Relief and Works Agency for Palestine Refugees in the Near East (UNRWA) provides them with free primary health and elementary-school services. It maintains electronic records to do so.

We aimed to establish a birth cohort of Palestinian refugees born between 1st January 2010 and 31st December 2020 living in five settings by linking mother obstetric records with child health and education records and to describe some of the cohort characteristics. In future, we plan to assess effects of size-at-birth on growth, health and educational attainment, among other questions.

Methods

We extracted all available data from 140 health centres and 702 schools across five settings, i.e. all UNRWA service users. Creating the cohort involved examining IDs and other data, preparing data, de-duplicating records, and identifying live-births, linking the mothers' and children's data using different deterministic linking algorithms, and understanding reasons for non-linkage.

Results

We established a birth cohort of Palestinian refugees using electronic records of 972,743 live births. We found high levels of linkage to health records overall (83%), which improved over time (from 73% to 86%), and variations in linkage rates by setting: these averaged 93% in Gaza, 89% in Lebanon, 75% in Jordan, 73% in West Bank and 68% in Syria. Of the 423,580 children age-eligible to go to school, 47% went to UNRWA schools and comprised of 197,479 children with both health and education records, and 2,447 children with only education records. In addition to year and setting, other factors associated with non-linkage included mortality and having a non-refugee mother. Misclassification errors were minimal.

Conclusion

This linked open birth-cohort is unique for refugees and the Arab region and forms the basis for many future studies, including to elucidate pathways for improved health and education in this vulnerable, understudied population. Our characterization of the cohort leads us to recommend using different sub-sets of the cohort depending on the research question and analytic purposes.

Keywords

electronic records; data linkage; mother child; Palestinian refugees; health records; education records; refugee birth cohort

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Introduction

Refugees and urban-poor populations remain under-studied globally because their unstable living circumstances make them difficult to research, especially longitudinally. The Arab region has few longitudinal cohorts [1], little research on refugees or the urban-poor, and limited research using individual-level electronic records at a large scale.

Large longitudinal studies are enormously beneficial in elucidating factors shaping human capital, including health and educational outcomes [2, 3]. The use of existing electronic records to build large birth-cohorts offers a cost-effective alternative to traditional birth cohorts, enabling researchers to answer questions relevant to populations over the life-course. Linked data make more information available, allowing analyses in different domains, for instance, understanding the effects of ill-health on educational attainment. Recently for example, linked administrative data have been used to model disease patterns and to examine factors associated with COVID-19 infection and related deaths to inform timely policy changes [4, 5].

Electronic data present challenges in terms of data-capture and linkage [6]; it is important to detect the extent of errors including misclassification, temporal data changes, missing data, and duplicated records and to identify the population included and excluded. Linking electronic data adds further challenges depending on the methods used for linkage (deterministic or probabilistic methods), the presence of duplicated records (causing additional linkage error), estimation of error rates (with challenges in obtaining a gold standard), and identification of the population (understanding who does and does not link) [6–8].

Population and settings

Palestinian refugees include all descendants of Palestine refugee males, who are "persons whose normal place of residence was Palestine during the period 1 June 1946 to 15 May 1948, and who lost both home and means of livelihood as a result of the 1948 conflict". Palestinian refugees comprise 20% of the global refugee population and have experienced displacement and marginalisation since 1948 [9]. Currently, around 5.8 million Palestinian refugees live in 58 camps and multiple informal gatherings in five settings: Jordan, Lebanon, Syria, West Bank, and Gaza Strip (representing an estimated 45% of all Palestinians) [9, 10]. The United Nations Relief and Works Agency for Palestine Refugees in the Near East (UNRWA) is responsible for providing free primary health and elementary-school services to the refugees [10], and runs 140 health centres and 702 schools to do so [11]. UNRWA also supports Palestinian refugees' access to secondary and tertiary health-care services via a partial reimbursement scheme.

Access to UNRWA services differs by setting (Box 1). In 2021, UNRWA recorded 3,090,084 refugees accessed their health services, indicating not all 5.8 million Palestinian refugees are UNRWA service recipients [12]. Some, particularly the better-off, may use alternative services in the host communities [12, 13], yet others may use a mix of UNRWA and other service providers. In 2021, UNRWA recorded that 526,646 students attended their schools; as with healthcare [11], not all Palestinian children enrol in UNRWA schools, and some use host-country public or private schools.

UNRWA has consistently invested in record- keeping, and now maintains electronic administrative databases to provide its health and education services, namely an electronic health records system (E-health) and an Education Management Information System (EMIS).

E-health was developed in 2010 as a web-based, patient-centred digital system to manage UNRWA's increasing workload and to improve the quality of its health care provision [14]. E-health started gradually in clinics and was updated in 2013 and 2017. EMIS was launched in the 2016/2017 school year to manage education data in UNRWA schools and improve overall educational quality. Both systems include identification numbers (IDs) which allow for deterministic linkage.

Aim

We aimed to build a live birth-cohort to enable us to explore the effects of risk factors and exposures in pregnancy (e.g., previous obstetric history, complications in pregnancy, and pollution, temperature, and conflict), and of factors recorded via the obstetric record, (e.g., pregnancy outcome, gestation, birthweight, multiples, and mode of delivery) on adverse health and educational outcomes among children.

We identified a group of women eligible to access UNRWA services with a pregnancy that ended from 2010-2020. For the subset with live births, we aimed to link information from mothers' obstetric records to UNRWA child health records and education records to create a live-birth cohort, and to describe some of its characteristics.

Methods

To create the cohort, we 1) examined IDs and other data, 2) prepared the data, de-duplicated records, and identified live-births 3) linked the mothers' and children's data using different deterministic linking algorithms, and 4) clarified reasons for non-linkage.

Examining IDs and other data

A cohort of refugees from E-health and EMIS

All records of pregnancies that ended between 1 January 2010 and 31 December 2020 (whether they resulted in live birth, early foetal death, stillbirth, miscarriage) were extracted from E-health, as were health and education records of children born in the same period in Jordan, Lebanon, Syria, West Bank and Gaza.

All the health information was stored in the E-health system while all the education data was stored in the EMIS system.

Figure 1 shows the key variables extracted from each of the three dataset: (1) mother E-health dataset including mother information, mother antenatal care (ANC) visit, mother obstetric records, (2) child E-health dataset including child information, child health data (including immunisation, growth monitoring, motor development, physical examination, outpatient visits, and laboratory results), (3) child EMIS

Box 1: Political, social, health and education system context of Palestinian refugees

	Country (setting) where Palestinian refugees are located				
	Jordan	**Lebanon**	**Syria**	**West Bank**	**Gaza**
Number of registered refugees reported by UNRWA in 2021 [11, 12]	2,334,789	482,676	575,234	883,950	1,516,258
Estimated percentage of total national population that are refugees (World Bank population data in 2021 [12, 15])	21%	9%	3%	30%	78%
Political/Social context	Most Palestinians have Jordanian nationality since 2009. Use of Jordanian government services permitted.	Palestinians' right to work & access to government services is severely constrained. Not eligible to use Lebanese public primary healthcare or schools.	Massive internal displacement since 2011. 137,234 Palestinians in Syria fled to Lebanon & Jordan; an estimated 438,000 remain.	Dual systems for Israeli settlers & Palestinians, restricting Palestinian rights and travel. Eligible to use public Palestinian Authority services.	Blockade & travel restrictions. Eligible to use public Palestinian Authority services.
Health and education context	UNRWA co-finances hospitalisation services.	UNRWA provides secondary school education. UNRWA co-finances hospitalisation.	Starting in 2011, UNRWA services affected by conflict. UNRWA co-finances hospitalisation.	Multiple checkpoints restricting access. UNRWA co-finances hospitalisation.	UNRWA co-finances hospitalisation services.
Number of UNRWA health centres in 2021 [11]	25	27	23	43	22
Number of UNRWA schools in 2021 [11]	161	65	102	96	278
Estimated pregnant Palestinian refugees using UNRWA antenatal care services in 2022 [16]	35%	63%	42%	54%	73%
Pregnant women using UNRWA antenatal care at least once with 4 or more antenatal visits in 2022 [16]	81%	75%	55%	90%	98%
Deliveries by trained personnel in 2022 [16]	100%	100%	100%	100%	100%
Children aged 12 months old receiving all vaccine immunisation (BCG, IPV, Poliomyelitis, DPT, Hepatitis B, Measles, Hib) in 2022 [16]	99%	97%	98%	100%	99%

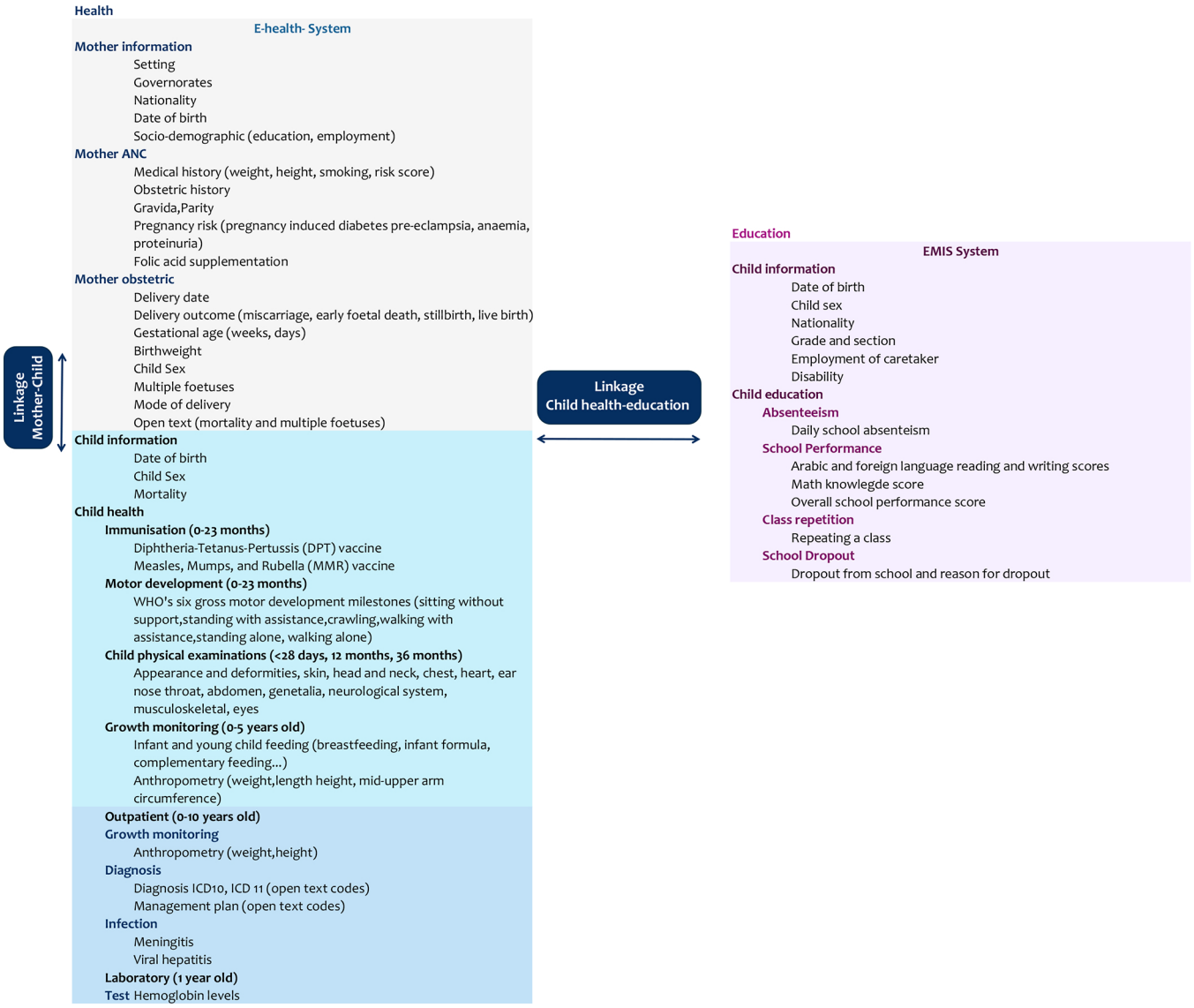
dataset including child education information, and child education.

Data from the mother's information included sociodemographic information and IDs with which to link mothers to their children. Mother's ANC records included women's medical history, reproductive health, and ANC received. Data from the mother's obstetric records included date of delivery, delivery outcome (live birth, stillbirth, early foetal death, miscarriage), multiple foetuses (twins/triplets/quadruplets), birthweight, gestational age, place of delivery, sex of live births, and mode of delivery. UNRWA partially covers childbirth costs, so neonatal information is gathered from the hospital records at billing and entered into the system after delivery as part of the women's obstetric records. Active surveillance of pregnancy outcomes for women who sought ANC takes place, with a call-back mechanism in case no pregnancy outcome is recorded.

UNRWA's primary care model provides for children to routinely undergo specific preventive measures, and it collects child health data on these accordingly, including immunisation as per host country schedules, growth monitoring (ages 0 to 59 months), motor development (ages 0 to 23 months), and periodic physical examinations (for new-borns and at 12 and 36 months). In 2017, they introduced mandatory screening for anaemia at 12 months. When care is sought for children who are ill, there may be additional outpatient records or laboratory-test results. This is an open cohort, for the children E-health records we extracted data from 01 January 2010 until 14 September 2021 (the day of the extraction) for the linkage.

Elementary school enrolment is mandatory (and free) from 6 years of age in all settings. Children born in 2010 would have reached age 6 and entered Grade 1 beginning in the 2016/17 academic year, with subsequent birth years entering school in the following years. Extraction of the education data was done in a yearly basis with total of 5 academic years extracted. Data

Figure 1: Variables extracted from maternal, child health records and child education records (grey mother E-health dataset, blue child E-health dataset, purple child EMIS dataset)



from EMIS captures information on students as they enter Grade 1 and progress in school from one year to the next. Extracted data included student characteristics, absenteeism, school performance, special education, class repetition and school drop-out.

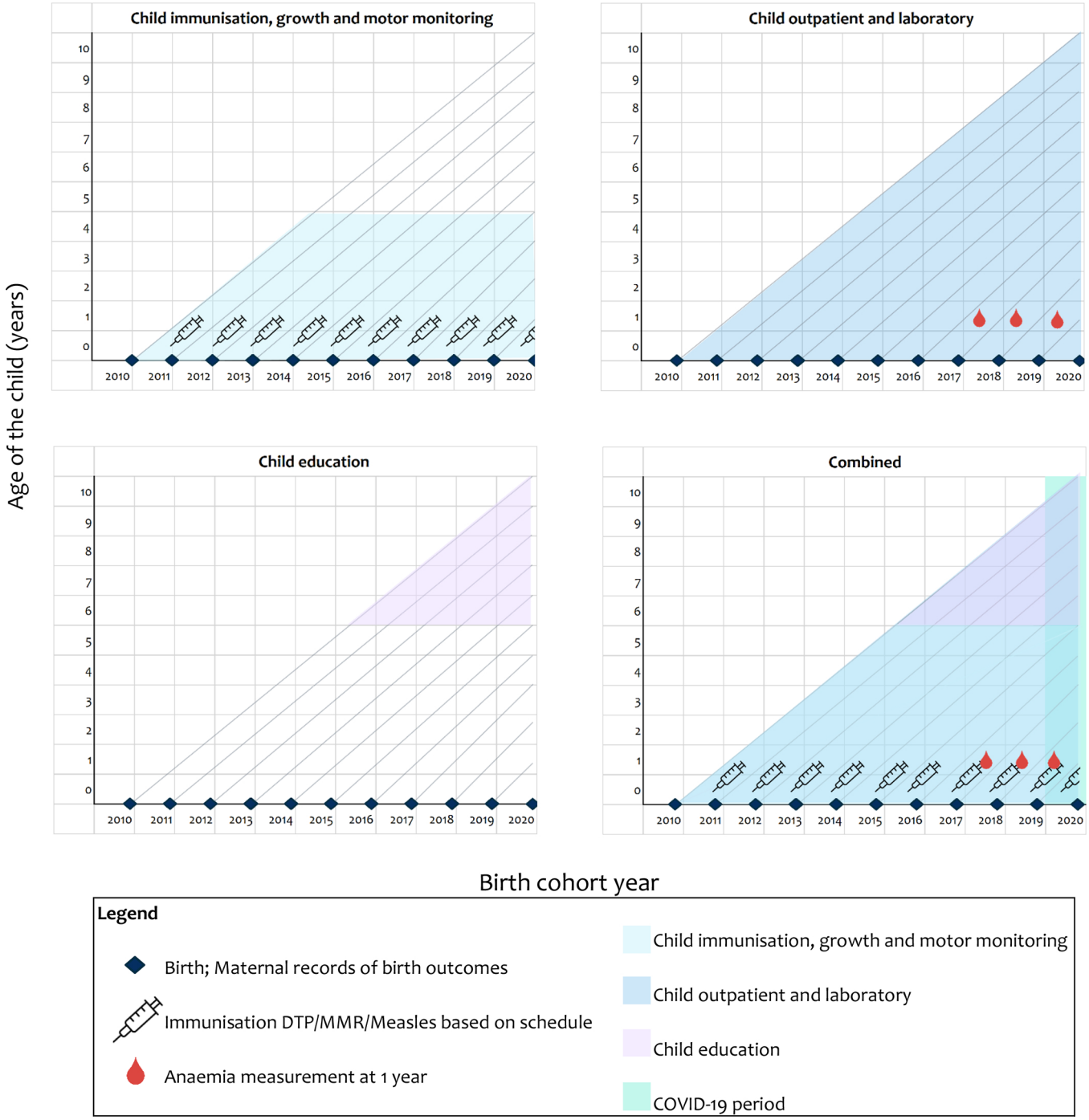
The Lexis diagram (Figure 2) indicates the different component datasets, and the time points when specific records could be accessed from E-health and EMIS to contribute to the birth cohort. The cohort (year of birth) is depicted as a blue diamond along the x-axis and the age of the child is on the y-axis. The shaded areas indicate the availability of data based on the cohort, age of the child, and the different types of records. For example, all children are expected to have records of routine preventive child health care (immunisation, growth, and motor monitoring records) up to 5 years of age, and education records starting at 6 years old. Haemoglobin level measurement for children at 1 year old (indicated using a red droplet) started in 2017. Outpatient and laboratory records are available at all ages (and into adulthood) for those needing these services.

Identifying IDs in different records

Six different IDs could potentially be used for linkage. The E-health system generates a unique Mother Medical File Number (MMFN) for each mother and a unique Child Medical File Number (CMFN) for each child. UNRWA also generates a unique refugee registration ID (RRIS) for each refugee and a family registration ID: MRRIS for mothers; CRRIS for their children; and FRRIS for families. As with birth registration, the CRRIS is generated when parents register their child in the system, so the first ID a child usually gets is the CMFN which is generated automatically by the E-health system when the child uses UNRWA services. In some cases, if the child was never taken to UNRWA services, the obstetric record might not have a CMFN. The CRRIS and FRRIS are also recorded in EMIS.

The different IDs available in the various mother, child health, and education records are shown in Figure 3, with pink and blue lines highlighting the IDs used to link across the various datasets. The obstetric records (column 3) include

Figure 2: Lexis diagram containing age of the child and source of the variables collected



data on neonatal outcomes without child-specific IDs. Child-specific IDs, the CMFN, are listed for each woman in the mother information records (column 1) showing all her children who have used UNRWA services; this is unlinked with neonatal outcomes.

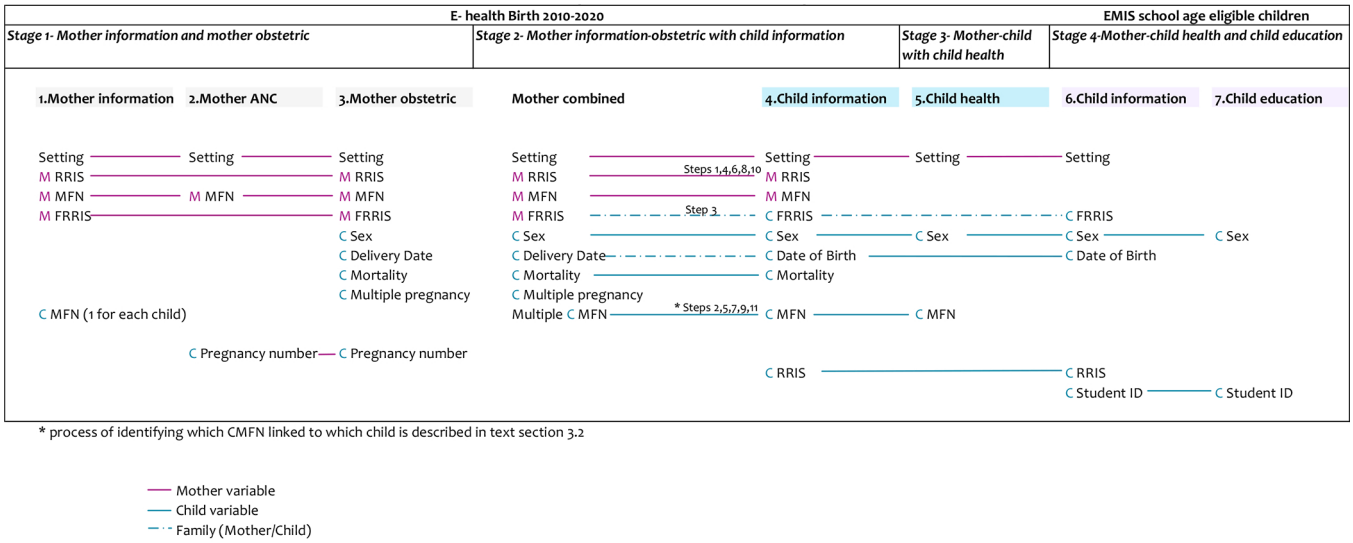
Data preparation, de-duplication of records and identification of multiple pregnancies

Data preparation involved cleaning specific open-text variables, selecting live births, distinguishing between multiples (twins, triplets, etc.,) and duplicated records, and removing the latter.

We cleaned open-text fields using text-mining tools to check different phrasings and spellings of "twins," "triplets," "quadruplets," and "multiples" (e.g., "tribblets") and of "death" (e.g., "died at 3 min") in English and Arabic. We then standardised the coding of these terms.

To link live births to children's health and education records, we excluded records of pregnancies that ended in miscarriage, early foetal death, or stillbirth, and records that were marked as training data or erroneous data (system-recorded errors). We then marked mothers' obstetric records with the same mother and the same delivery date as being either potential multiple pregnancies or duplicated records.

Figure 3: Steps in linkage of the different datasets (indicating the IDs used for linking in the different steps)



M RRIS	Mother refugee registration ID
M FRRIS	Mother family refugee registration ID
M MFN	Mother medical file number
C RRIS	Child refugee registration number
C FRRIS	Child family refugee registration ID
C MFN	Child medical file number
Steps	ID used for a specific step in the multi-step deterministic linkage

Data linkage using multi-step deterministic methods

The data linkage was conducted in four stages, linking: Stage 1) the mothers' information to the mother's ANC and the mother's obstetric outcomes; Stage 2) the mother's data from Stage 1 to the child information dataset; Stage 3) the dataset from Stage 2 to the child health datasets; and Stage 4) the information from Stage 2 to the child education dataset. The overall ID linkage stages are presented in Figure 3. When doing the linkage, we blocked on setting because each setting generates its own data (which are concatenated in UNRWA headquarters) and refugees rarely move across settings, and to help with managing a very large data set.

We ran the linkage process twice. The first time included only multiple pregnancies and duplicated records and aimed to distinguish duplicated records from multiple pregnancies based on the stages 1-4 described above. In some cases, data for multiples were entered as a single birth, with open text indicating the delivery resulted in twins, triplets, or quadruplets. We generated (and flagged) synthetic records for these missing multiples (additional twins, triplets, etc.,) based on the original obstetric record. This involved creating a record for each child we knew about to: (1) redress a limitation in the data structure as designed in E-health (2) allow us to have a more comprehensive dataset with proper denominator of live births, (3) retain information on maternal variables such as age and education, as well as ANC variables. These maternal and ANC attributes apply equally to all foetuses in a given pregnancy. It was only birthweight that is potentially incorrect. This information is clearly flagged in the dataset, and we record clear information to data users on how these variables can be used effectively.

Duplicated records were those with no mention of being a multiple, and where the records did not link to two or more different child IDs. We removed these duplicates leaving only one record, and then re-ran the linkage stages 1-4 with all the records (multiples and de-duplicated records, and all non-duplicate records). We removed the duplicated records that had missing data in one record entered in the birthweight measure as compared to the other records. Where duplicate records had contradicting information, we kept the last record of the duplicated records.

We calculated the percentage linking after adding synthetic records for missing multiples and removing duplicated records. We also assessed percentages after removing children with missing CMFNs (i.e., only keeping children that used UNRWA services).

Stage 1- linking mother's data sets

We first used the MMFN to link the mother's information with her ANC records and her obstetric outcomes. The mother's information includes a CMFN of all her children, without information on their birth order, date of birth, and sex. The mother's obstetric record lists the child's sex, delivery date, and multiple pregnancies, but does not have a child ID, for example, a CMFN.

Stage 2- linking mother information- obstetric with child information (from E-health)

In Stage 2, we merged the Stage 1 mother datasets (1–3) with the child information dataset (4) via 11 steps. In all steps, we blocked on setting to ensure this was identical in both mother records and child records. In steps 1 to 9, we linked

the singleton births, then in steps 10 and 11, we linked multiple births. Since the MRRIS is the most accurate ID (most used in UNRWA to refer to individual refugees), we used this first as the "best linkage," followed by linkage based on the CMFN.

Because the child's information had the date of birth and the CMFN, we could then match the date of delivery/birth upon linking to the CMFN from the mother's information, ensuring the obstetric record was given to the correct child. This approach worked for singleton or twins of discordant sex, but not for multiples of concordant sex.

In steps 1 to 3, we linked based on records having an identical month and year of delivery/birth, the same sex of the child, and the same MRRIS (step 1), same CMFN (step 2), and same FRRIS (step 3). In steps 4 to 5, we linked based on records having a delivery/birth date within plus or minus 90 days of each other and the same MRRIS (step 4), or the same CMFN (step 5). Then we allowed the delivery/birth date to be plus or minus 180 days and the same mother MRRIS (step 6), or the same CMFN (step 7). This was done to take into account the data entry errors in the delivery date or the date of birth. In steps 8 and 9, we removed the requirement for identical sex in steps 1 and 2, and linked based on MRRIS ID (step 8), and the same CMFN (step 9).

For twins, triplets, and quadruplets (multiples) we linked based on identical dates of delivery/birth and same mother MRRIS ID (step 10) and same CMFN (step 11).

Stage 3- linking mother-child information with child health

We used the CMFN to link the dataset from Stage 2 (which linked datasets 1-4) to the child's health records (dataset 5) including immunisation, growth monitoring, motor development, haemoglobin testing, outpatient visits, and laboratory results records.

Stage 4- linking mother-child health data with child education

Children from Stage2 who reached age 6 years or above were linked to EMIS datasets 6 and 7 based on the CRRIS, identical setting, sex, and month and year of birth.

Reasons for failure to link

We developed hypotheses about structural (legitimate) and other reasons for data to not link and tested these using a classification and regression (CART) decision tree approach [17] to identify groups at substantial risk of not linking. CART repeatedly separates data into two groups, one with high levels of non-linkage and one with low by testing different cut-off points (for example the different year of delivery/birth), and splits the data based on the best within-group homogeneity.

Information on mortality, mother's refugee status, year of delivery/birth, sex of the child, birthweight, and gestational age were available and were used to predict non-linkage. Mortality of the child (whether neonatal or infant or other) was included in the mother's obstetric records (thus this information is available in both linked and unlinked data). We also generated a low risk of mortality group (normal birthweight, term and singleton and not recorded as dead), recorded mortality, and a composite of low birthweight, preterm, or multiples without recorded mortality (as a measure of being a high risk of mortality that may not be recorded). Children of non-refugee mothers, but where the male parent is a refugee, are included in these datasets because they are eligible for UNRWA services.

We also ran a multivariable regression analysis looking at determinants of failure to link (Appendix).

The data cleaning, linkage and multivariable analyses were conducted using Stata software (StataCorp. Stata Statistical Software: Release 17. College Station, TX: StataCorp LL). The CART analysis was conducted using R software and rpart package (R Core Team, 2022, version 4.2.1 R Foundation for Statistical Computing, Vienna, Austria).

Results

Examining IDs and other data

From 1 January 2010 until 31 December 2020, a total of 1,158,354 pregnancy outcomes were extracted (Figure 4). For the linkage, we excluded 181 system-recorded errors as indicated in the open text and a total of 172,545 miscarriages, early foetal death, and stillbirth records and 181 system-recorded errors as indicated in the open text (Figure 4).

Data preparation and de-duplication of records

3,851 birth records were synthetically added when pregnancy outcomes were marked as multiples (twins, triplets, or quadruplets), but only one birth record was available. In some cases, we had one record indicating both death and multiple (for example "1 twin died while the other survived"), another record indicating this was synthetically added. A total of 45,095 records had at least one other record with the same Mother IDs and the same delivery date. We were able to distinguish 18,378 as multiple pregnancies (as noted in the open text variable), 9,981 as singleton records, and 16,736 as duplicated records. We dropped the latter.

This resulted in a total of 972,743 live birth records, born to women with an obstetric record, recorded in all five settings, of which 424,616 became eligible for school enrolment in the study time-period. From the child health records, in E-health, a total of 1,089,568 were extracted for the linkage. A total of 279,758 child education records were extracted from EMIS for the linkage. A total of 12,245 records mentioned death in an open text variable.

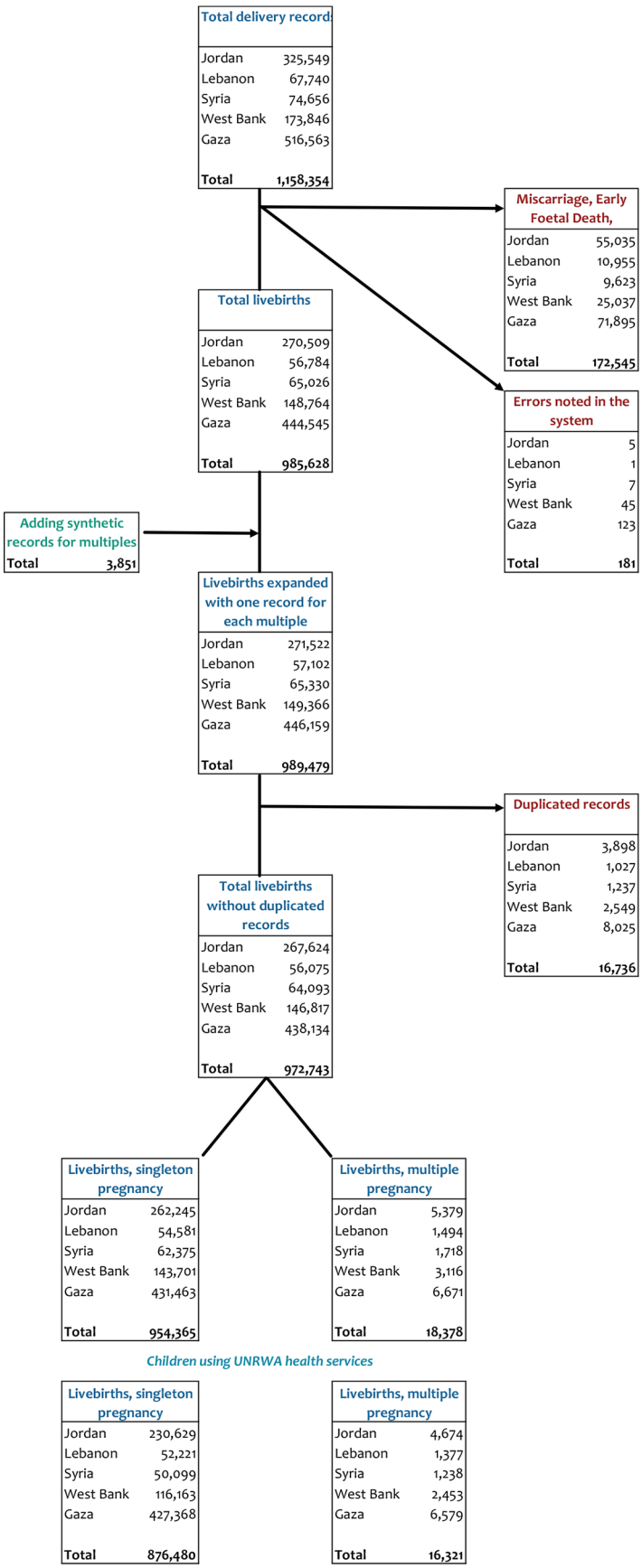
Data linkage

Deterministic linkage mother with child health records (Steps 1 to 11)

Linkage increased from 69% in step 1 to 83% in step 11 (Table 1). The percentage linkage between mother and child records improved from 73% in 2010 to 86% in 2020 (Figure 5). Gaza had the highest linkage, followed by Lebanon, Jordan, Syria, and the West Bank (Figure 5).

In 79,942 cases, there was no CMFN in the mother's records, most likely because their children did not use UNRWA services. By removing records with missing CMFN (in the

Figure 4: Data preparation and de-duplication of records



unlinked dataset) to make a birth cohort of UNRWA health service users (mother used UNRWA ANC or obstetric services and child had at least one record within the E-health) linkage improved to 91% overall, from 81% in 2010 to 94% in 2020. We refer to these as the "Stage 2 dataset" and the "Stage 2 dataset with children that used UNRWA health services".

Table 1: Mother-child linkage steps: matching requirements

Mother-child link Steps	Field/ Setting	Sex	Multiple/ Duplicated records	ID used	Date of birth/ Delivery date match	Numbers	Linkage (%) N = 972,743	Linkage (%) children using UNRWA health services N = 892,801
1	Exact	Exact	No	M RRIS	Month and Year	674,968	69%	76%
2	Exact	Exact	No	C MFN	Month and Year	708,586	73%	79%
3	Exact	Exact	No	F RRIS	Month and Year	732,802	75%	82%
4	Exact	Exact	No	M RRIS	±90 days	751,110	77%	84%
5	Exact	Exact	No	C MFN	±90days	752,916	77%	84%
6	Exact	Exact	No	M RRIS	±180 days	773,816	80%	87%
7	Exact	Exact	No	C MFN	±180 days	774,556	80%	87%
8	Exact		No	M RRIS	Month and Year	787,608	81%	88%
9	Exact		No	C MFN	Month and Year	788,239	81%	88%
10	Exact	Exact	Multiple	M RRIS	Month and Year	811,221	83%	91%
11	Exact	Exact	Multiple	C MFN	Month and Year	811,871	83%	91%

M RRIS Mother refugee registration ID.
C MFN Child medical file number.
F RRIS Family refugee registration ID.

Figure 5: Percentage of mother-child linkage over time (a) overall (b) Stage 2 by setting and (c) Stage 2 children that use UNRWA services

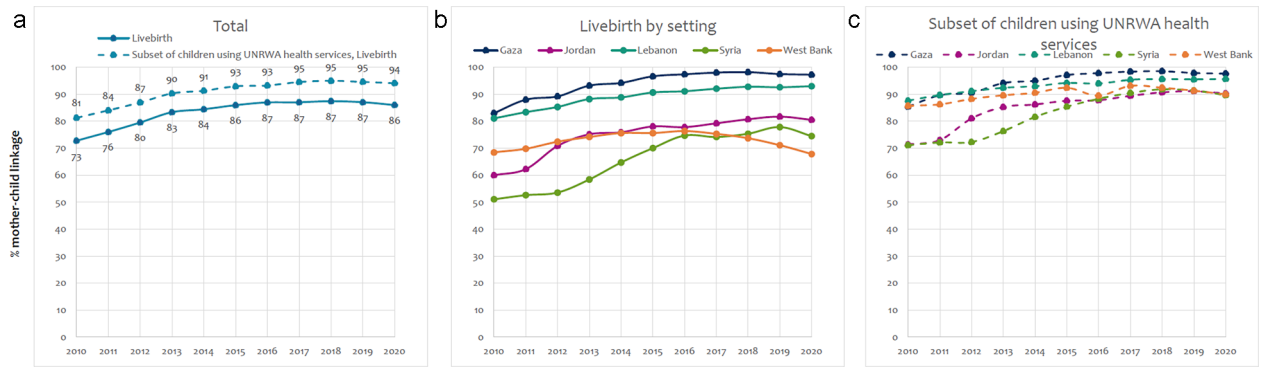


Figure 6 shows the percentage contributed by each linkage step per year. The percentage linking in steps 1 and 2 increased over time. Errors in the identical recording of the delivery/birth date were allowed for steps 4/5 (± 90 days) and step 6/7 (± 180 days); they decreased over time. Errors in recording sex (steps 8/9) were small and consistent over time. The percentage of multiples linking (steps 10/11) was the same across all years.

Deterministic linkage of mother-child health records with education records

The dataset from Stage 2 was linked to child health records (Stage 3) and education records (Stage 4). Linkage of the Stage 2 dataset of children that use UNRWA services to the child health records was extremely high at 98% (Figure 7).

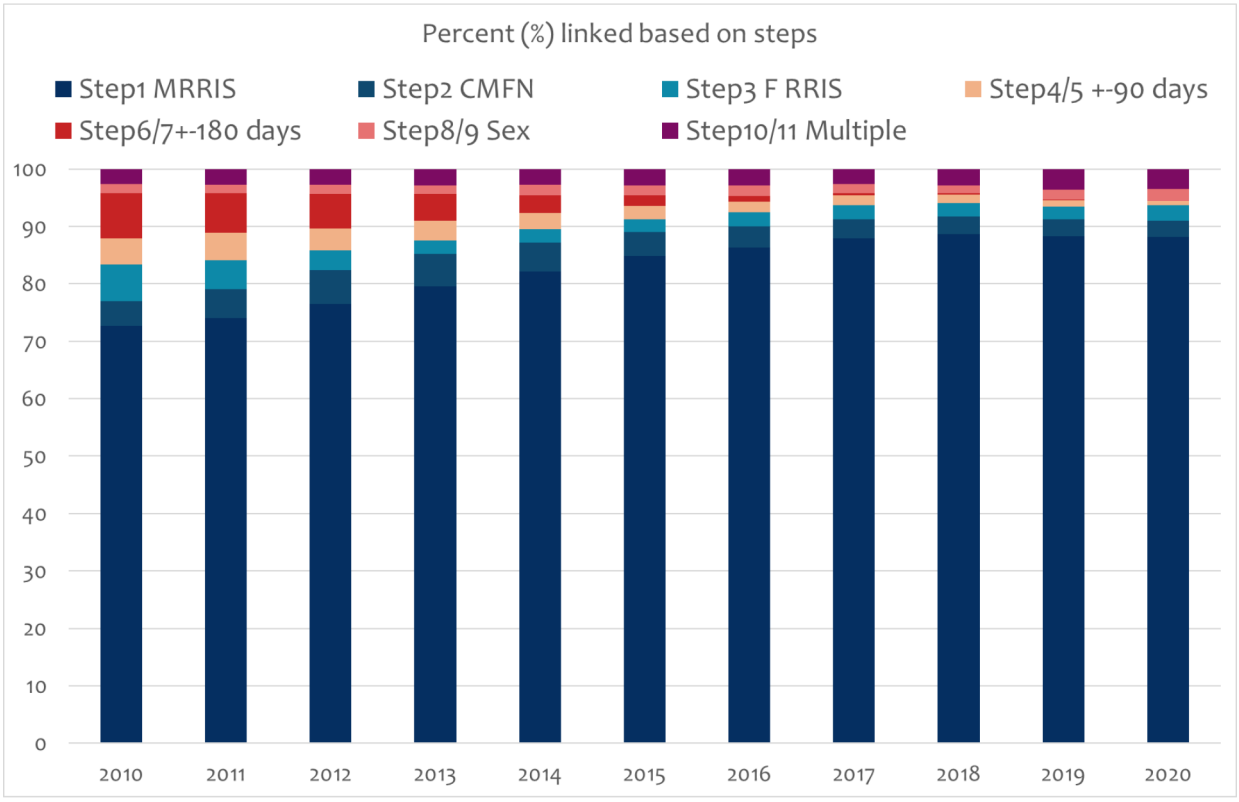
The live birth dataset had 424,616 records of children at an eligible age for school enrolment. These were linked to the EMIS data using CRRIS (available in the child health information records and the child education records). Around half of the children were linked (47%), but linkage differed by setting, with the highest linkage in Gaza (77%), Syria (72%), and Lebanon (64%), and the lowest in West Bank (33%) and Jordan (31%). When we looked at linkage among those using UNRWA schools (education service users as denominator instead of among UNRWA health access users), coverage increased overall to 90%, and in Gaza (94%), Lebanon (94%), West Bank (87%), Jordan (83%), and Syria (72%).

Reasons for failure to link

Early mortality (as recorded in the obstetric records), and migration soon after birth were hypothesized as the main structural reasons why the obstetric and child health datasets might not link. Unlinked data had a higher percentage of early mortality and an increased presence of children vulnerable to mortality risks such as low birthweight or preterm infants even if their deaths weren't explicitly recorded (Appendix Table 1). Unlinked data also contained a larger proportion of non-refugee mothers as compared to refugee mother. Unfortunately, we couldn't assess migration-related non-linkage.

Over time, unlinked data decreased, likely due to improved reporting, recording, and data entry (Figure 5 and Figure 6). Minimal data errors were identified in sex (1% error), location (0.05% error) or for recording live births as stillbirths (0.006%

Figure 6: Percentage linked by each of the 11 steps, over time (different year of birth cohorts)



M RRIS	Mother refugee registration ID
C MFN	Child medical file number
F RRIS	Family refugee registration ID

error) (Appendix Table 1). We found 69% of multiple pregnancies were of the same sex.

Figure 8 illustrates a decision tree segregating UNRWA-serviced Stage 2 children into various groups based on linkage levels. Three variables mortality, mother's refugee status, and year of birth divided the data into four risk groups. The graph displays (1) group size (percentage of births the group represents out of all births), the percentage unlinked data in each group, the percentage of unlinked data out of all unlinked data.

Mortality (group1) was the smallest group (1% of births) but had the highest prevalence of unlinked data (78%), followed by group2 without mortality recorded but with non-refugee mothers (4% of births with 44% of unlinked data), followed by group 3 (without morality, with a refugee mother, and with year of birth 2010-2012), which had 25% of births and 21% of unlinked data. No mention of mortality and having a refugee mother and a year of birth from 2013 onwards (group4) was the largest group (70% of births) and had the lowest prevalence of unlinked data (12%).

We also quantified the association between a failure to link and variables linked with structural lack of linkage (setting, mother's non-refugee status, recorded mortality, risk factors for early mortality) and to reporting errors (setting, year) using logistic regression models (Appendix Table 2). Syria had the highest odds of data not linking followed by Jordan, West Bank and Lebanon as compared to Gaza. As compared to low risk of mortality group (normal birthweight, term and singleton and not recorded as dead), recorded mortality, and a composite of low birthweight, preterm, or multiples without recorded mortality (as a measure of being a high risk of mortality that may not be recorded) had higher odds of not linking. Non-refugee mothers compared to refugee mother also had higher odds of not linking. The odds of not linking decreased over time.

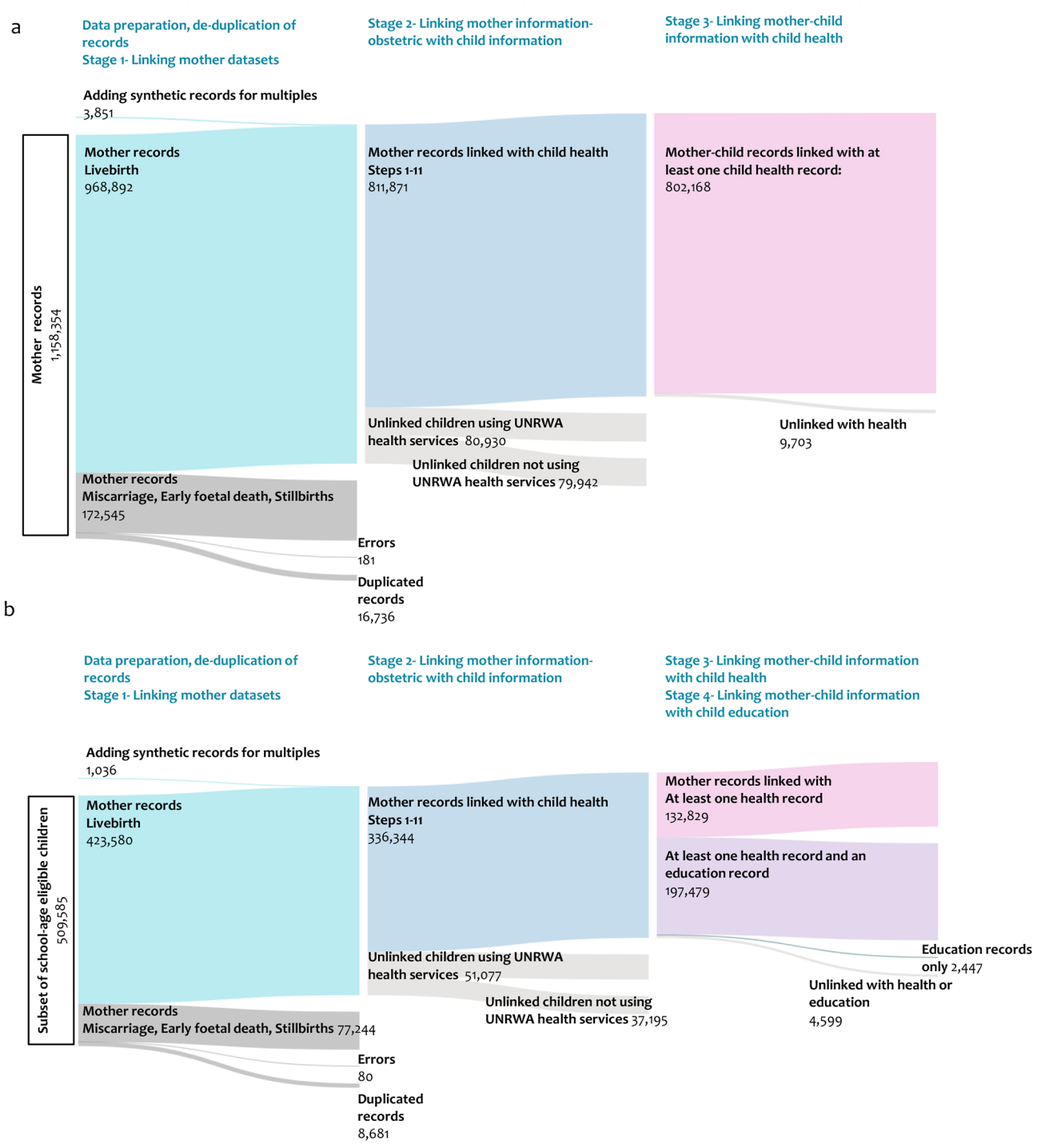
Discussion

We established a birth cohort of Palestinian refugees living in five settings from 2010-2020, using electronic medical records of 972,743 live births, and by linking mother and child health and education records. We found (1) high levels of linkage overall, which improved over time, (2) variations in linkage rates in the five different settings, and (3) factors associated with failure to link including the birth year, setting, mortality record (or risk factors for early mortality) and having a non-refugee mother.

Establishment of a palestinian refugee cohort

Endresen and Øversen (1994) [18] and Zureik and Tamari (2001) [19] have previously noted the research potential of UNRWA's administrative data. Our study is the first use of these data to build a birth-cohort of Palestinian refugees. It provides a significant resource

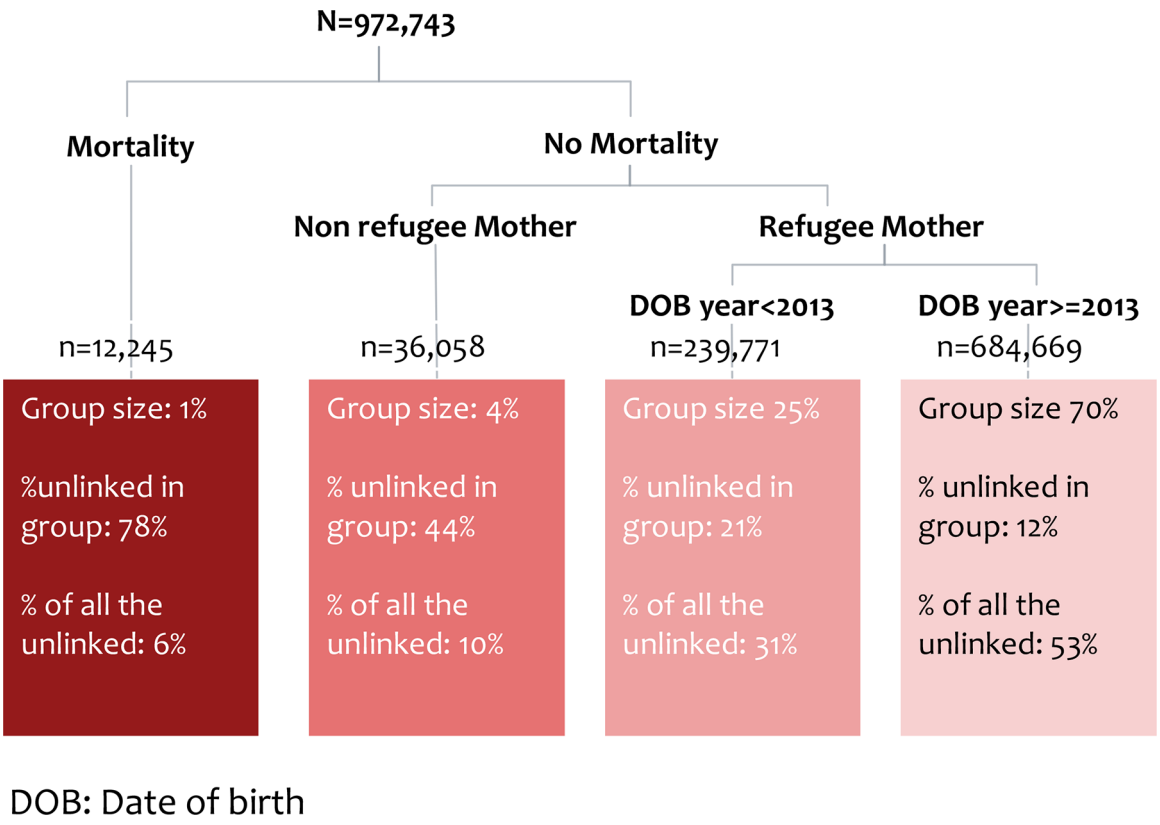
Figure 7: Linkage of (a) maternal records to child outpatient records, (b) maternal records of school-aged eligible children to child outpatient and education records



for future understanding of associations, mechanisms, and problems for protracted refugees and urban poor, filling important gaps in the literature. Victora and Barros note that except for Brazil and India, the top 20 countries publishing on cohorts are all high-income [1]. Since exposures, disease patterns, policies, and health systems differ by setting, our longitudinal dataset will provide new possibilities to study a wide spectrum of policy-relevant questions that apply to urban-poor populations. For example, a 2023 review found that most studies examining the effect of size at birth on subsequent child wellbeing outcomes have been in high-income countries [20] or have not considered size for gestational age; such analyses are possible in our birth cohort. Another unusual feature of our cohort is that it includes five settings and services clustered in 140 health facilities and 702 schools, allowing for context-specific and comparative questions.

Using multi-step deterministic algorithms, we reached a linkage rate of 83% overall for health records, with rates improving from 71% in 2010 to 86% in 2020. This is comparable to other studies linking mothers and children using deterministic methods, for example a linkage rate of 82% in Brazil [21]. The linkage percentage is even higher

Figure 8: CART decision tree to determine the unlinked data



DOB: Date of birth

when defining the cohort as children who use UNRWA health services (91%). We note that linkage improved over time as experience with E-health increased and mis-recording in date of birth decreased (contributions of steps 4/5 and 6/7 to overall linkage decreased). Mis-classification data-entry errors were low (1% error for sex, 0.006% error for the delivery outcome, and 0.05% error for setting). Among children eligible for school, 47% linked, as not all children who used UNRWA health services also went to UNRWA schools. Among children attending UNRWA schools, 90% linked with E-health, indicating that children attending UNRWA schools were more likely to use UNRWA health services. It is possible to explore ways to increase the linkage with education data by loosening the criteria used for linkage (as was done for the mother-child linkage), for example if the date of birth criteria was loosened, as was done for health records in Stage 4.

Characteristics of the population linking

It is essential to recognise that the linked cohort is mainly of those children who used UNRWA services at least once. Access to, and use of, non-UNRWA services differs by setting and is reflected in the percentage of data linking to health and education. More children from Jordan and the West Bank are unlinked (probably because there are alternative choices available for refugee children) while those in Lebanon, Gaza and Syria have fewer options to use non-UNRWA services. In 2019, the Multiple Indicator Cluster Survey in Palestine found that 72% of children aged 5–17 in Gaza accessed UNRWA services, compared to only 22% in the West Bank [22], though this partly reflects the proportions of these populations that are refugees (67% and 30% respectively, see Table 1).

The setting also reflects the timing of the introduction of E-health and the overall quality of record keeping and data entry which can in turn affect linkage. There are several indications from previous work [23] that records from Syria have the poorest recording of birth dates, and that data quality (assessed via digit preference and heaping) are weakest in Syria and Jordan. The conflict situation in Syria has almost certainly impacted the accuracy of the data collected and the linkage process. Migration might prevent the use of children's health services. No studies of numbers of Palestinian-refugee specific migration were found in the literature, but news reports document that the adverse impacts of the conflict in Syria and the economic collapse in Lebanon on Palestinian refugees, have led to drownings during attempted illegal migrations [22, 23].

Linkage improvements over time are most likely to be because the E-Health system improved but may also be due to increased use of free UNRWA services as economic hardship foreclosed other options. Setting thus becomes a complex construct that encompasses both structural conditions, mortality, out-migration and data errors as reasons for non-linkage and for exclusion from the cohort.

Future analysis and recommendations

The established, high-quality birth cohort presents a unique opportunity to explore key research questions concerning Palestinian refugees and urban-poor populations. For future analyses, we point out some considerations to enhance validity.

First, data quality and linkage improved over time, especially from 2013 on, and again from 2017 on, (these years were identified by the CART analyses and were also when UNRWA updated its E-health system). Researchers may wish

to restrict their analyses to data from these years or consider running sensitivity analyses to ensure data quality in early years is not affecting results.

Second, the characteristics of the data that linked need to be understood to avoid selection bias, and properly translate research to policy changes for specific populations. The service-use context suggests that our cohort (of UNRWA service users) is most likely to be generalisable to the entire population of Palestinian refugees in in Gaza, Lebanon and Syria. By contrast, refugees from Jordan and West Bank appeared to use a greater variety of non-UNRWA services or a mix of UNRWA and non-UNRWA services, potentially leading to only the most vulnerable refugees accessing UNRWA services. Our CART analysis also showed children with refugee fathers, but non-refugee mothers, were also less likely to link, possibly because non-refugee mothers could provide their children with access to alternative services. The CART analysis proved to be a useful method for identifying distinct groups within non-linkage data by utilising a combination of different variables and could be used for other linkage studies.

Third, most cohorts in the literature are based in a single country, whereas ours is in five settings (4 countries). This allows for the possibility to examine variations across populations and clusters from five settings, 140 health clinics, and 702 schools. Setting may well be an effect-modifier though, so analyses combining more than one setting need to consider this.

Fourth, multiples (twins, triplets, etc.,) are a challenge in datasets, and many researchers exclude them, even though they are at high risk of adverse outcomes. We retained this important subgroup in our cohort. However, researchers may need to exclude multiples from analyses when using birthweight as an exposure, or alternatively to use imputation methods or sensitivity analyses. This is because some multiples did not have a record for each child, so we created (and flagged) a synthetic record for the second or third neonate (twin or triplet, etc.,) based on the original obstetric record, affecting mainly the birthweight variable where using the same weight for each birth could lead to misclassification. In case of duplicated records with contradicting birthweight results, we propose that future studies using this cohort to conduct a sensitivity analysis on the effect of choosing a different record. Moreover, even when birthweights of all multiples were recorded, we could not be certain which child they belonged to unless the sex was discordant, since the obstetric records had no child ID. Other variables affected by the lack of a child ID (i.e., gestational age, mode of delivery, date of birth, place of delivery) are not problematic because they can be assumed to be identical or very similar for all babies within multiple pregnancies. Moreover, even the potential discordance of birthweight in multiples can be quantified; the literature reports only 16% of multiples have birthweights that are more than 20% different.

Fifth, and finally, this analysis provides opportunities to improve the E-health system. As we showed, examining mortality using our data would require further work to identify deaths and to assess the survival status of children lost-to-follow-up. Child health records do contain a variable to record the date of death, but most deaths occur early, before most neonates are brought into the primary care facilities for services. Deaths are recorded on the obstetric record, but in a free text format that needs cleaning, UNRWA also has a death registration system, but this is voluntary, and families may have little reason to report deaths, leading to under-reporting. This analysis pinpointed to UNRWA the need for a more accurate system to capture mortality data. The multivariable analysis characterising the failure to link found that neonates at higher risk of morality (low birthweight, preterm, or multiple pregnancy) had higher odds of not linking even though they were not reported as dead. This suggests deaths were missed and that researchers interested in mortality will need to examine the full birth cohort (including unlinked data) and include other sources (RRIS) or verification of the survival or migration status of children lost to follow-up.

This dataset offers a tremendous resource for answering important research questions on human capital development of urban-poor and of refugees. Some examples of planned research include exploring the effect of being post-term on size-at-birth and mortality outcomes, the effects of size-at-birth on child obesity, the association between recurrent infection and school performance, or the effects of exposure to conflict or high temperature on birth outcomes and child health and education attainment. However, this study has some limitations. We limited our evaluations of internal data quality to the characteristics of individuals that did or did not link, and to data recording and data-entry error rates based on date of birth/delivery, sex, setting and pregnancy outcome. There was no gold standard to evaluate the true or false matches, or the sensitivity and specificity of the linkage...[24]. UNRWA is consistently seeking to improve its system and this analysis allowed us to pinpoint points of changes to improve the data captured by E-health system.

In future, we hope it will be possible to identify funds to allow data to be shared based on specific requests, subject to review by an independent research review board. Due to the vulnerable position of refugees, and the sensitive nature of their information, utmost care is needed to protect their privacy and to ensure research does not stigmatise them. UNRWA, being the primary collector of personal data of Palestinian refugees, has established a robust data protection system. We would seek to ensure specific components, such as de-identified participant data, linkage procedures, and the statistical analysis plan may be shared for designated analyses to be permitted under a formal access agreement.

Conclusion

We established a Palestinian refugee birth cohort from 2010-2020 using electronic medical records of 972,786 live births, linking mother and child health from 140 primary clinic and education records from 702 schools. We also established criteria for selecting different sub-sets of the cohort depending on the research question and the analytic purposes. Since exposures, disease patterns, policies, and health systems differ by setting, this creates an invaluable resource for future research aiming to elucidate pathways for improved health and education in this vulnerable and understudied population.

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Role of funder/sponsor statement

The funder had no role in study design, data collection, data analysis, data interpretation, or writing.

Statement on conflicts of interests

AS, GB, HA, SA, GP, and RI are employed by UNRWA. The other authors (ZJ, MS, HG, OC) declare no competing interests.

Contributors statement

OC conceived the use of UNRWA electronic records for linkage; ZJ, HG, AS, and OC designed the study approach; AS, GB, HA, SA, GP and RI guided the understanding of the dataset structure, GB, HA, SA and RI supported in the extraction of the data; GP encrypted the data; MS, HG, and OC supervised the data analysis; ZJ and OC analysed the data. ZJ wrote the first draft. All authors contributed to the writing of the paper. All authors read and approved the final version.

Ethics statement

Approval to use de-identified encrypted data was obtained from ethics committees of the London School of Hygiene and Tropical Medicine, Nagasaki University, and UNRWA's research review board. No identifiers (apart from encrypted IDs) were shared with researchers outside UNRWA.

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Abbreviations

ANC:	Antenatal care
C:	Child
E-health:	Electronic Health records system
EMIS:	Education Management Information system
F:	Family
M:	Mother
MFN:	Medical file number
RRIS:	Refugee registration number
UNRWA:	United Nations Relief and Works Agency for Palestine Refugees in the Near East

Appendix Table 1: Hypotheses

Hypotheses			Link	Unlinked
Structural (legitimate) reasons for data not to link				
Early mortality (before the child used UNRWA services or got an MFN)				
1	More deaths among the unlinked	Mortality	0.3%	6.0%
2	More multiples among the unlinked because they have higher early mortality (even if one or both are not registered as a death)	Multiple	1.4%	4.4%
3	More LBW/PT among the unlinked because LBW/PT have higher early mortality (even if not registered as a death)	Preterm (Gestational age <37 weeks)	7.7%	10.9%
		Low Birthweight <2500)	5.6%	9.3%
Child used other services (and never used UNRWA services)				
4	More mothers who are not Palestinian among the unlinked because non-refugee mothers have alternative options for child health and education	Mother RRIS missing in health	2.5%	10.3%
5	More children with a missing MFN (in the mother dataset) are unlinked because children did not use UNRWA services, so a C MFN was not generated	Missing C MFN	0.0%	49.7%
6.a	More families from Jordan and West Bank are unlinked mother and child (because they have more choices). Lebanon, Gaza, and Syria have fewer choices for other services *6ca and (6a or 6b) for in opposite directions*	% Linkage health		
		Jordan	74.8%	25.2%
		Lebanon	89.1%	10.9%
		Syria	67.8%	32.2%
		West Bank	72.8%	27.2%
		Gaza	93.9%	6.1%
6b	More children in Jordan, West Bank do not link to education services because they have more alternative options. Lebanon, Gaza and Syria have fewer choices for other education services	% Link education		
		Jordan	31.9%	68.1%
		Lebanon	63.5%	36.5%
		Syria	72.2%	27.8%
		West Bank	32.6%	67.4%
		Gaza	77.1%	22.9%
Migration (before the child used UNRWA services or got an MFN)				
6.c.	More families from Lebanon and Syria are unlinked (because they have higher migration). Cannot test but might contribute to a higher proportion of unlinked. *Cannot be distinguished from other causes in 4.a.*			

Continued

Appendix Table 1: Continued

Lack of linkage due to reporting, recording or data entry errors			
Data entry errors in any of the IDs (namely Mother/ C MFN, FRRIS.....)			
7	Linkage will improve over time as experience with electronic medical records improved	Figure 5 and Figure 6-Improvement of linkage	
8	Very recent data has more zero in CRRIS as it takes more time to register them	%Missing C RRIS	
		2010	2.0%
		2012	3.8%
		2014	5.7%
		2016	8.8%
		2018	12.0%
		2020	38.9%
Ages mis-recorded/ recorded approximately (heaped on 1 or 15^{th} or in January)			
9	Linkage based on steps +/- 90 and +/- 180 will decrease	Figure 5- decrease in linkage errors	
7	Linkage will improve over time as expertise in electronic medical records improved	Figure 5 and Figure 6- Improvement of linkage	
Sex mis-recorded			
10	Attempt to link unlinked kids to any sex.	A total of 13,683.	Error 1.4 %
Location mis-recorded			
11	Attempt to link unlinked kids to any location	A total of 477 links. Error 0.05%	
Live birth miscoded as stillbirth (so was excluded from the start)			
12	Attempt to link unlinked children to stillbirths	A total of 56 links. Error 0.006%	
Stillbirth miscoded as a live birth			
	Cannot test	Might be like step 12	
Distinguishing of duplicated records from multiples			
13	The percentage of same-sex multiples.	The sex ratio observed in the data is 1.03 male (50.7%) to 1 female (49.3%). In our dataset same sex multiples (69%); discordant multiples are 31%. This 69% is plausible if we assume that ∼30% of multiples are monozygotic (so same sex as per published reports) and around half of dizygotic multiples are same sex $(0.3+(0.7(0.5068^2+0.4932^2)) = 0.30+0.35 = 65.0\%$ of multiples expected to be same sex.	

Appendix Table 2: Multivariable logistic regression model of the association of different population characteristics of children using UNRWA services and odds of linkage (N = 892,801)

		Adjusted OR (95%CI)
Setting	Gaza (ref)	1.0
	Jordan	3.2 (3.1-3.2)
	Lebanon	1.4 (1.3-1.4)
	Syria	4.3 (4.2-4.4)
	West Bank	2.4 (2.3-2.4)
Mother ID	Refugee (ref)	1.0
	Not a refugee	2.7 (2.6-2.8)
Dead or at risk of early mortality	Normal birth weight, term and singleton and not recorded as dead (ref)	1.0
	Low birthweight, or preterm or multiple, and not recorded as dead (at risk of early mortality)	1.6 (1.6-1.6)
	Recorded as dead	47.0 (44.8-49.3)
Year of birth	2010	1.0
	2011	0.8 (0.8-0.8)
	2012	0.6 (0.5-0.6)
	2013	0.4 (0.4-0.4)
	2014	0.4 (0.4-0.4)
	2015	0.3 (0.3-0.3)
	2016	0.3 (0.3-0.3)
	2017	0.2 (0.2-0.2)
	2018	0.2 (0.2-0.2)
	2o19	0.2 (0.2-0.2)
	2020	0.2 (0.2-0.2)

Chapter 4- Post-term births as a risk factor for small-for-gestational-age and infant mortality, using 45.7 million electronic birth records from Brazil, Mexico, and Palestinian refugees

To explore the exposure of interest, I focused on examining size at birth. Initially, I investigated the nine phenotypes of size at birth as proposed in the umbrella review (Chapter 2), using the cohort established in Chapter 3, and then assessed the size at birth phenotypes association with infant mortality. Using Palestinian refugee data, I analysed these nine phenotypes (see Table 1 and Figure below). In the manuscript, I collapsed the data for all Palestinian refugees to avoid confusion across all 5 settings of Palestinian refugees. Because I was interested whether these association held in other settings, I approached colleagues working in Mexico and Brazil and conducted the same analysis.

Table 1- Prevalence (%) of nine sizes at birth phenotypes for Palestinian refugees by setting.

Palestinian refugees in	Gaza	Jordan	Lebanon	Syria	West Bank
Preterm- SGA	0.7	1.1	1.0	0.8	0.9
Preterm- AGA	5.5	6.4	6.9	5.0	5.4
Preterm- LGA	2.0	1.7	1.9	1.7	1.3
Term- SGA	6.6	10.2	8.4	9.3	8.0
Term- AGA	71.6	73.2	71.2	78.5	73.6
Term- LGA	10.9	5.8	9.5	3.7	9.1
Post-term-SGA	0.7	0.6	0.3	0.4	0.4
Post-term- AGA	2.0	0.9	0.9	0.5	1.2
Post-term- LGA	0.2	0.0	0.1	0.0	0.1

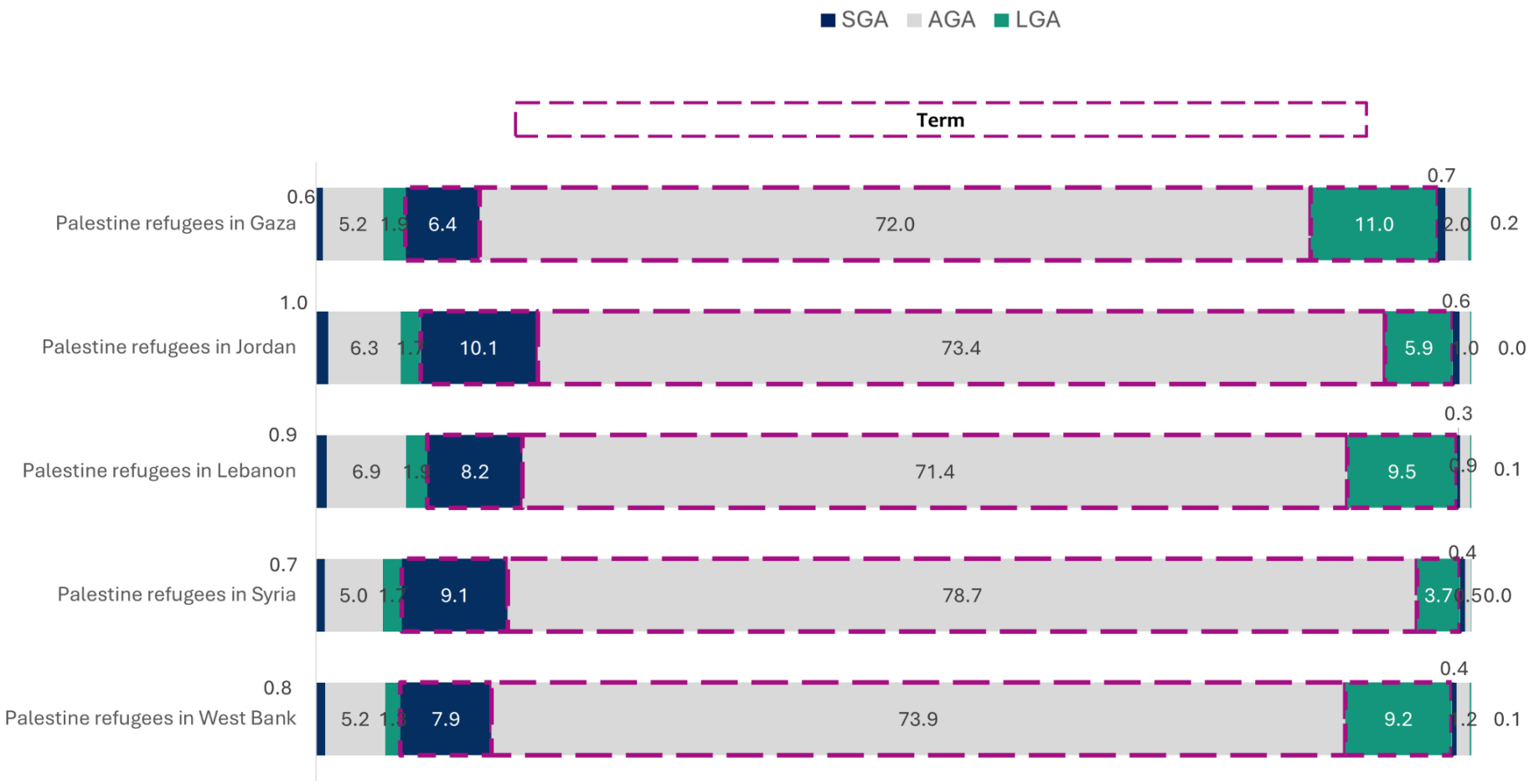

Figure 4- Nine sizes at birth phenotypes for Palestinian refugees by setting.

RESEARCH PAPER COVER SHEET

SECTION A – Student Details

Student ID Number	2004086	**Title**	Ms
First Name(s)	Zeina		
Surname/Family Name	Jamaluddine		
Thesis Title	Establishing a Palestinian Refugee Birth Cohort Using Electronic Health Records to Investigate the Effects of Size at Birth on Child Wellbeing		
Primary Supervisor	Oona Campbell		

SECTION B – Paper already published.

Where was the work published?	Paediatric and Perinatal Epidemiology		
When was the work published?	17/11/2024		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	Not applicable		
Have you retained the copyright for the work? *	Yes	Was the work subject to academic peer review?	Yes

* Attach evidence of permission from the copyright holder (publisher or other author) to include this work.

SECTION C – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper.	ZJ and OC conceived the study. ZJ, LI, EP and JP cleaned the data. ZJ, LI and EP, analysed the data for Palestinian refugees (ZJ), Mexico (LI) and Brazil (EP), with guidance from OC and HB. ZJ, HB and OC wrote the first draft of the manuscript. EO provided the extrapolation of the INTERGROWTH21. LTD, HG, MS, AS, LM and MB supported in interpreting the findings and writing the analysis. All authors read and approved the final version.

SECTION D

Student Signature	
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ORIGINAL ARTICLE

Paediatric and Perinatal Epidemiology WILEY

Post-term births as a risk factor for small for gestational age births and infant mortality in Brazil, Mexico, and Palestinian refugees: An analysis of electronic birth records

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Abstract

Background: Post-term pregnancy, defined as reaching or exceeding 42 + 0 weeks of gestation, is known to be associated with unfavourable birth outcomes. High-income countries have responded to this risk by widely adopting labour induction protocols in late-term, but many low- and middle-income countries have not. However, understanding underlying mechanisms linking post-term births to adverse newborn and infant outcomes remains limited.

Objective: To investigate the (a) prevalence of post-term, (b) the risk factors associated with post-term (c) the association between post-term births and the risk of small-for-gestational-age (SGA) neonates and of infant mortality in middle-income settings.

Methods: We used existing electronic datasets from the general population of Brazil, Mexico, and Palestinian refugees. Regression models were used to explore the associations between post-term birth and SGA and infant mortality.

Results: We analysed 21,335,033 live births in Brazil (2011–2018), 23,416,126 in Mexico (2008–2019), and 966,102 in Palestinian refugees (2010–2020) ($N = 45,717,261$). Post-term deliveries accounted for 3.1% of births in Brazil, 1.2% in Mexico, and 2.1% in Palestinian refugees. Post-term births had approximately three times the risk of resulting in SGA neonates compared to term births. Additionally, post-term neonates exhibited a 15% to 40% increased risk of infant mortality compared to term infants. Notably, post-term SGA neonates faced a significantly increased risk of infant mortality compared to term appropriate for gestational age neonates.

Conclusions: These findings emphasise the critical significance of implementing induction strategies to prevent post-term pregnancies and mitigate the associated risks of SGA neonates and subsequent infant mortality. Moreover, the study highlights the importance of

Oona M. R. Campbell and Hannah Blencowe are joint senior authors.

accurately determining gestational age and using INTERGROWTH-21st charts to improve the identification of SGA cases, enabling targeted interventions. This is especially relevant because post-term SGA neonates may not exhibit low birthweight (a commonly used risk marker) and, therefore, may miss out on required specialised attention.

KEYWORDS
electronic records, foetal growth restriction, induction, infant mortality, middle-income countries, post-term gestation, small for gestational age

1 | BACKGROUND

Post-term pregnancy, defined as gestation of 42 + 0 weeks or more, is associated with adverse birth outcomes.[1] Post-term pregnancy can lead to placental insufficiency, which compromises the oxygen and nutrient supply, resulting in foetal growth restriction; this in turn can lead to stillbirth, small size for gestational age at birth, and subsequent mortality for newborns. Whilst post-term pregnancies are relatively uncommon, they carry a significant risk of preventable mortality. Guidelines aimed at reducing stillbirths recommend inducing labour at 41 + 0 weeks gestation,[2,3] or as early as 39 + 0 weeks.[4–6] These practices are widely adopted in higher-income countries, resulting in few post-term births.

In low- and middle-income countries (LMIC), where the highest burden of adverse perinatal and infant outcomes lies, little is known about the prevalence of post-term births, its risk factors, or its consequences. In part, this is because some LMIC countries do not record gestational age well (using low birthweight (<2500 g) as a proxy for neonatal risk instead) and thus have little information on post-term birth. However, some middle-income countries are recording gestational age on a routine basis.

It is increasingly recognised that combining gestational age and birthweight to identify babies which are small for gestational age (SGA) is a more accurate predictor of early morbidity and mortality than using a birthweight threshold.[7] Additionally, global standards for size for gestational age were only made available recently via the development of global foetal and newborn size charts based on a large, diverse, and representative sample of pregnancies from different populations by the International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st). This has led to suitable benchmarks from LMICs and facilitated international comparisons.[8,9]

A recent study spanning 23 countries generated six newborn types, focusing on preterm versus term and three sizes at birth (SGA, appropriate for gestational age [AGA], and large for gestational age [LGA]).[7,10] They found SGA babies had an increased mortality risk compared to AGA in both preterm and term gestations[10] (excluding post-term). They did not investigate the relationship for post-term neonates.

In this study, we used data from Brazil, Mexico, and Palestinian refugees in Jordan, Lebanon, Syria, the West Bank, and Gaza to expand the six newborn types to nine by including post-term SGA, AGA and LGA dimensions. These populations record gestational age and birthweight and reflect contexts where there are no national policies in place to promote induction before post-term is reached.

Synopsis

Study Question

What is the prevalence of post-term pregnancy? What is the association between post-term pregnancies and the risk of small-for-gestational-age (SGA) neonates and of infant mortality?

What is already known

Post-term pregnancies are associated with adverse birth outcomes. Preterm is the greatest contributor to infant mortality, however, more research is needed to estimate the contribution of SGA to infant mortality when pregnancies reach 42 weeks of gestation or beyond. Mechanisms linking post-term to adverse newborn and infant outcomes are poorly understood. High-income nations have adopted labour induction protocols and thus have very few post-term births. In many middle and low-income countries, pregnancies commonly extend beyond term.

What the study adds

This study highlights the persistent issue of post-term births even in settings able to estimate gestational age. It indicates that women with less education are more likely to have post-term birth and that post-term birth increases the risk of SGA and infant mortality. It emphasises the need for proactive induction strategies before pregnancies reach the post-term stage. It also underscores the importance of accurately measuring gestational age and supports the use of international growth standards, e.g., INTERGROWTH-21st charts, to identify those with SGA and at increased risk of infant mortality for appropriate interventions.

We estimated the prevalence of post-term, and whether (1) maternal education and age increased the risk of post-term, (2) whether post-term pregnancy increased the risk of SGA and (3) whether post-term or post-term SGA increased the risk of infant mortality.

2 | METHODS

2.1 | Data sources

We analysed routinely collected individual-level electronic data of births in Brazil, Mexico, and Palestine refugees. Brazilian and Mexican data are national, while Palestinian refugees' data are from Jordan, Lebanon, Syria, West Bank and Gaza. Palestinian refugees are protracted refugees (hosted in these five settings since 1948) and they are best characterised as a largely urban poor population. Information on GDP per capita and infant mortality rate in each of the countries, showing broad commonality, is presented in Supporting Information.

2.1.1 | Brazilian data

We extracted data from 1 January 2011 to 31 December 2018 from Brazil's Live Birth Information System (Sistema de Informa*ções* sobre Nascidos Vivos—SINASC) obtained from the Centre for Data and Knowledge Integration for Health (CIDACS). SINASC is a nationwide registry, based on the Declaration of Birth, a mandatory document filled by the birth assistant, i.e., a healthcare professional. SINASC covers over 95% of all live births in Brazil and includes information on mothers (age, parity, educational attainment, place of residence, marital status, race/skin colour, obstetric history) and live birth (sex, birthweight, length of gestation, multiples and presence of congenital anomalies).[11]

2.1.2 | Mexican data

We extracted data from 1 January 2008 to 31 December 2019 from Mexico's National Information Subsystem of Livebirths (SINAC), a public dataset administered by the Ministry of Health. We included all live births and deaths registered. SINAC includes information on mothers (age, parity, educational attainment, antenatal care), live births (sex, birthweight, length of gestational age, multiple), and health care facilities (type of facility and state/municipality of delivery), with an estimated coverage of 90% from the target population.[12] Data on foetal and neonatal deaths were extracted from the National Institute of Statistics and Geography (INEGI). Livebirth and death certificates are mandatory in the country and collected by healthcare workers or administrative personnel.[13] To assess infant mortality, we used a previously linked dataset with live births and deaths from day 0 to 365 after birth.[14]

2.1.3 | Palestinian refugee data

The United Nations Relief and Works Agency for Palestinian refugees in the Near East (UNWRA) provides free primary healthcare services to Palestinian refugees in Jordan, Lebanon, Syria, West Bank, and Gaza, including free antenatal care services. The Palestinian refugee population is not composed of recent refugees but rather represents a more stable, urban poor population. We extracted anonymised obstetric record data from UNRWA electronic medical records between 1 January 2010, and 31 December 2020.[15] Obstetric records of pregnancy outcomes were collected retrospectively during postnatal care, the child's first vaccination visit, and by telephone follow-up and are included in the electronic medical records. Detailed pregnancy outcomes included birthweight, gestational age at delivery, mode of delivery, malpresentation, multiplicity (twins etc) and sex of the child.

In all three datasets, gestational age was estimated from the last menstrual period (LMP) or ultrasound. However, the estimation method was not recorded in the data, nor was there a no record of accuracy (e.g., the trimester of the first ultrasound or the certainty of the LMP).

2.2 | Inclusion and exclusion

All pregnancies, including singletons and multiples, resulting in at least one live birth, were included in the main analysis. Stillbirths were excluded as comparable data were not available in Brazil.

The data quality of birthweight and gestational age measurement were explored in detail in previous studies for Brazil, Mexico, and Palestinian refugees,[10,16] including assessments of data, heaping, digit preference, and range of values. We excluded values with extreme/implausible birthweights (more than 6 kg) or gestational ages (less than 22 weeks and more than 44 weeks).

2.3 | Newborn types

We defined nine newborn types based on three newborn gestational categories: preterm birth (between 22 + 0 and 36 + 6 weeks), term birth (37 + 0 to 41 + 6 weeks), and post-term (42 + 0 to 44 + 6 weeks) and size for gestational age. We assigned size at birth using birthweight, gestational age, and sex according to the INTERGROWTH-21st standards into SGA, <10th percentile, AGA, 10th to 90th percentiles, and LGA, >90th percentile.[8–10,17] The nine resulting newborn types were: preterm-SGA, preterm-AGA, preterm-LGA, term-SGA, term-AGA, term-LGA, post-term-SGA, post-term-AGA, and post-term-LGA.

2.4 | Statistical analysis

We assessed the prevalence of post-term and of the nine newborn types for Brazil, Mexico, and Palestinian refugees. We used log-binomial regression models to estimate relative risks (RR) for the association between maternal characteristics (education and age at delivery) and post-term birth, excluding preterm pregnancies. Log-binomial regression models were employed to explore the

association between post-term birth and the outcomes of SGA or AGA, excluding LGA. We used generalised linear models with log-binomial regression to estimate the relative risk for the association between the nine newborn types and infant mortality (death in the first year of life). Special focus was given to understanding risks for post-term and post-term SGA infants. We adjusted the Palestinian model for location, including Gaza, Jordan, Lebanon, Syria, and the West Bank.

Finally, we calculated the population attributable risk (PAR) for each exposure with the following formula where *pr* is the prevalence and *RR* is the relative risk:

$$\text{PAR for type of interest} = \frac{\text{pr(type of interest)(RR(type of interest} - 1))}{\sum_{\text{all types}} \text{pr(type)} \times \text{RR(type)}}$$

All analyses were adjusted for the study setting and were undertaken using Stata (StataCorp, College Station, TX, USA) and R statistical software.

2.5 | Missing data and analysis datasets

The percentage of missing data was limited: 9.0% for the Brazil dataset, 5.5% for Mexico, and 0.7% for Palestinian refugees (Figure 1). We excluded these missing entries. When exploring the association of maternal education and age with post-term births, the comparator was term birth. When investigating the association between post-term births and SGA, the comparator was AGA. The exclusion of preterm births and LGA births respectively decreased the sample size.

2.6 | Sensitivity analysis

We conducted a sensitivity analysis of the association between post-term and SGA using a sub-analysis considering SGA <3rd percentile, LGA >97th percentile and excluding multiple pregnancies.

For the Palestinian refugee dataset, as records were extracted in August 2021, the youngest children (born after September 2020) had a truncated time period for the risk of infant mortality. We conducted a sensitivity analysis by only including those with a full year of follow-up.

2.7 | Ethics approval

Ethical approval was obtained from the Federal University of Bahia's Institute of Public Health Ethics Committee (reference number 18022319.4.0000.5030), the Centre of Investigation in Health Sciences, Anahuac University, Mexico (reference number 202214), UNRWA Research Board and London School of Hygiene and Tropical Medicine (reference number 25467). We used administrative de-identified data to analyse the data, consent was waived by ethical boards.

3 | RESULTS

The three datasets included a total of 49,373,861 births among which 23,439,789 were in Brazil, 24,955,172 in Mexico, and 978,900 in the five settings hosting Palestinian refugees. The Brazil data

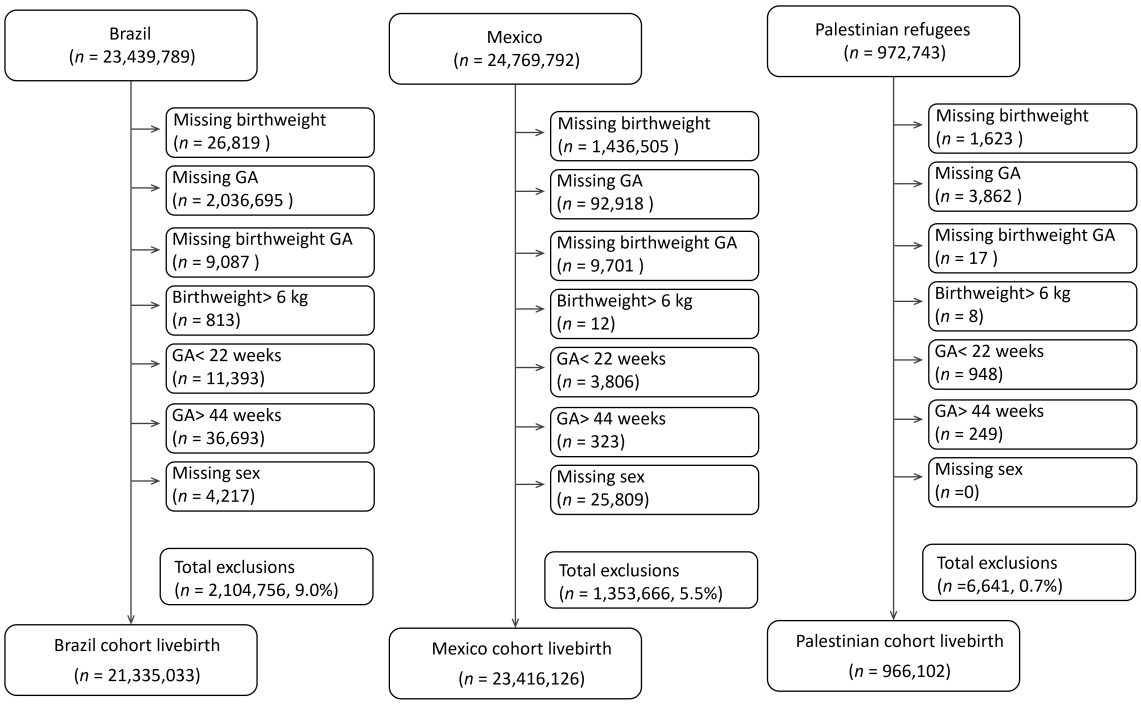

FIGURE 1 Flow chart describing total birth and exclusion in the three datasets (some cases in the exclusion might have overlaps).

did not include stillbirths, so we excluded them in the Mexican and Palestinian datasets. The final dataset for analysis was 45,717,261 live births (93.0% of the dataset live births) after excluding data with missing gestational age or birthweight, extreme birthweights or gestational ages and missing sex (Figure 1).

Among the three studied populations, Brazil showed the highest prevalence of post-term births, followed by Palestinian refugees, with Mexico having the lowest prevalence (Table 1). For SGA births, Palestinian refugees had the highest prevalence, followed closely by Brazil, with Mexico showing the lowest prevalence (Table 1). The pattern for post-term SGA births mirrored that of overall post-term births, with Brazil having the highest prevalence, followed by Palestinian refugees, and Mexico with the lowest (Table 1). In all three datasets, women with higher education levels (secondary, diploma, or university level education) had lower risks of post-term live birth compared to those with lower educational levels (Table 2). Maternal age was not associated with post-term livebirth in the Mexican or Palestinian datasets. In Brazil, older women had a lower risk of post-term livebirth as compared to women aged less than 20 (Table 2).

Post-term live births had around three times the risk of being SGA compared to those born at term (Table 3). Analyses of size for gestational age categories by week of gestation showed an increased prevalence of SGA births from 41 weeks onwards in all three datasets (Figure 2). Post-term infants had an increased risk of infant mortality compared to term in Brazil (Table 4). In all three datasets, post-term SGA newborns in particular had higher risks of infant mortality as compared to term AGA in Brazil, Mexico and Palestinian refugees (Table 4). Sensitivity analyses excluding infants with less than 1 year follow-up showed similar results to the main analyses (Supporting Information). An analysis focusing on infants classified SGA below the 3rd percentile and LGA above the 97th percentile showed similar results (Supporting Information) as did sub-analyses excluding multiple pregnancies (Supporting Information). At the population level, most infant deaths were attributed to preterm-AGA, whilst a smaller portion of infant mortality was attributed to post-term births, or post-term SGA (Table 4).

4 | COMMENT

4.1 | Principal findings

This study explores post-term births and the risk of SGA and infant mortality in three middle-income country datasets. We found the prevalences of post-term were between 1.2% and 3.1%, and the prevalence of post-term SGA was between 0.3% and 0.8%. Maternal education increased the risk of post-term birth and post-term birth was associated with a three-fold increase in the risk of SGA. We also found that being born post-term increased the risk of infant mortality compared to term, and post-term SGA was associated with an almost

TABLE 1 Prevalence of the nine types of newborns, among livebirths in three datasets.

	Brazil		Mexico		Palestinian refugees	
	(*N* = 21,335,033)	%	(*N* = 23,416,126)	%	(*N* = 966,102)	%
Gestational age						
Preterm	2,465,209	11.6	1,499,502	6.4	78,467	8.2
Post-term	669,704	3.1	268,651	1.2	20,458	2.1
Size for gestational age						
SGA	1,699,048	8.0	1,661,891	7.1	89,682	9.3
LGA	3,464,621	16.2	2,145,224	9.2	102,875	10.7
Nine types of size for gestational age						
Preterm						
Preterm-SGA	182,696	0.9	143,423	0.6	7477	0.8
Preterm-AGA	1,491,029	7.0	1,246,947	5.3	53,986	5.6
Preterm-LGA	791,484	3.7	109,132	0.5	17,004	1.8
Term						
Term-SGA	1,338,224	6.3	1,453,089	6.2	76,772	8.0
Term-AGA	14,22,424	67.4	18,174,206	77.6	705,857	73.0
Term-LGA	2,639,472	12.5	2,020,678	8.6	84,548	8.8
Post-term						
Post-term-SGA	178,128	0.8	65,379	0.3	5433	0.6
Post-term-AGA	457,911	2.2	187,858	0.8	13,702	1.4
Post-term-LGA	33,665	0.2	15,414	0.1	1323	0.1

Abbreviations: AGA, appropriate for gestational age; LGA, large for gestational age; SGA, small for gestational age.

TABLE 2 Maternal age and education level: prevalence and association with post-term pregnancy (excluding preterm) in all three datasets.

	Brazil		Mexico		Palestinian refugees[a]	
	Prevalence excluding preterm (%)	Relative risk for being post-term (excluding preterm) RR (95% CI)	Prevalence excluding preterm (%)	Relative risk for being post-term (excluding preterm) RR (95% CI)	Prevalence excluding preterm (%) All sample	Relative risk for being post-term (excluding preterm) RR (95% CI)
Maternal education level[b]	*N* = 18,613,172	*N* = 18,613,172	*N* = 21,597,782	*N* = 21,597,782	*N* = 847,953	*N* = 847,953
Basic	22.6	1.00 (Reference)	14.5	1.00 (Reference)	32.3	1.00 (Reference)
Secondary	59.1	0.64 (0.63, 0.64)	56.8	0.81 (0.80, 0.82)	42.7	0.84 (0.82, 0.87)
Bachelor's and above	18.3	0.28 (0.28, 0.29)	27.1	0.51 (0.50, 0.52)	25.0	0.71 (0.68, 0.74)
Maternal age	*N* = 18,884,790	*N* = 18,884,790	*N* = 21,856,780	*N* = 21,856,780	*N* = 887,506	*N* = 887,506
Under 20 years old	17.5	1.00 (Reference)	19.9	1.00 (Reference)	9.8	1.00 (Reference)
20–24 years	25.5	0.89 (0.89, 0.90)	29.8	1.01 (1.00, 1.02)	25.9	1.01 (0.96, 1.07)
25–29 years	24.5	0.73(0.73, 0.74)	24.6	0.95 (0.94, 0.96)	31.8	1.05 (1.00, 1.10)
30–34 years	19.8	0.57 (0.56, 0.57)	16.2	0.92 (0.90, 0.93)	19.7	1.03 (0.98, 1.09)
35–39 years	10.2	0.48 (0.48, 0.49)	7.5	0.91 (0.90, 0.93)	9.8	1.01 (0.95, 1.07)
40–44 years	2.3	0.50 (0.49, 0.51)	1.6	0.99 (0.96, 1.02)	2.8	0.96 (0.88, 1.06)
45 plus	0.2	0.62 (0.58, 0.66)	0.1	1.10 (0.99, 1.20)	0.3	0.61 (0.43, 0.85)

Abbreviations: CI, confidence interval; RR, relative risk.

[a]Adjusted for setting where Palestinian refugee reside.

[b]Maternal education level was defined by context as in Brazil (0, 7, 8, 12, 12+ years), Mexico (primary and lower secondary (≤11 years), upper secondary and academy professional degree (12, 14 years) and bachelor's and above (≥15 years)) and Palestinian refugees (basic, then intermediate secondary diploma then university and higher degrees.).

TABLE 3 Association of post-term with small for gestational (SGA) (excluding large for gestational age) in all three datasets.

	Brazil	Mexico	Palestinian refugees[a]
	Relative risk (95% CI)	Relative risk (95% CI)	Relative risk (95% CI)
	N = 17,870,412	*N* = 21,270,902	*N* = 863,227
Preterm	1.27 (1.26, 1.28)	1.40 (1.39, 1.40)	1.23 (1.20, 1.25)
Term	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Post-term	3.25 (3.24, 3.27)	3.49 (3.46, 4.51)	3.04 (2.97, 3.11)

Abbreviation: CI, confidence interval.

[a]Adjusted for setting where Palestinian refugees reside.

doubling of the risk of death in infancy compared to term AGA. These findings have important implications for policies to reduce post-term births to reduce preventable mortality and morbidity.

4.2 | Strengths of the study

The availability of large electronic datasets enabled us to investigate the associations between post-term and post-term-SGA and the adverse outcomes of SGA and mortality in three datasets, even though post-term and post-term-SGA pregnancies are relatively uncommon.

4.3 | Limitations of the data

We recognise the limitations of our analysis, many due to well-known challenges of collecting and using routine birth data. Gestational age may have been inaccurate, as the datasets contained a combination of the LMP and ultrasound measurements without distinguishing between them or reporting the gestational age at ultrasound dating. Repeating this analysis including only those with more certain gestational age assessment, e.g., based on first-trimester ultrasound or certain LMP would have been useful, but was not possible.[18] Nevertheless, while measurement error might explain the higher prevalence of SGA, it is unlikely to explain the mortality associations seen for post-term SGA newborns compared to term- AGA.

Birthweight, which should be measured with standard processes (within 1 h of birth, calibrated scales etc) is sub-optimally measured in many LMIC settings, and heaping of birthweight heaping may have contributed to over- and under-estimates of SGA newborns.[19]

In addition, errors might result from using the INTERGROWTH 21st chart for gestational ages above 43 weeks which are based on extrapolation. However, we observed a notable increase in SGA even at 41 and 42 gestational weeks included in the original INTERGROWTH-21st charts.

While the largest effect of post-term is on stillbirth risk, stillbirth data is not available for Brazil, and we excluded it for comparative analysis across the settings.

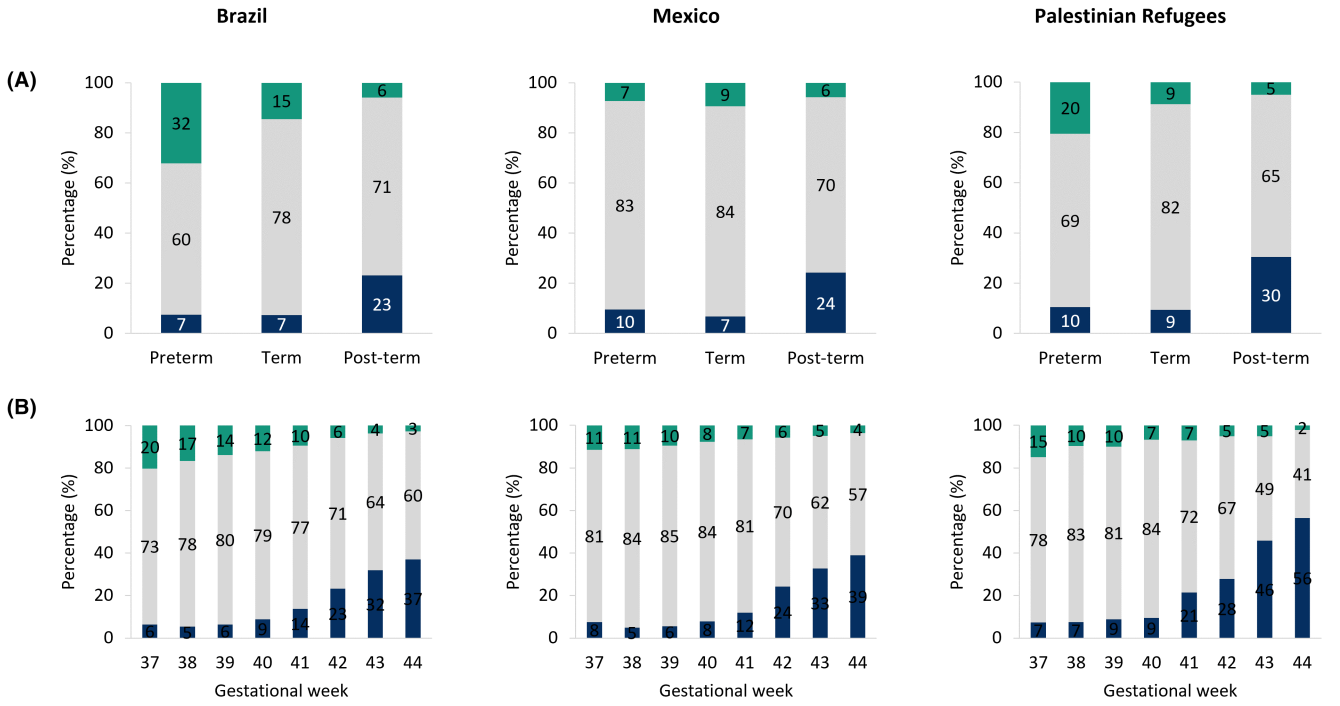

FIGURE 2 Distribution of size for gestational age by (A) preterm, term and post-term live births and (B) by week of gestation for term and post-term live births in Brazil, Mexico, and Palestinian refugees. (blue SGA, grey AGA, green LGA)

TABLE 4 Relative risk of the association between nine newborn types and infant mortality in all three datasets (SGA is highlighted in blue) and population attributable factor (PAR).

	Brazil		Mexico		Palestinian refugees[a]	
	Relative risk (95% CI) (*N* = 21,308,005)	PAR % (95% CI)	Relative risk (95% CI) (*N* = 23,416,126)	PAR % (95% CI)	Relative risk (95% CI) (*N* = 966,102)	PAR % (95% CI)
Gestational age						
Preterm	12.11 (12.00, 12.21)	56.0 (55.8, 56.2)	3.21 (3.17, 3.25)	12.4 (12.2, 12.6)	9.76 (9.43, 10.11)	41.7 (40.9, 42.6)
Ter (Reference)	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Post-term	1.39 (1.34, 1.43)	0.7 (0.6, 0.8)	1.16 (1.12, 1.22)	0.2 (0.1, 0.2)	1.15 (0.99, 1.33)	0.2 (0.0, 0.4)
Size at birth						
SGA	3.61 (3.57, 3.64)	17.6 (17.4, 17.7)	1.25 (1.23, 1.27)	1.8 (1.6, 1.9)	2.72 (2.60, 2.84)	12.5 (12.0, 13.2)
AGA (Reference)	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
LGA	0.87 (0.86, 0.88)	−1.7 (−1.8, −1.5)	0.91 (0.90, 0.93)	−0.6 (−0.7, −0.5)	2.08 (1.9, 2.19)	9.1 (7.7, 9.8)
Nine newborn types						
Preterm-SGA	42.08(41.50, 42.67)	13.3 (13.2, 13.3)	3.78 (3.66, 3.91)	1.4 (1.4, 1.5)	20.94 (19.64, 22.33)	7.9 (7.6, 8.1)
Preterm-AGA	15.28 (15.11, 15.45)	35.9 (35.8, 35.9)	3.26 (3.22, 3.30)	10.4 (10.2, 10.5)	9.31 (8.90, 9.73)	23.0 (22.7, 23.2)
Preterm-LGA	6.01 (5.98, 6.11)	6.7 (6.7, 6.7)	2.34 (2.24, 2.46)	0.6 (0.5, 0.6)	14.13 (13.36, 14.93)	11.7 (11.4, 11.9)
Term-SGA	4.48 (4.41, 4.55)	7.9 (7.8, 7.9)	1.20 (1.18, 1.22)	1.1 (1.0, 1.2)	2.88 (2.71, 3.06)	7.4 (7.0, 7.8)
Term-AGA (Reference)	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Term-LGA	0.85 (0.83, 0.87)	−0.7 (−0.8, −0.6)	0.97 (0.96, 0.99)	−0.2 (−0.3, −0.1)	1.05 (0.96, 1.14)	0.2 (−0.2, 0.6)
Post-term-SGA	3.15 (3.01, 3.29)	0.6 (0.6, 0.7)	1.34 (1.24, 1.46)	0.1 (0.1, 0.1)	2.09 (1.67, 2.63)	0.3 (0.2, 0.5)
Post-term-AGA	1.16 (1.11, 1.22)	0.1 (0.1, 0.2)	1.14 (1.08, 1.20)	0.1 (0.1, 0.1)	1.06 (0.86, 1.30)	0.0 (−0.1, 0.2)
Post-term-LGA	1.55 (1.34, 1.79)	0.0 (0.0, 0.1)	0.96 (0.79, 1.17)	0.0 (0.0, 0.0)	1.08 (0.56, 2.07)	0.0 (0.0, 0.1)

Abbreviations: AGA, appropriate for gestational age; CI, confidence interval; LGA, large for gestational age; PAR, population attributable factor; SGA, small for gestational age.

[a]Adjusted for settings where Palestinian refugees reside.

4.4 | Interpretation

The prevalence of post-term in our populations is at the lower end of global estimates, possibly because of the high rates of caesarean sections in these settings.[20] Although the prevalence of post-term pregnancies is relatively low, the associated risks are high. The 3.1% proportion of post-term births observed in Brazil corresponds to 669,709 live births, a significant number. This translates to a preventable mortality of 0.5% PAR in infant mortality, suggesting that addressing these cases can lead to better health outcomes. The exact causes of post-term birth remain unclear, but some studies have suggested that hormonal and genetic factors and obesity may play a role.[21–23] Irrespective of the biological causes, access to good quality care following guidelines should avert post-term births. In our study, we showed that higher maternal education is associated with a reduced risk of post-term birth, suggesting that socioeconomic factors enable access to medical care. In this analysis, women with higher education levels were more likely to receive quality antenatal care, and a higher number of visits with first-trimester gestational age assessment, potentially expediting their delivery post-date.[24–26]

While social disadvantage is an important factor in overall health outcomes (particularly in post-term pregnancies), it is not the primary driver of the increased risk of infant mortality associated with post-term pregnancies.

As pregnancy progresses beyond the expected delivery date, there is a higher likelihood of placental dysfunction because of infarction, fibrin deposition, and calcification.[27] In some cases, placental function might further deteriorate if exacerbated by infections or by chronic mild hypertension.[27] Placental dysfunction compromises the placental ability to efficiently transfer oxygen and essential nutrients to the developing foetus.[27] Consequently, the foetus experiences inadequate nourishment and may result in foetal growth restriction manifested as SGA, this is seen in Mexico, Brazil, and Palestinian refugees. This may also explain the higher stillbirth rates seen in post-term pregnancies reported in the literature.[1]

Our study also indicated that post-term and post-term SGA newborns have an elevated risk of infant mortality in the first year of life compared to infants born at term and at AGA term respectively. The increased risk of mortality in post-term SGA infants may be attributed to various complications, including birth asphyxia, respiratory distress syndrome (e.g., meconium aspiration syndrome), increased susceptibility to infections and hypoglycaemia cause mortality.[1,28] In addition, post-term and LGA are associated with birth trauma, increased hospitalisation, cerebral palsy, Wilms tumour and others.[29]

The effect size from the three populations indicates a consistent pattern of association, however, differences in the exact magnitude of the effects between the three datasets may be due to unmeasured and thus uncontrolled confounding factors, such as maternal obesity, which are associated with the exposure of being post-term and the outcome of neonatal mortality[30] and which may differ in prevalence among the three populations. In addition, potential misclassification due to methods used for gestational age measurement may have impacted comparability. Notably, Mexico shows the greatest divergence, likely due to challenges with gestational age measurement in this setting.

In terms of implications, the study highlights the need for (1) increased access to antenatal care to better assess gestational age and potentially identify SGA in utero, (2) induction to avert post-term births (3) and postnatal assessment of size for gestational age, to ensure that SGA babies with birthweights <2500 grams are recognised as being at higher risk and managed appropriately.

Our data indicate that there is a need to increase the induction of labour before post-term in middle-income countries. The results of this study are generalizable to other contexts where pregnancies reach post-term stage. This requires accurately measuring gestational age, to prevent inadvertent iatrogenic preterm or early-term birth associated with inaccurate assessments. Another clinical implication is the need to adopt internationally comparable growth charts e.g., INTERGROWTH21st newborn standards are a useful tool to assist in the effective identification of SGA, and hence increased risk including postnatally and especially in post-term babies. These standards are increasingly being adopted and we utilised them in our analyses to facilitate international comparisons.[7]

Recent guidelines by the World Health Organisation (WHO) and The National Institute for Health and Care Excellence (NICE) advocate for induction at 41 weeks of gestation,[2,3] and show the potential to reduce perinatal complications without increasing caesarean section rates. It is particularly important it is possible to do this without increasing caesarean prevalence, among Brazil, Mexico, and Palestinian refugees, as rates are already high.[16,31–33] Implementing a policy of inducing at 41 weeks in Brazil, Mexico, and the settings where Palestinian refugees reside could contribute to reducing preventable mortality and morbidity. In settings where a national policy for induction at 41 weeks is not well established, and there are plans to introduce one, ensuring proper access to first-trimester antenatal care and accurate gestational age assessment using LMP and ultrasound is essential to ensure women are not induced too soon. Challenges in implementing ultrasound measurements in middle-income countries must be addressed to optimise perinatal care.[34]

Postnatal care for post-term SGA newborns may be overlooked when relying solely on birthweight for risk stratification, as happens with current newborn risk stratification in many low- and middle-income countries. Using low birthweight <2500 g, misses post-term SGA babies as they are unlikely to be low birthweight and more likely to be normal or even high birthweight. For example, a 2850 g female newborn or a 3000 g male newborn born at 42 weeks of gestation (post-term) would be classified as having a normal birth weight but is actually at the 5th percentile on the INTERGROWTH21 charts and is classified as SGA. For example, in the Palestinian data, focusing on low birthweight alone would miss 6% of the SGA births that are not low birthweight; among post-term births, the comparable figure is 25% that are SGA but not low birthweight. Our study demonstrates

the value of the birthweight for gestational age percentile charts over low birthweight thresholds in helping to identify post-term SGA newborns, and so enabling tailored neonatal care and interventions (e.g., regular blood glucose monitoring) for this vulnerable subgroup.[35]

Future research should focus on understanding the causes and timing of infant mortality among post-term SGA newborns. Despite the primary focus of our study on post-term SGA, we recognise the significance of exploring the implications of LGA prevalence on adverse outcomes, particularly in countries experiencing nutritional transitions and rising obesity rates. Finally, understanding the association between post-term SGA and future risk factors, including chronic diseases, remains a relatively unexplored area in the existing literature.[29]

5 | CONCLUSIONS

In conclusion, this study analyses routine data from middle-income settings and extends the previously used vulnerable newborn types to highlight, post-term births and their, association with poorer outcomes of SGA and infant mortality at 1 year.

These findings emphasise the necessity for policy strategies targeting the reduction of post-term pregnancies. This will require scaling up of universal first-trimester gestational age measurement, developing and implementing labour induction strategies for pregnancies at 41 weeks gestation and assessing size at birth for all to enable appropriate risk assessment and identify additional care needs.

AUTHOR CONTRIBUTIONS

ZJ and OC conceived the study. ZJ, LI, EP and JP cleaned the data. ZJ, LI and EP, analysed the data for Palestinian refugees (ZJ), Mexico (LI) and Brazil (EP), with guidance from OC and HB. ZJ, HB and OC wrote the first draft of the manuscript. EO provided the extrapolation of the INTERGROWTH21. LTD, HG, MS, AS, LM and MB supported in interpreting the findings and writing the analysis. All authors read and approved the final version.

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CONFLICT OF INTEREST STATEMENT

The authors report no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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 Chapter 5- Examining size at birth and rapid weight gain in the first year of life as a risk factor for childhood overweight/obesity

In this Chapter, I address a key gap identified in Chapter 2 and explore the association between size at birth (discussed in Chapter 4) and childhood overweight/obesity using cohort data from Palestinian refugees (Chapter 3). I focus on childhood overweight/obesity as an outcome because: 1) the umbrella review (Chapter 2) found inconclusive results on the effects of birth size on overweight/obesity; 2) high-quality growth data were available in the UNRWA e-health system; and 3) there was an opportunity to explore childhood overweight/obesity in a context experiencing a nutritional transition for which there is limited previous research.

RESEARCH PAPER COVER SHEET

SECTION A – Student Details

Student ID Number	2004086	**Title**	Ms
First Name(s)	Zeina		
Surname/Family Name	Jamaluddine		
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SECTION C – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper.	ZJ and HG conceived the study. ZJ cleaned and analysed the data with guidance from OC, HG and EO. ZJ wrote the first draft of the analysis. ZJ interpreted the findings and wrote the first draft of the manuscript. HG and EAF provided support in interpreting the findings. All authors read and approved the final version.

SECTION D

Student Signature	
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Early Growth Trajectories and Subsequent Childhood Overweight or Obesity: Exploring the Association of Size at Birth and Rapid Weight Gain in the First Year with Overweight among Palestinian refugees

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Keywords: Size at birth, Small for Gestational Age, Rapid Weight Gain, Childhood Overweight

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Structured Abstract

Background

Understanding the effect of early growth trajectories on childhood overweight/obesity is crucial. This study explores the association between size at birth, rapid weight gain in the first year of life, and subsequent overweight/obesity in childhood among Palestinian refugees.

Methods

This longitudinal study utilized data from 388,347 live birth records linked to child growth monitoring records from the United Nations Relief and Works Agency (UNRWA) e-health system, covering births from January 1, 2010, to December 31, 2020. The cohort included children aged 0-59 months from five regions: Gaza, Jordan, Lebanon, Syria, and the West Bank. Size at birth was categorized using INTERGROWTH-21st standards, and growth trajectories were monitored to assess rapid weight gain (defined as an increase of 0.67 in weight for age z-score from birth until 12 months of age) and overweight/obesity (defined as weight for height score greater than +2 z-score at any time point after 24 months of age) occurrences. Multilevel mixed-effects models and structural equation modelling were employed to analyse the associations.

Findings

Small for gestational age (SGA) children had lower odds of exclusive breastfeeding (aOR=0.83), higher odds of rapid weight gain (aOR=2.39) and lower odds of overweight/obesity (aOR=0.50) compared to appropriate for gestational age (AGA) children. Conversely, large for gestational age (LGA) children showed lower odds of rapid weight gain (aOR=0.35) but higher odds of being overweight/obese (aOR=2.76) as compared to AGA. Rapid weight gain in the first year was strongly associated with overweight/obesity at 24-59 months (aOR=6.53) after adjusting for child age and setting. Exclusive breastfeeding was associated with a lower odds of rapid weight gain and subsequent overweight/obesity.

Interpretation

Rapid weight gain in infancy, regardless of birth size, is a significant predictor of childhood overweight/obesity. Exclusive breastfeeding appears to mitigate the risk of rapid weight gain and subsequent overweight/obesity, highlighting its protective role. These insights emphasize the need for targeted public health strategies to address early growth patterns and promote breastfeeding in Palestinian refugee populations.

Introduction

To address the rising global prevalence of childhood overweight/obesity, it is essential to understand the underlying mechanisms contributing to overweight/obesity during the critical "first 1000 days" of a child's life (1). Published research suggests that perinatal influences (including in-utero shocks), small size at birth, and early life growth patterns may determine health and developmental outcomes in childhood and later in adult (1).

A substantial body of evidence links small size at birth (including low birth weight, being small for gestational age and prematurity) with undernutrition (wasting and stunting) during the first five years of life (1). However, the evidence regarding the association between small size at birth and childhood overweight/obesity is inconclusive (1). A recent umbrella review identified four reviews which included eight meta-analyses on the effect of small size at birth on overweight/obesity in childhood (1). Of these eight meta-analyses, three meta-analyses, two using low birthweight and one using term small for gestational age (SGA) as the exposure, found no effect (3/8 meta-analyses), one using preterm birth as the exposure showed an increased effect (1/8 meta-analyses), and four using low birthweight as exposure showed a reduced effect (4/8 meta-analyses) on childhood overweight/obesity (2-5). The inconsistencies in these associations may arise due to different ways of defining the exposure; early studies primarily focused on low birth weight (6/8 meta-analyses) rather than SGA (1/8 meta-analyses) (2-5). Other explanations include the fact that low birthweight encompasses both preterm and SGA infants, but the risk factors for, and mechanisms leading to preterm birth and SGA are different and reflect distinct intrauterine growth conditions, which could result in differential growth patterns postnatally.

It has been proposed that infants born small may experience accelerated postnatal growth in response to intrauterine nutrient deprivation, and this rapid postnatal growth can lead to childhood obesity (6, 7), that potentially track towards adverse metabolic outcomes in the long term (8-10). This perspective highlights the potential importance of growth trajectory as a critical determinant of future overweight and obesity.

However, discussions on rapid weight gain often fail to distinguish between the expected catch-up growth in premature infants and accelerated growth in term infants (11, 12). This distinction is important particularly as rapid weight gain in premature infants may result from a different physiological process than rapid weight gain in term infants. Premature infants, for instance, require catch-up growth to achieve developmental milestones that might have occurred in utero, whereas accelerated growth in term infants might indicate excessive caloric intake or suboptimal feeding practices.

Studies emphasize that children experiencing rapid weight gain during infancy, particularly those born with low birth weight, face a higher likelihood of becoming overweight or obese (13). This trajectory has further been associated with increased abdominal adiposity (14) and heightened insulin resistance, predisposing these individuals to metabolic syndrome and related conditions term (8-10, 13, 15). Notably, not all low-birth-weight infants undergo rapid weight gain; some maintain lower growth trajectories throughout childhood, which might confer different health risks or benefits. Research did not distinguish whether low birthweight was associated with prematurity, or occurred in term babies, which might explain heterogeneity in growth rates post birth (13, 16). The timing of weight gain also appears critical. Evidence suggests that excessive weight gain during infancy may have a more pronounced impact on long-term fat accumulation and metabolic health compared to weight gain occurring later in childhood (7, 16). This highlights infancy as a sensitive period for shaping future health outcomes through growth and weight patterns.

A systematic review focusing on the effect of rapid weight gain underscores the need for further research, particularly with adequate sample sizes, on SGA individuals and on the trajectory of rapid weight gain among those who were SGA versus AGA (16).

In addition to rapid weight gain itself, other postnatal factors that influence weight gain such as child dietary patterns and physical activity have been linked to overweight/obesity. Breastfeeding specifically has been proposed as a mitigating factor in reducing the risk of overweight/obesity (17). Studies examining the association between birth size and overweight/obesity, however, are scarce due to the limited availability of longitudinal cohorts that collect these data.

In brief, there are gaps pertaining to 1) inconclusive evidence regarding the effect of small size at birth on the risk of overweight/obesity, 2) evidence on the differential effects of being born preterm, post-term, SGA, LGA on overweight/obesity in childhood and 3) limited longitudinal research encompassing postnatal factors, notably breastfeeding and rapid weight gain.

We use SGA as the exposure in this analysis enabling us to identify individuals with a birth weight lower than expected for their gestational age, reflecting intrauterine growth restriction rather than preterm birth with appropriate weight for gestational age. Furthermore, as recommended in a recently published umbrella review, (1) in order to investigate associations between size at birth and child outcomes, we distinguish between nine phenotypes using a combination of gestational age categories (preterm, term post-term) and birthweight (small (SGA), appropriate (AGA) and large (LGA) for gestational age).

In the context of child growth, we distinguish between rapid weight gain for premature infants and for term, preterm, post-term SGA. Rapid weight gain for premature infants mirrors the weight deposition that would normally occur during foetal development but that occurs outside the uterus since the infant was born too soon. Rapid weight gain for SGA, whether in preterm or full-term babies, refers to a significant increase in a child's weight over a short period with a proposed definition of an increase of 0.67 in weight-for-age z-score (18).

Objectives

This study aims to understand of how newborns with different size at birth and gestational age categories grow during the first year of life, and how their growth trajectory is associated with the subsequent risk of occurrence of overweight/obesity. Specifically, this study investigates the association between nine sizes at birth and gestational age categories (9 phenotypes) and 1) exclusive breastfeeding during the first 6 months, 2) rapid weight gain in the first 12 months, and 3) the occurrence of overweight/obesity in children aged 24 to 59 months.

Methods

1. Description of the population/data source

For this analysis, we use a recently established Palestinian refugee birth cohort, generated from the electronic health records (e-health system) of the United Nations Relief and Works Agency (UNRWA). Palestinian refugee children live predominantly in settings that have experienced a significant shift in dietary patterns, aligned with a nutrition transition over the last decade. This has led to an elevated prevalence of overweight or obesity, including among children (19). UNRWA provides Palestinian refugees with free primary healthcare services via 140 clinics in five operational settings: Gaza, Jordan, Lebanon, Syria and the West Bank. This includes routine growth monitoring data collected. This study leverages the newly established cohort which spans livebirths from 01 January 2010 to December 31, 2020 (20).

The full dataset used in this analysis encompasses 388,347 live birth records derived from maternal obstetric records linked to child growth monitoring records for children aged 0-59 months. We restricted the dataset to livebirths with at least one observation after 24 months. The records were extracted on September 14, 2021, making this the last date growth monitoring could be recorded.

Birth outcomes, including the date of birth, gestational age in weeks (based on last menstrual period calculated in the system), and birth weight in grams from hospital records, were recorded in the obstetric history module by nurses or midwives caring for pregnant women.

The growth monitoring data, including the date of the visit, weight in kg, length/height in centimetres, head circumference in cm, and feeding practices (as a multiple-choice response including breastmilk, infant formula, complementary feeding) were routinely collected by trained UNRWA nurses and recorded in the electronic health records growth monitoring section.

2. Characteristics of the population

We assessed loss to follow up in the cohort by examining age at the last recorded growth monitoring visit and comparing it to the child's current age on September 14, 2021, stratified by cohort year. Additionally, we investigated the frequency of growth-monitoring visits across various age groups of children, categorized by cohort year, to discern trends in timing of anthropometric measurements. Cox regression was used to characterize children lost-to-follow-up within their respective cohorts, including by sex and maternal education. We excluded multiple live births (twins, triplets etc.,) from our analysis, as we could not accurately determine the distinct birthweight of each newborn when dealing with multiple newborns of the same sex (20).

3. Operationalizing exposure/outcome/ mediator/ confounder variables

We assessed missing data, heaping, digit preference, and range of values for birthweight, gestational age, weight, and height variables. Implausible birthweight, weight and height measurements were excluded. We compared our values to those from population-based surveys in host countries, or associations previously described in the literature (e.g., sex ratio at birth, increasing birthweight with parity).

Size at birth

In the e-health system gestational age is determined by last menstrual period. It required cleaning as it was recorded in an open text format with variations such as "38wk+2days," and with different spellings (e.g., "wk", "wks", "weeks", "weks").

Gestational age categories were defined as preterm (22+0 to 36+6 weeks), term (37+0 to 41+6 weeks), and post-term (42+0 to 44+6 weeks). We used gestational age, birthweight and sex according to the INTERGROWTH-21st standards to assign size at birth as SGA, (<10th percentile), AGA, (between the 10th to 90th percentiles), and LGA, (>90th percentile) (21-27). The nine resulting newborn gestational age and size phenotypes were defined as preterm-SGA, preterm-AGA, preterm-LGA, term-SGA, term-AGA, term-LGA, post-term-SGA, post-term-AGA, and post-term-LGA.

Exclusive breastfeeding

Exclusive breastfeeding was defined as breastfeeding without any infant formula or additional foods other than breast milk for the first 6 months of life.

Anthropometry

Weight-for-age z-scores (WAZ) and weight-for-height z-scores (WHZ) were derived using age- and sex-specific WHO growth standards (2006). Extreme z-scores, defined as those exceeding +5 or below -5 z-scores, were excluded from the analysis. Adjustments were made for gestational age (28-30) for preterm infants (gestational age<37), by applying INTERGROWTH-21st standards for WAZ and WHZ to generate z-scores up to 64 weeks post-conception (or 24 weeks post full term (40 weeks of gestation)) (31). After 64 weeks, we shifted to using WHO growth standards. This adjustment was necessary because preterm infants have different growth patterns compared to term infants, and using WHO standards from birth for preterm infants would lead misclassify their growth status during early life compared to term.

Rapid weight gain was defined as a change in WAZ scores of more than 0.67 z-score from birth until 12 months, indicating a crossing of major percentile line in growth standard (2nd, 9th, 25th, 50th, 75th, 91st, and 98th percentile line) (7, 18). In a sensitivity analysis, rapid weight gain was also examined for a period starting after 40 weeks post conception until 12 months of age (52 weeks post birth). This additional analysis was conducted to account for potential differences in growth patterns between preterm and full-term infants during the early postnatal period.

Overweight/obesity was defined as a WHZ score greater than +2 z-score at any time point after 24 months of age. Additionally, in a second sensitivity analysis we explored repeated overweight/obesity event, defined as a WHZ score exceeding +2 on two or more separate occasions after 24 months of age.

We conducted sensitivity analyses using 1) analysis starting at 40 weeks post conception (to exclude the early period of growth of postnatal growth for preterm infants), 2) repeated overweight/obesity, defined as a WHZ score exceeding +2 z-scores on at least two

separate occasions after 24 months of age, and 3) Body Mass Index (BMI) z-score instead of WHZ to define overweight/obesity defined as exceeding +2 z-scores at any point after 24 months of age.

4. Statistical analysis

The analyses were conducted using Stata 18 (StataCorp, College Station, TX, USA) and R statistical software. Both logistic and multilevel mixed-effects models were applied to assess the association between size at birth, exclusive breast feeding, and rapid weight gain with overweight/obesity, adjusting for setting and child age in months. We first examined size at birth as (SGA/AGA/LGA) adjusting for gestational age categories and for child age and setting (model1). We then examined the nine sizes at birth phenotypes as exposure (model2). We also employed generalized structural equation (GSEM) modelling to estimate direct and indirect paths for a recursive path model hypothesized to connect, size at birth (nine categories preterm-SGA, preterm-AGA, preterm-LGA, term-SGA, term-LGA, post-term-SGA, post-term-AGA, post-term-LGA as compared to a reference of term-AGA), exclusive breastfeeding under 6 months (no, yes), rapid weight gain within 1 year (no, yes), and at least once overweight/obesity between 24-59 months (no, yes), adjusting for setting and child age. Figure 2 includes the path explored and the odds ratios. We assessed the direct and indirect and total effect of 3 main pathways simultaneously.

- Size at birth→ overweight/obesity (after 24 months)
- Size at birth → exclusive breastfeeding (0-6 months)→ overweight/obesity (after 24 months)
- Size at birth → exclusive breastfeeding (0-6 months)→ rapid weight gain (birth till 12 months)→ overweight/obesity (after 24 months)

Ethics statement

We obtained approval to use de-identified encrypted data from the London School of Hygiene and Tropical Medicine, Nagasaki University, and UNRWA's research review board reference number 25467).

Results

1. Cohort of Palestinian refugee children in five settings and data quality

A total of 388,347 singleton live births had a recording of birthweight and at least one measurement of weight and height after 24 months. These corresponded to 4,183,934 weight and height observations and formed the basis of the analysis. The detailed cohort selection is presented in Supplementary material 1.

Data quality for the 388,347 singleton livebirths is detailed in Supplementary materials 2 to 4. In general, data quality was high, with limited missing data (total 0.3% for size at birth and 0.1% for weight and height) or implausible data (total 0.02% for size at birth and 0.58% for weight and height).

2. Characteristics of Palestinian children cohort

Table 1 presents the prevalence of exclusive breastfeeding practices under six months of age, rapid weight gain during the first year of life, and the occurrence of overweight/obesity between 24 and 59 months, with differences seen across settings.

Birth-size and exclusive breastfeeding varied across the five settings. SGA percentages ranged from 7.5% in Gaza to 11.2% in Jordan, and LGA percentages from 4.8% in Syria to 12.8% in Gaza. Exclusive breastfeeding ranged from 35.4% in Jordan to 77.5% in Syria.

We also investigated rapid weight gain within the first 12 months of life from birth, with percentages of rapid weight gain ranging from 22.2% in Gaza to 34.4% in Lebanon. Finally, the occurrence of overweight/obesity in children aged 24 to 59 months was examined. Table 1 presents both single and recurrent instances, and the percentage of overweight/obesity children (at least once) ranged from 2.4% in Syria to 6.7% in Lebanon.

3. Association of size at birth with exclusive breastfeeding, rapid weight gain, and overweight/obesity

Figure 1 shows growth curves of weight for height z-score by weeks of age (from conception), size at birth, nine phenotypes and five settings. Table 2 displays the

adjusted associations between size at birth and exclusive breastfeeding for 6 months, rapid weight gain and overweight/obesity.

Size at birth and exclusive breastfeeding

After adjusting for setting and child age, SGA children exhibited 17% lower odds of exclusive breastfeeding (adjusted odds ratio (aOR= 0.83;95% CI: 0.81-0.85) as compared to AGA children while LGA children also showed 5% lower odds of exclusive breastfeeding (aOR= 0.95, 95% CI: 0.93-0.97) (Table 2, model1). Preterm children had 55% lower odds of exclusive breastfeeding (aOR= 0.45, 95% CI: 0.44-0.47) as compared to term children. Specifically, preterm-SGA infants were associated with 73% lower odds of exclusive breastfeeding (aOR= 0.27, 95% CI: 0.24-0.30) as compared to AGA term children (Table 2, model1).

Size at birth and rapid weight gain

After adjusting for setting and child age, SGA children had 2.39 times the adjusted odds of rapid weight gain (95% CI: 2.32-2.45) compared to AGA children (Table 2, model1). Conversely, LGA children displayed lower adjusted odds (aOR=0.35, 95% CI: 0.33-0.36). Preterm children had substantially higher odds of rapid weight gain (aOR: 1.22, 95% CI: 1.18-1.26), compared to term children, while post-term children exhibited lower odds (aOR: 0.66, 95% CI: 0.62-0.70) (Table 2, model1). Rapid weight gain defined from 40 weeks of gestation till 12 months (Supplementary material 5) shows similar patterns. This excludes all weight gain data before 40 weeks from conception to exclude the period of expected catch-up of preterm infants.

Size at birth and overweight/obesity

SGA children exhibited half the odds of being overweight/obese (aOR=0.50, 95% CI: 0.46-0.56) compared to AGA children after adjusting for setting and child age. In contrast, LGA children displayed substantially higher adjusted odds of being overweight/obese (aOR=2.76, 95% CI: 2.59-2.95) (Table 2, model1). Examining gestational age categories, neither preterm nor post-term were associated with overweight/obesity as compared to

term (Table 2, model1). Repeated overweight/obesity measures (Supplementary material 5) showed similar results.

4. Association of rapid weight gain with overweight/obesity

Table 3 shows the association between rapid weight gain and overweight/obesity among children aged 24 to 59 months adjusted for setting and child age.

Rapid weight gain and overweight/obesity stratified by size at birth

Rapid weight gain was associated with an increased odds of overweight/obesity (aOR=6.53, 95% CI: 6.15-6.94). When stratified by birth size, children born SGA, AGA, LGA all exhibited varying degrees of increased adjusted odds for overweight/obesity associated with rapid weight gain, with LGA children showing the highest adjusted odds at 9.29 (95% CI: 7.98 to 10.83). When stratifying by gestational age, we found that being a preterm child with rapid weight gain was associated with an increased odds of having an overweight/obesity measurement, but that the odds were lower (aOR=4.45, 95% CI: 3.66-5.42 versus 6.53) than for rapid weight gain overall. Term children had the most elevated adjusted odds (aOR=6.83, 95% CI: 6.41-7.28), followed by preterm children (aOR= 4.45 (3.66-5.42)) and post-term (aOR=4.31, 95% CI: 2.90-6.39).

Stratifying by combinations of gestational age and birth weight as risk factor indicate a complex interplay of these factors in shaping the adjusted odds of being overweight/obese. The results revealed that rapid weight gain was associated with increased odds of overweight across most categories, with the strongest association observed in term infants born LGA. This group had the highest adjusted odds ratio of 10.13 (95% CI: 8.59-11.94). Among term infants, a clear gradient was evident, with the risk increasing from SGA to LGA. For preterm infants, AGA babies had the highest risk (AOR 6.75, 95% CI: 5.29-8.61), followed closely by LGA infants. Preterm SGA infants had the lowest aOR overall, at 1.69 (95% CI: 0.77-3.70), and this was the only group where the confidence interval included 1, suggesting a potentially non-significant association. Post-term infants showed fewer clear associations, with post-term AGA having the highest aOR in this group at 5.53 (95% CI: 3.45-8.85). Overall, these findings suggest that

rapid weight gain is a significant risk factor for overweight, particularly in term and preterm infants born AGA or LGA.

Rapid weight gain and overweight/obesity stratified by breastfeeding practices

Furthermore, when exploring the odds of overweight/obesity while stratifying by breastfeeding practices, the association of rapid weight gain with overweight/obesity varied according to breastfeeding practices, with rapid weight gain associated with overweight/obesity without exclusive breastfeeding (aOR=7.01, 95% CI: 6.47-7.59) and with exclusive breastfeeding (aOR=5.72, 95% CI: 5.16-6.35).

For analyses related to this, we included a table in supplementary material 5 exploring the association between size at birth adjusting for rapid weight gain and/or exclusive breastfeeding.

5. Structural equation model indirect/mediation pathways

The likelihood of being overweight/obese varies significantly across different birthweight and gestational age groups, with notable mediation effects through breastfeeding and rapid weight gain (Figure 2 and Table 4).

Among preterm and term infants, those born SGA had an increased total effect on the odds of being overweight/obese, largely driven by an indirect effect through rapid weight gain, despite a substantially lower direct effect. Preterm AGA infants exhibited an increased total effect, with modest indirect effects through the combination of breastfeeding and rapid weight gain. LGA infants showed a higher direct effect among preterm, term and post-term of overweight/obesity and lower indirect effects through rapid weight gain. This suggests that being born LGA may have a more direct influence on later overweight/obesity risk, independent of mediating factors like breastfeeding and rapid weight gain.

When analysing these data with BMI z-score to define overweight/obesity instead of weight for height z-score, we find similar results (Supplementary material 5)

Discussion

This study emphasizes the importance of rapid weight gain in infancy, irrespective of the size at birth, as being associated with overweight/obesity in childhood. It also unveils that children classified as SGA have lower exclusive breastfeeding rates, and consequently an increased likelihood of rapid weight gain.

Specifically, our study shows that:

1) Rapid weight gain is associated with overweight/obesity in early childhood.
2) Being born LGA is positively associated with overweight/obesity between the ages of 24-59 months, while being born SGA decreases odds of overweight/obesity at the same ages.
3) Rapid weight gain during the first year of life (12 months), either measured at birth or after 40 gestational weeks, is associated with overweight/obesity at ages 24-59 months, irrespective of birth size.
4) Breastfeeding may reduce the likelihood of rapid weight gain, thereby decreasing the likelihood of overweight/obesity between 24-59 months.

Unlike many studies in the literature which rely primarily on cross-sectional data (32, 33), small sample sizes (34-36), or take place in high-income countries (37), our study provides a nuanced understanding of growth trajectories and the occurrence of overweight/obesity during early childhood. We used a large longitudinal dataset for an in-depth exploration of a range of size-at-birth phenotypes, including those with low prevalence such as preterm. The study also enabled us to study this pathway in Palestinian refugees living in five middle-income settings undergoing a nutritional transition.

Large for gestational age and rapid weight gain in infancy: main pathway to childhood overweight/obesity

Rapid weight gain in infancy, regardless of size at birth, operates through distinct pathways leading to overweight/obesity (Table 3). Children experiencing rapid weight gain in the first year of life had 6.53 times the odds of being overweight/obese after 24 months

than those who did not experience this. This aligns with a meta-analyses showing odds ratio of 4.12 (confidence interval range: 1.83-9.28 with high heterogeneity I^2 = 89.5%), and adds to the body of literature examining this phenomenon (13). In contrast, considering birth size we find that SGA was associated with reduced odds of overweight/obesity (aOR=0.50).

During early childhood, adipose tissue develops rapidly. Excessive energy intake can increase the number and size of fat cells, leading to adiposity (excess body fat) (38, 39). Rapid weight gain during this period can lead to metabolic dysregulation, including insulin resistance and altered appetite. Infants of low birthweight or SGA are more likely to have higher adrenal androgen levels, insulin resistance, and central fat deposition, and thus heightening vulnerability to weight gain and adiposity (15, 40-42). In our study, we found that SGA infants had higher odds of having rapid weight gain (aOR=2.39), which elevated the risk of being overweight/obese.

Our umbrella review on this topic showed that high birthweight was associated with subsequent risk of being overweight/obese (1), our study further emphasizes that being LGA, not just high birthweight, is a key factor in overweight/obesity children. Despite LGA being associated with a reduced likelihood of rapid weight gain (aOR=0.35), LGA was independently associated with an increased risk of overweight/obesity (aOR=2.76). LGA infants face challenges in maintaining balanced body proportions from birth onwards, as their weight gain outpaces their gain in height (43). Even preterm LGA infants are more susceptible to becoming overweight/obese compared to both preterm AGA and term AGA infants. Furthermore, when considering birth size, the combination of LGA and rapid weight gain confers the highest odds of overweight/obesity, highlighting the importance of addressing this dual risk factor (aOR=10.13).

Our findings also emphasize the positive association of exclusive breastfeeding for at least six months with a lower risk of subsequent overweight/obesity during childhood (24 to 59 months) mediated by having a lower odds of rapid weight gain (aOR=0.66). Studies suggest that the nutritional composition of breast milk, including hormones like leptin and ghrelin involved in appetite and energy balance regulation (44), plays a crucial role in protecting against overweight/obesity. A study noted that formula or mixed-fed infants

had higher energy intakes at four months, and this was associated with increased weight gain from birth to age one, two, or three years, as well as higher BMI at ages one to five years (45). In our study, SGA and preterm infants had a reduced odd of exclusive breastfeeding, while having an elevated risk of rapid weight gain.

Strength and limitations

The robustness of our data is supported by consistently high-quality results across all sensitivity analyses, affirming the study's internal validity. These analyses include examining one setting at a time, restricting rapid weight gain to gain after gestational age over 40 weeks, using BMI z-score instead of WHZ score for overweight/obesity classification, and examining repeated overweight/obesity instead of using a single measurement of overweight/obesity after 24 months.

This study leverages administrative electronic growth monitoring data collected regularly, distinguishing it from cohorts with less frequent measurements and enabling the assembling of a large dataset. However, the specific intervals between data collection time points vary, and certain variables relevant to the association, such as dietary diversity and complementary feeding, are not included. Additionally, the data may be susceptible to selection bias, as the most vulnerable infants and children might not have attended regular growth monitoring sessions. Since growth monitoring was limited to children under five, it was not possible to examine whether this association persisted among older children, adolescents and adults. The SEM model assumed exclusive breastfeeding was a determinant of rapid weight gain, but some evidence suggests the reverse causality, where rapidly growing infants are more likely to be kept exclusively breastfed, whereas slower-growing infants are more likely to have other foods introduced early. A study found that slower weight gain in exclusively breastfed infants during the first 2-6 weeks predicted earlier discontinuation of exclusive breastfeeding between 2-5 weeks and 6-11 weeks (46).

In addition, electronic health records are subject to information bias, especially when it comes to exclusive breastfeeding, prevalences in Syria in this study were high indicating potential over reporting of exclusive breast feeding. Due to data availability, we limited

the rapid weight gain analysis to the period from birth to 12 months and did not separate the analysis into two intervals: birth to 6 months and 6 to 12 months.

To define rapid weight gain, we opted for a WAZ increase of >0.67 from birth to 1 year, despite the existence of other methods like conditional relative weight gain which account for previous weight and growth patterns. We chose this method because it is widely used in the paediatric literature and facilitates comparisons with growth charts (13). While it has limitations in capturing subtle growth changes, it provides a straightforward and clinically intuitive assessment of rapid weight gain in our diverse study population. In our study, we used WHZ adjusting in the model for age and sex of the child based on WHO criteria to define overweight and obesity in children (47). Our analysis showed similar results when using WHZ or BMI z score. However, both BMI z scores and WHZ have limitations in accurately reflecting body composition, particularly in young children. Future studies incorporating direct measurements of fat mass and lean mass would provide more precise assessments of body composition and obesity risk in this age group. Recent research by Wright et al. suggests that current BMI centile cutoffs may over diagnose obesity in children under 6 years old (48). Their study found that young children with high BMI centiles had lower fat mass index than older children with the same BMI centile and raised fat levels were less common in younger children(48). These findings highlight the need for age-specific considerations when assessing overweight and obesity in young children and underscore the importance of body composition studies to accurately measure fat mass and lean mass in this population.

Recommendation and conclusion- childhood overweight/obesity prevention strategies

To effectively mitigate the risk of childhood overweight/obesity, multiple actions are imperative during the life course: 1) prevention of the occurrence of LGA, and 2) promotion of exclusive breastfeeding.

Preventing the occurrence of LGA involves early and consistent prenatal care, coupled with the management of gestational diabetes. Maintaining appropriate maternal weight gain during pregnancy contributes to preventing excessive foetal growth. High and/or

rapid gestational weight gain in early and mid-pregnancy, even with subsequent strict weight control, is associated with an elevated risk of LGA (49). Regular ultrasounds and growth scans help monitor foetal development, allowing timely interventions if necessary. Gestational diabetes is also linked with LGA, making its management crucial in preventing excessive foetal growth (50). The prevalence of gestational diabetes is on the rise in the region, coinciding with an increase in the prevalence of overweight/obesity among pregnant mothers (51). Further research on this issue is needed among Palestinian refugees, while efforts are underway to measure and detect better excessive weight gain during pregnancy (52).

The findings also highlight the importance of infant feeding practices in mitigating rapid weight gain during infancy, suggesting that interventions promoting exclusive breastfeeding may offer a practical and effective means for preventing obesity. Notably, low exclusive breastfeeding prevalence among Palestinian refugees (22.1 % in Lebanon, 28.5% in Syria, 17.8% in Jordan and 38.9 in the State of Palestine (53)) necessitate enhanced policies to promote breastfeeding, recognizing its pivotal role in preventing childhood overweight/obesity.

In the setting of this study, the prevalence of rapid weight gain was between 22-34 percent, similar to levels seen in high income countries (13). While it is important to address rapid weight gain during growth monitoring, the potential risks and consequences of early identification and intervention for overweight/obesity in children must be carefully considered. A recent call noted that healthcare professionals should routinely screen for rapid weight gain in infants and engage in non-stigmatizing, culturally sensitive discussions with families when rapid weight gain is identified (54). These discussions should focus on promoting healthy practices, including appropriate feeding methods, sleep routines, and responsive parenting, rather than solely emphasizing obesity risks. Comprehensive support should be provided, encompassing breastfeeding encouragement, guidance on formula feeding and complementary foods, sleep support, and education on growth charts and monitoring, all tailored to the infant's developmental stage and the family's cultural background (54). However, research is needed to develop and evaluate effective interventions for rapid weight gain in infants, particularly focusing on culturally appropriate strategies that can be implemented. There is a concern that

focusing too heavily on changes in growth percentiles during the critical developmental period may result in unintended consequences that could outweigh the benefits of targeted interventions (55). These risks include unintended or unknown side effects of interventions, such as poor nutrition, stunted linear growth, and negative impacts on emotional development.

The study's findings underscore the role of rapid weight gain in explaining the association between small size at birth and childhood overweight/obesity. Our results highlight the interplay of factors contributing to childhood overweight/obesity among Palestinian refugees, emphasizing the significance of considering birth characteristics, feeding practices, and early growth patterns in devising effective preventive strategies. By addressing gaps in the existing literature, our study significantly advances the understanding of early-life determinants influencing childhood overweight/obesity, providing valuable insights for the development of public health strategies focused on prevention and intervention.

Table 1- Characteristics of the study population.

	Palestinian refugees from:				
	Gaza	**Jordan**	**Lebanon**	**Syria**	**West Bank**
Number= 388,347 livebirth	221,346	85,551	25,205	12,045	44,200
Maternal education Number	217,677	80,543	24,023	12,034	41,545
%Basic	19.3	41.2	60.9	64.6	27.8
%Secondary	40.2	41.1	15.0	18.1	38.4
%Diploma	5.7	9.3	8.0	7.3	6.8
%University and higher	34.9	8.4	16.1	10.0	27.0
Size for gestational age Number	220,643	84,719	25,091	11,983	43,852
%SGA	7.5	11.2	8.3	9.4	8.6
%LGA	12.8	8.1	11.6	4.8	11.1
Gestational age Number	220,998	85,092	25,123	11,991	43,891
% Preterm	6.5	7.4	7.6	4.9	6.1
% Post-term	3.2	1.5	1.2	0.8	1.9
Nine phenotypes Number	220,643	84,719	25,091	11,983	43,852
Preterm					
%Preterm-SGA	0.4	0.7	0.5	0.4	0.6
%Preterm-AGA	4.5	5.4	5.5	3.5	4.4
%Preterm-LGA	1.7	1.4	1.6	1.0	1.2
Term					
%T-SGA	6.4	10.1	7.5	8.6	7.7
%T-AGA	73.1	74.3	73.8	81.9	74.5
%T-LGA	10.8	6.7	10.0	3.8	9.8
Post-term					
%Post-term-SGA	0.7	0.5	0.3	0.3	0.4
%Post-term-AGA	2.2	1.0	0.9	0.4	1.4
%Post-term-LGA	0.3	0.1	0.1	0.0	0.1
Exclusive breastfeeding Number	205,388	81,784	20,556	8,624	39,328
%Exclusive breastfeeding at 6 months	40.4	35.4	39.6	77.5	55.0
Rapid weight gain from birth to 12 months Number	178,711	78,799	16,693	6,903	35,582
%Rapid weight gain	22.2	29.7	34.4	28.0	28.4
Overweight/obesity at 24-59 months Number	221,346	85,551	25,205	12,045	44,200
%Overweight (1+ measurements)	3.4	4.7	6.7	2.4	6.4
%Overweight (2+ measurements)	2.9	3.6	5.9	1.5	4.9

Figure 2- Weight for Height z-score by A) gestational age B) size for gestational age C) phenotype D) setting. Age in weeks from conception.

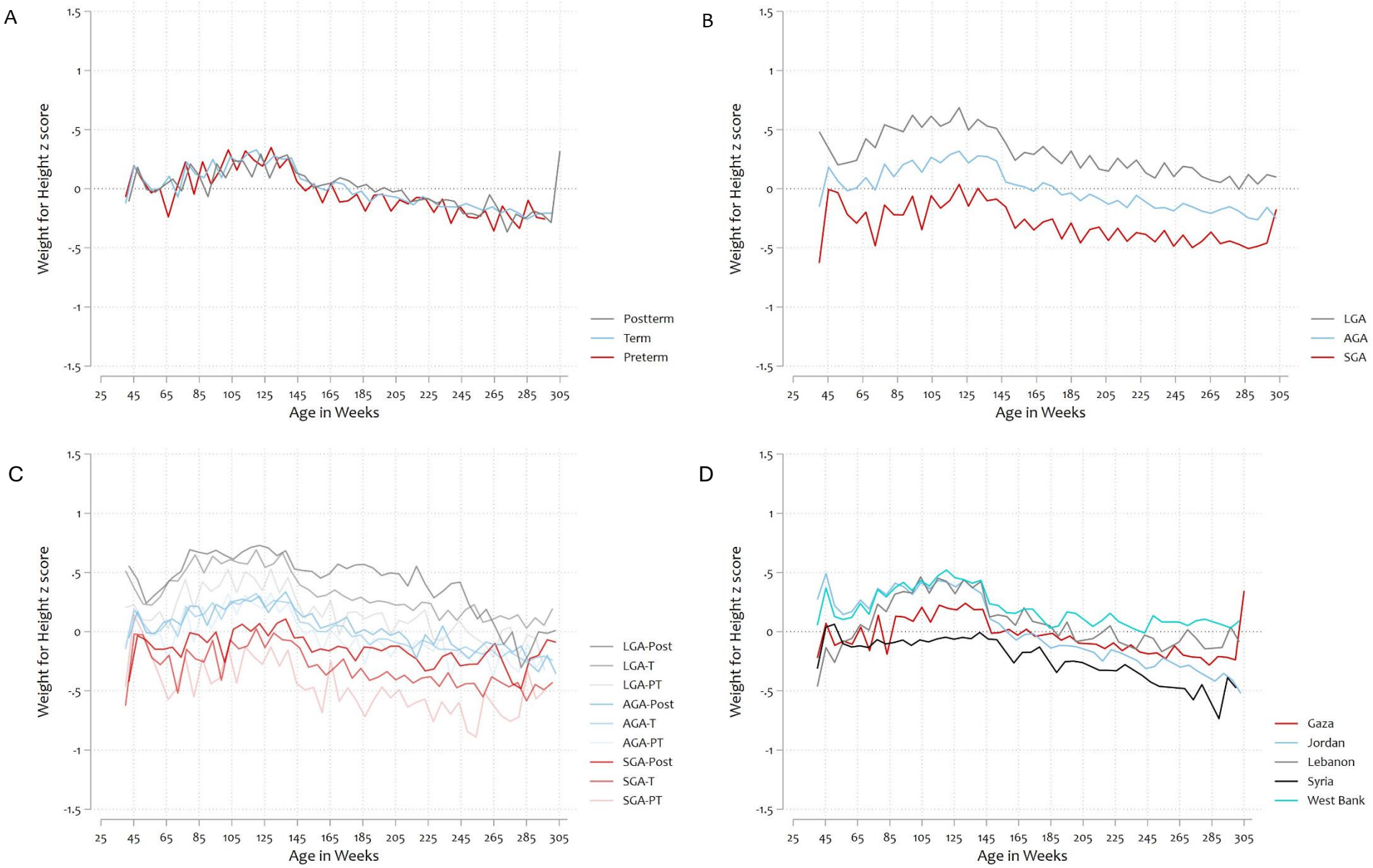


Table 2- The association of size at birth and gestational age with A) exclusive breastfeeding at 6 months, B) rapid weight at 12 months and C) overweight/obesity (24 months-59 months). Models adjusted for setting and child age.

Model1	**A**		**B**		**C**	
	Exclusive Breastfeeding 6 months		**Rapid weight gain at 12 months**		**Overweight/obesity 24-59 months**	
Number children	aOR* N=353,763	95% CI	aOR* N=315,932	95% CI	aOR** N=380,406	95% CI
SGA	0.83	(0.81-0.85)	2.39	(2.32-2.45)	0.50	(0.46-0.56)
AGA (reference)	1.00	--	1.00	--	1.00	--
LGA	0.95	(0.93-0.97)	0.35	(0.33-0.36)	2.76	(2.59-2.95)
Preterm	0.45	(0.44-0.47)	1.22	(1.18-1.26)	1.11	(1.00-1.21)
Term (reference)	1.00	--	1.00	--	1.00	--
Post-term	1.16	(1.12-1.22)	0.66	(0.62-0.70)	1.09	(0.92-1.28)
Model 2	**A** **Exclusive Breastfeeding 6 months**		**B** **Rapid weight gain at 12 months**		**C** **Overweight/obesity 24-59 months**	
Preterm-SGA	0.27	(0.24-0.30)	4.20	(3.78-4.65)	0.36	(0.24-0.55)
Preterm-AGA	0.41	(0.39-0.42)	1.20	(1.16-1.25)	1.28	(1.14-1.42)
Preterm-LGA	0.61	(0.58-0.65)	0.36	(0.33-0.40)	2.39	(2.02-2.83)
Term-SGA	0.82	(0.80-0.85)	2.35	(2.29-2.41)	0.51	(0.46-0.57)
Term-AGA (reference)	1.00	--	1.00	--	1.00	--
Term-LGA	0.90	(0.88-0.93)	0.35	(0.34-0.37)	2.85	(2.66-3.06)
Post-term-SGA	1.13	(1.04-1.24)	1.39	(1.26-1.54)	0.74	(0.52-1.04)
Post-term-AGA	1.09	(1.03-1.15)	0.70	(0.65-0.75)	0.89	(0.73-1.08)
Post-term-LGA	1.14	(0.97-1.33)	0.22	(0.16-0.31)	5.58	(3.72-8.36)

aOR= adjusted odds ratio

*Logistic regression adjusted for the setting and child age ** Multilevel mixed logistic regression adjusted for the setting, age of the child

Table 3- The association between rapid weight gain with overweight/obesity (24 months-59 months) stratified by size at birth groups. Models adjusted for setting and child age.

			Overweight/obesity after 24 months to 59 months	
Exposure		N=	aOR*	95CI
Rapid weight gain	Total	312,337	6.53	(6.15-6.94)
Rapid weight gain	Stratified by			
	SGA	25,866	4.52	(3.64-5.62)
	AGA	248,949	8.36	(7.79-8.97)
	LGA	36,774	9.29	(7.98-10.83)
Rapid weight gain	Stratified by			
	Preterm	21,746	4.45	(3.66-5.42)
	Term	282,938	6.83	(6.41-7.28)
	Post-term	7,653	4.31	(2.90-6.39)
Rapid weight gain	Stratified by			
	Preterm-SGA	1,463	1.69	(0.77-3.70)
	Preterm-AGA	15,359	6.75	(5.29-8.61)
	Preterm-LGA	4,871	5.83	(3.77-9.02)
	Term-SGA	22,701	4.96	(3.92-6.26)
	Term-AGA	228,326	8.57	(7.96-9.23)
	Term-LGA	31,226	10.13	(8.59-11.94)
	Post-term-SGA	1,675	4.69	(1.76-12.47)
	Post-term-AGA	5,224	5.53	(3.45-8.85)
	Post-term-LGA	557	4.75	(1.26-17.88)
Rapid weight gain	Stratified by			
	Not exclusive breastfeeding	189,444	7.01	(6.47-7.59)
	Exclusive breastfeeding	119,223	5.72	(5.16-6.35)

aOR= adjusted odds ratio

Exclusive breastfeeding and overweight/obesity 0.81 (0.77-0.86)

Figure 2- Recursive path model of size at birth, exclusive breastfeeding, rapid weight and overweight/obesity at least once, adjusted for setting and child age. Numbers shown are adjusted odds ratio (aOR) with 95% CI.

Size at birth	Exclusive breastfeeding aOR	Rapid weight gain aOR	Overweight aOR
Preterm-SGA	0.28 (0.24-0.31)	3.91 (3.53-4.34)	0.34 (0.24-0.48)
Preterm-AGA	0.41 (0.39-0.42)	1.13 (1.09-1.17)	1.16 (1.08-1.26)
Preterm-LGA	0.60 (0.57-0.64)	0.34 (0.31-0.37)	2.21 (1.96-2.49)
Term-SGA	0.82 (0.80-0.84)	2.37 (2.30-2.43)	0.47 (0.43-0.51)
Term-AGA	1.00 (reference)	1.00 (reference)	1.00 (reference)
Term-LGA	0.90 (0.88-0.92)	0.34 (0.33-0.35)	2.48 (2.36-2.61)
Post-term-SGA	1.10 (1.01-1.20)	1.35 (1.22-1.50)	0.62 (0.46-0.83)
Post-tem-AGA	1.06 (1.01-1.12)	0.66 (0.61-0.70)	0.92 (0.78-1.07)
Post-term-LGA	1.11 (0.95-1.30)	0.21 (0.15-0.29)	3.12 (2.28-4.27)

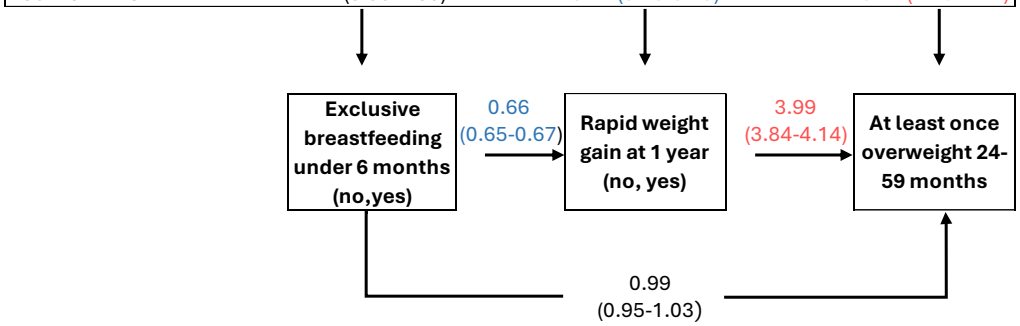


Table 4- Pathway linking size at birth, exclusive breastfeeding, rapid weight to overweight/obesity at least once, direct and indirect effect adjusted for setting and child age

Overweight/obesity	**Preterm-SGA**		**Preterm-AGA**		**Preterm-LGA**	
	aOR	95%CI	aOR	95%CI	aOR	95%CI
Total effect	2.26	(1.39-3.13)	1.39	(1.26-1.52)	0.50	(0.41-0.59)
Direct effect	0.34	(0.21-0.46)	1.16	(1.07-1.25)	2.21	(1.94-2.47)
Indirect effect						
via breastfeeding	1.00	(0.96-1.06)	1.01	(0.97-1.04)	1.01	(0.98-1.02)
via breastfeeding rapid weight gain	6.69	(5.63-7.75)	1.19	(1.12-1.27)	0.27	(0.20-0.26)

Overweight/obesity	**Term-SGA**		**Term-AGA**		**Term-LGA**	
	aOR	95%CI	aOR	95%CI	aOR	95%CI
Total effect	1.54	(1.40-1.70)	reference		0.56	(0.52-0.60)
Direct effect	0.47	(0.43-0.51)	reference		2.48	(2.36-2.61)
Indirect effect						
via breastfeeding	1.00	(0.99-1.01)	reference		1.00	(1.00-1.00)
via breastfeeding rapid weight gain	3.30	(3.13-3.46)	reference		0.23	(0.21-0.24)

Overweight/obesity	**Post-term-SGA**		**Post-term-AGA**		**Post-term-LGA**	
	aOR	95%CI	aOR	95%CI	aOR	95%CI
Total effect	0.93	(0.63-1.25)	0.51	(0.41-0.61)	0.35	(0.15-0.54)
Direct effect	0.62	(0.43-0.80)	0.92	(0.77-1.06)	3.12	(2.15-4.10)
Indirect effect						
via breastfeeding	1.00	(1.00-1.00)	1.00	(1.00-1.00)	1.00	(0.99-1.00)
via breastfeeding rapid weight gain	1.52	(1.30-1.73)	0.56	(0.50-0.61)	0.11	(0.05-0.16)

Supplementary Material

Supplementary material 1– Characteristic of the linked population

A total of 709,064 livebirths from among 972,743 in Gaza, Jordan, Lebanon, Syria and West Bank between 01/01/2010 and 31/12/2020 were linked with growth monitoring records up to their last visit before 14/09/2021. Most of the livebirth records (709,064) had at least one growth monitoring visit (87%), with a total of 6,309,046 growth monitoring records. There were no differences in loss to follow up by sex or maternal education using Kaplan Meier curves and Cox regression (details below).

Total livebirth records from the mother obstetric records were linked to growth monitoring records of children. Syria did not collect growth monitoring until 2011. The highest extent of linkage between livebirths and growth monitoring records was observed in Gaza (92%), while the lowest was in Syria (78% partly because growth monitoring began later). The extent of growth monitoring data collected by cohort year and their quality improved (Supplementary Figure S.1.3). The percentage of linkage increased over time as the programme was implemented.

Figure S.1.2 shows that the mean number of growth monitoring visits per child varied across the settings and the cohort years. Figure S.1.2 describes the years and sites of peak performance. Jordan served as the pilot setting for growth monitoring, resulting in higher levels of observation at the beginning of the implementation of the e-health system. Gaza and Lebanon had the highest number of visits. The year 2016 had the highest mean number of visits for the total, reflecting the improvement in measurement practices from the earlier cohorts, while also being the point at which those born in 2010 would have reached 59 months. From 2017 onwards the younger cohorts had fewer visits recorded because they had not yet reached age 59 months, and their growth monitoring data collection was still ongoing.

We then focused our analysis on individuals with recording at 24 months onwards. This limited the data available to 388,347 livebirths linked to growth monitoring. We will refer to this dataset of singleton as the “overweight UNRWA analysis” dataset.

Age lost to follow-up.

To compare among settings, sex, and maternal education, we present Kaplan Meier curves and Cox regression adjusting for setting, sex and maternal education as potential determinants of age lost to follow-up.

Settings. We restricted this analysis to cohort of children who would have reached the age of 24-59 months by 2020, cohorts born in 2010 to 2015. Figure S.1.4 shows that over time data collection improved with median age of last measurement increasing (meaning data is collected at even more delayed ages). The clearest trend was observed in Gaza (Figure 3) which shows an increase in the median age of last measurement from 2010 to 2015, increasing from 21 till 45 months. The median age of the last growth monitoring visit did not change much from 2010 till 2015 in Jordan, Lebanon, or Syria (Figure 1.3). In the West Bank, the median age of last measurement decreased from 2010 to 2015, from 48 to 36. In 2015 the median age at last measurement was oldest in Lebanon (48 months), followed by Gaza (45 months), West Bank (36 months), Syria (31 months), and Jordan (27 months).

Education. Just a very slight difference one (in secondary as compared to basic education) or no difference was observed in the age at last measurement by maternal education.

Sex. No difference was observed in the age at last measurement by sex of the child. The hazard ratio for sex was 1.00 (95%CI; 0.99,1.00).

Table S.1.1- Flowchart of data “loss”.

Palestinian refugees in	Total livebirth records	Livebirths records linked with any records of child health outcomes (including growth monitoring)	Livebirths excluding multiples (twins/triplets…)	Singleton livebirths linked with growth monitoring records	Singelton livebirths with a growth monitoring measure at 24 to 59 months
Gaza	438,134	411,279	406,490	377,959	221,346
Jordan	267,624	200,271	197,295	175,612	85,551
Lebanon	56,075	49,972	48,968	41,821	25,205
Syria	64,093	43,439	42,647	30,751	12,045
West Bank	146,817	106,910	105,155	82,921	44,200
Total	972,743	811,871	800,555	709,064	388,347

Figure S.1.2- Mean number of growth monitoring visits per child in each setting and cohort.

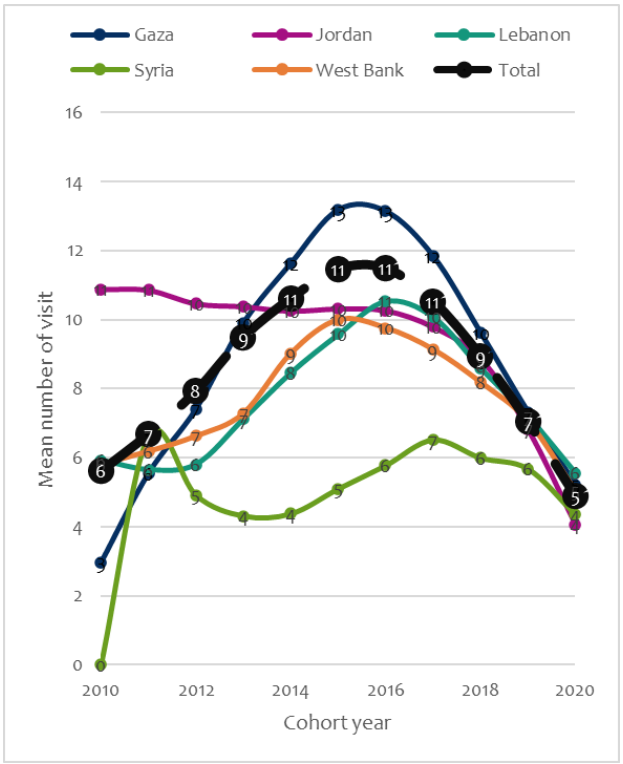


Figure S.1.3- Number of livebirths linked to growth monitoring records by cohort year and by setting in the “overweight UNRWA analysis” dataset.

Figure S.1.4- Survival plots of age at last observation stratified by setting and cohorts (2010-2015) for the children reaching the age of 59 months.

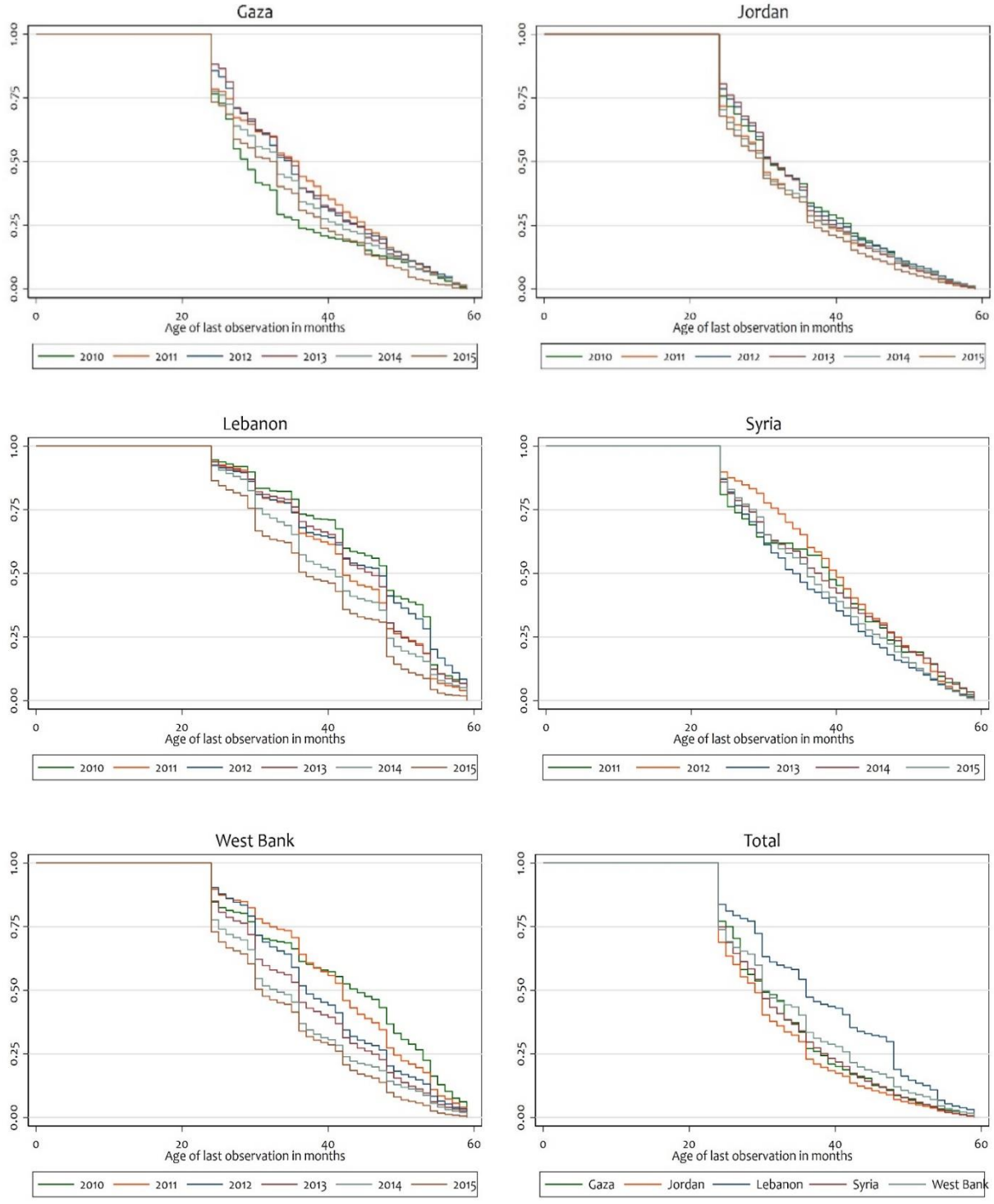


Figure S.1.5- Median age of last observation by setting.

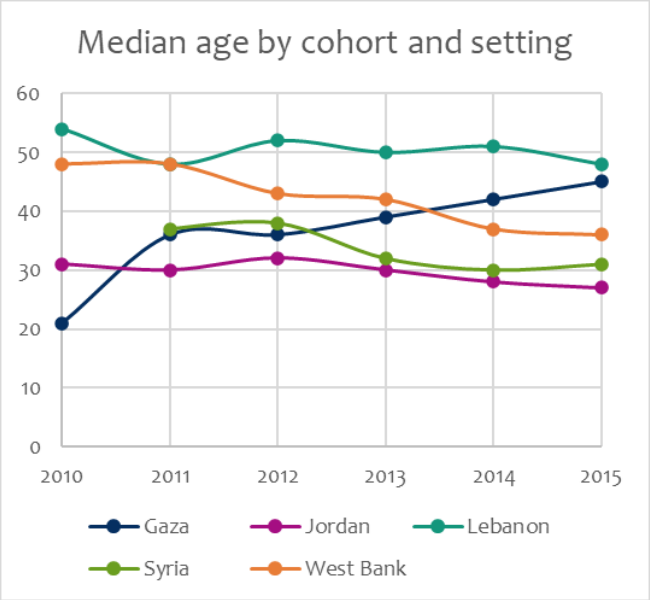
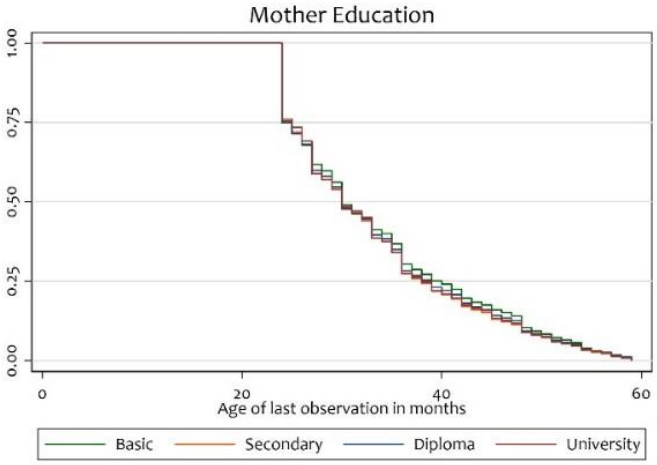


Figure S.1.6- Survival plots of age at last observation stratified by sex and by education cohorts (2010-2015) for the children reaching the age of 59 months.



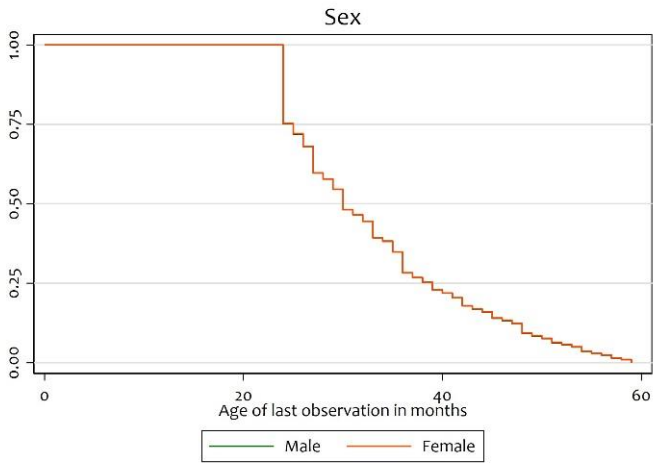


Table S.1.7- Crude association between child sex, mother education setting and last visit in month as outcome using the "overweight UNRWA analysis" dataset.

	Hazard ratio	95% CI
Child sex		
Male (reference)	1.00	
Female	0.99	(0.99,1.00)
Mother education		
Basic (reference)	1.00	
Secondary	1.02	(1.01,1.03)
Diploma	0.99	(0.98,1.02)
University	1.01	(1.00,1.02)
Setting		
Gaza (reference)	1.00	
Jordan	1.16	(1.14, 1.16)
Lebanon	0.63	(0.62,0.64)
Syria	0.83	(0.80, 0.86)
West Bank	0.83	(0.82, 0.84)

Supplementary material 2- Quality of size at birth data

Quality of the data

This section looks at the quality in the analysis dataset, focusing on a cohort of singleton children with at least one measurement of weight and height after 24 months). Out of the 388,347 livebirths 686 had missing birthweight information, 1,247 had missing gestational age data, and 5 had both missing (Table S.2.1). Implausible gestational ages beyond 44 weeks (n=121) were also dropped. Implausible or missing data were minimal compromising 0.53% of livebirths (Table S.2.1)

When analysing digit preference for birthweight data, we observed that 99% of the data had a zero in the first digit position, 93% in the second digit position, 31% the third digit position. We identified a higher occurrence of heaping at 3,000 grams in the birthweight variable especially in Syria (Figure S.2.2). Additionally, we found that there were notable instances of heaping at other specific weights, including 1,000 grams and 500 grams.

We present a two-way scatter plot of birthweight and gestational age for live births to identify implausible data points (Figure S.2.3). A consistent and expected pattern is observed when examining the percentage of birthweight classification within different gestational age groups (Figure S.2.3). We encountered a few data points that were deemed very unlikely based on gestational age/birthweight.

Overall, the quality of the birthweight and gestational age data is good, with some concern on reporting accuracy (with respect to heaping in measurement).

External validity

To further investigate the validity of data from the UNRWA dataset, we compared findings with the most recent literature on LBW and preterm prevalence on the host countries while noting that most comparators do not specify refugee sub-populations. In UNRWA dataset, LBW ranged from 6.19 to 10.5%, aligning with similar percentages reported in Lebanon 12.6% and in the State of Palestine 10.4% (56). Regarding SGA and preterm SGA, our data datasets findings align with prevalence published in the most recent global analysis of SGA prevalence, suggesting a similar pattern to Western Asia and Northern Africa region (Table S.2.5).

Figure S.2.1- Histogram of birthweight by settings using the “overweight UNRWA analysis” dataset.

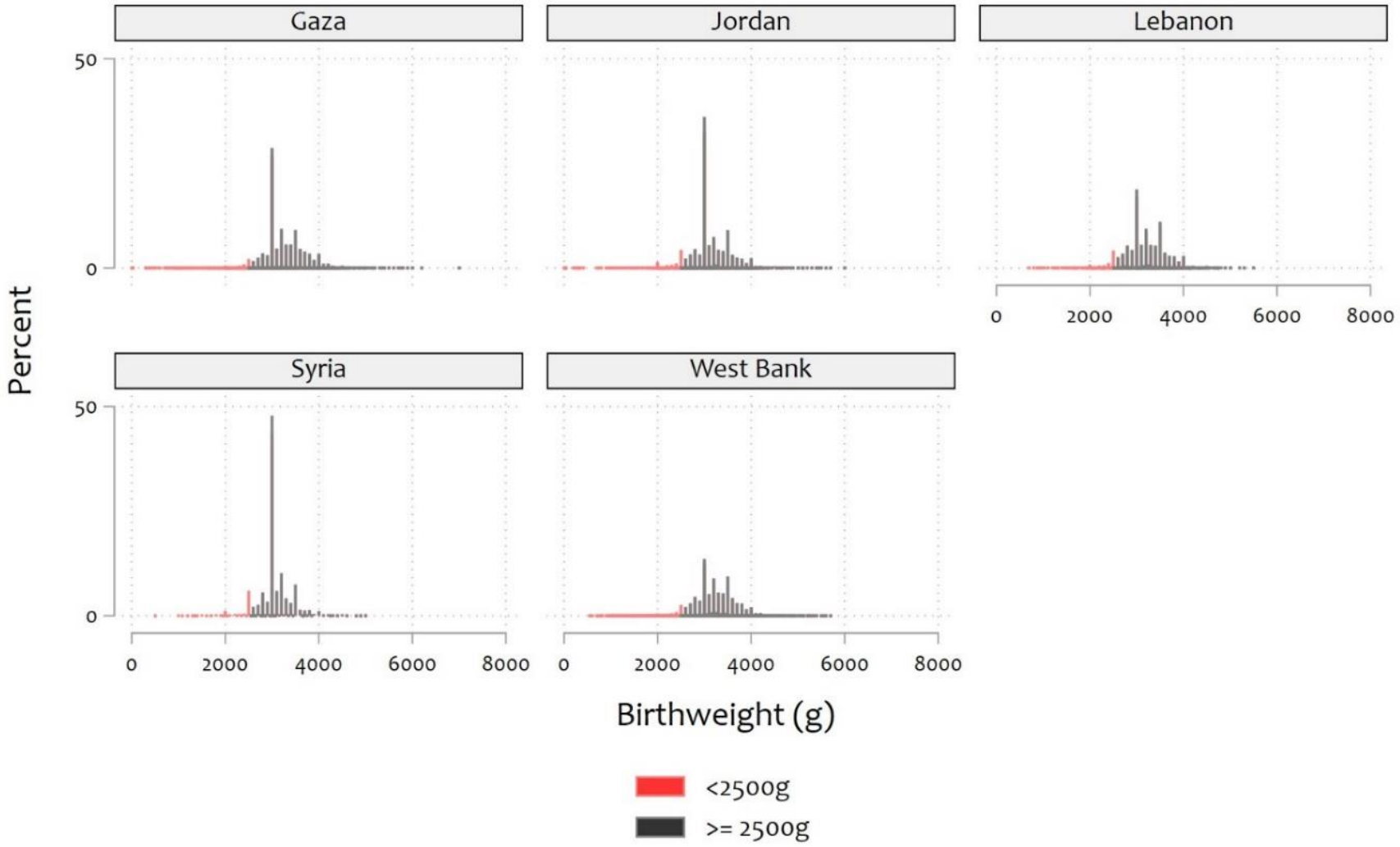


Table S.2.2- Data quality and missing data using the "overweight UNRWA analysis" dataset.

	Gaza	Jordan	Lebanon	Syria	West Bank	Total
Missing birthweight	257	360	31	5	33	686
Missing gestational age	348	454	82	54	309	1,247
Missing both birthweight and gestational age	0	5	0	0	0	5
Gestational age >44	98	13	1	3	6	121
Total missing	703	832	114	62	348	2,059
Percent of livebirth missing	0.32%	0.97%	0.45%	0.51 %	0.79%	0.53%

Figure S.2.3- Scatterplot of birthweight and gestational age by setting using the "overweight UNRWA analysis" dataset.

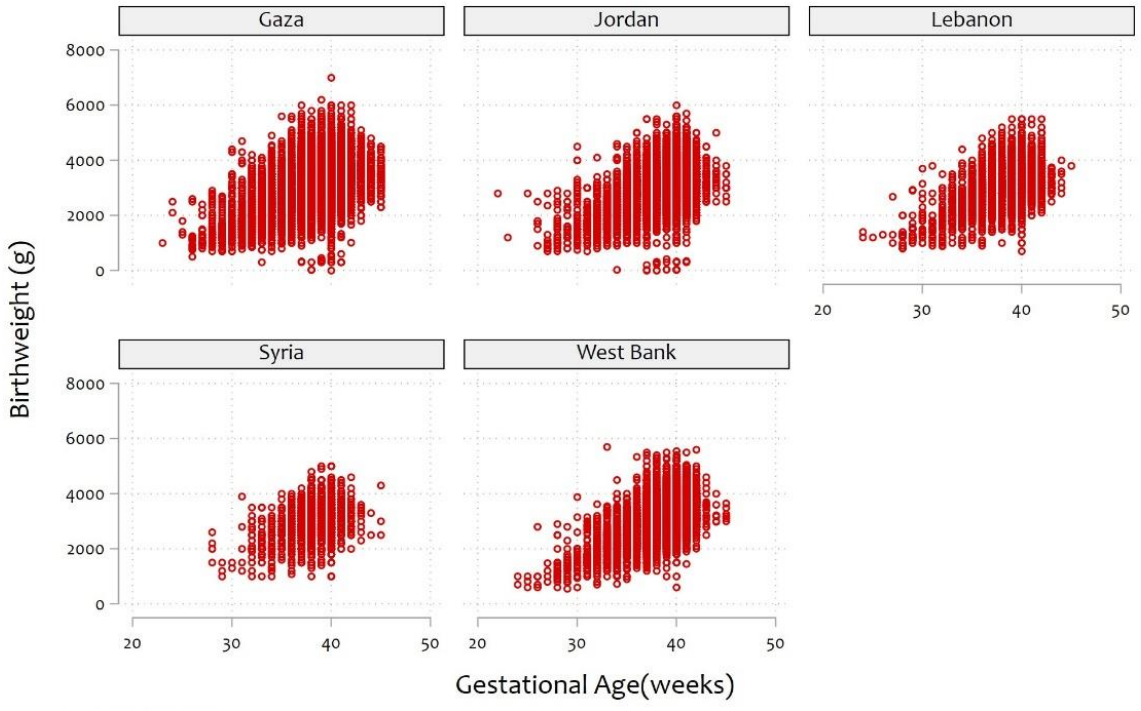


Figure S.2.4- Birthweight and gestational age using the "overweight UNRWA analysis" dataset (low birthweight <2500, normal birthweight 2500-4000grams high birthweight >4000).

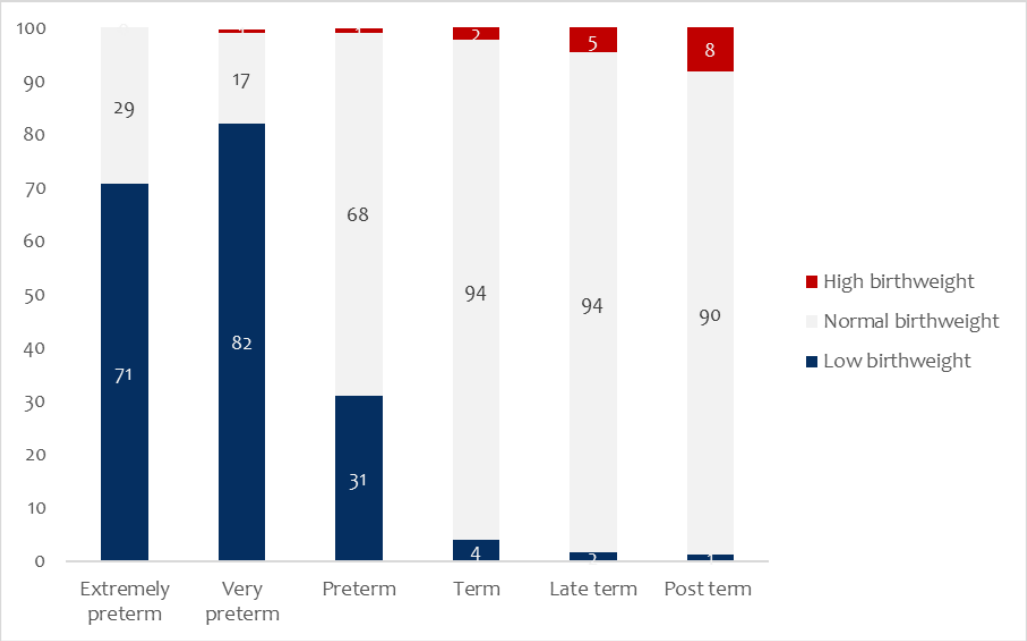


Table S.2.5-Percentage of small size at birth in global literature as compared to the Palestinian refugee e-health.

	Preterm SGA	Preterm non-AGA LGA	Term SGA
Palestinian refugees (e-health)	0.5	6.2	7.5
Western Asia and Northern Africa (57)	0.8 (0.6-1.0)	8.3 (8.0-8.5)	7.2 (4.3-11.7)
Global (57)	1.1 (0.9-3.1)	8.8 (6.8-9.0)	16.3 (14.9-18.9)

Supplementary material 3- Quality of growth monitoring data

Quality of the data

UNRWA growth activities use trained personnel to measure supine length for children aged up to 23 months and standing height for children aged 24–59 months using infant meters and stadiometers, respectively. The measuring boards used to collect anthropometric measures included ShorrBoards, Seca 217, or locally manufactured boards. Child age was calculated by subtracting the date of interview from the date of birth reported in the questionnaire and was treated as a continuous measure ranging from 0 to 59 completed months (age was floored).

A total of 6,209,913 growth monitoring visits were recorded. We then limited the data to those we used in the analysis based on the cohort definition (at least one measurement after 24 months). Remaining data used for the growth monitoring analysis 4,167,538. We identified missing data in weight and height (0.1%) (Table S.3.1). After generating the z-scores, we excluded 24,425 z-scores that were deemed implausible (0.6%) based on WHO guidelines (Table S.3.1). As expected, the distributions of HAZ, WAZ, and WHZ followed a normal distribution pattern (data not shown)

Pattern of data collection

Figure S.3.2 shows the peak age in months when growth monitoring data was collected by the different cohort years. We assume that the data on growth were collected in regular intervals of age during routine monitoring and immunization schedule. The number of growth monitoring visits decreased over time.

Figure S.3.2 compiles the peaks observed in the different settings. A total of 33.2% of observations were recorded during these “regular” months, while 66.8% were recorded in “irregular” months. As compared to children who were only measured during the “regular months” the children measured during the irregular period had higher mean number of outpatient visits (data not shown), suggesting that the measurement in “irregular months” may be linked to children who were more “vulnerable” or ill and who might have lost weight leading to fluctuation in weight gain due to sickness. To assess selection bias, we conducted the analysis with and without the measurement of irregular months and find similar results (this is not shown).

Table S.3.1- Cleaning of growth monitoring.

	N	Percentage of data excluded (%)
Initial N	**4,183,934**	
Weight equal to 0	3,090	0.07%
Weight missing	288	0.01%
Height equal to 0	2,526	0.06%
Height missing	60	0.001%
Total Excluded weight or height due to missing or equal to 0	3,543*	0.08%
Implausible WAZ HAZ WHZ (HAZ<=-5 or HAZ>=5 or WHZ<=-5 or WHZ>=5 or WAZ<=-5 or WAZ>=5)	24,425	0.58%
Total excluded in the analysis	27,968	0.66%

*Possibility of overlap

Figure S.3.2- Peaks of measurement by age and cohort using the overweight UNRWA analysis" dataset.

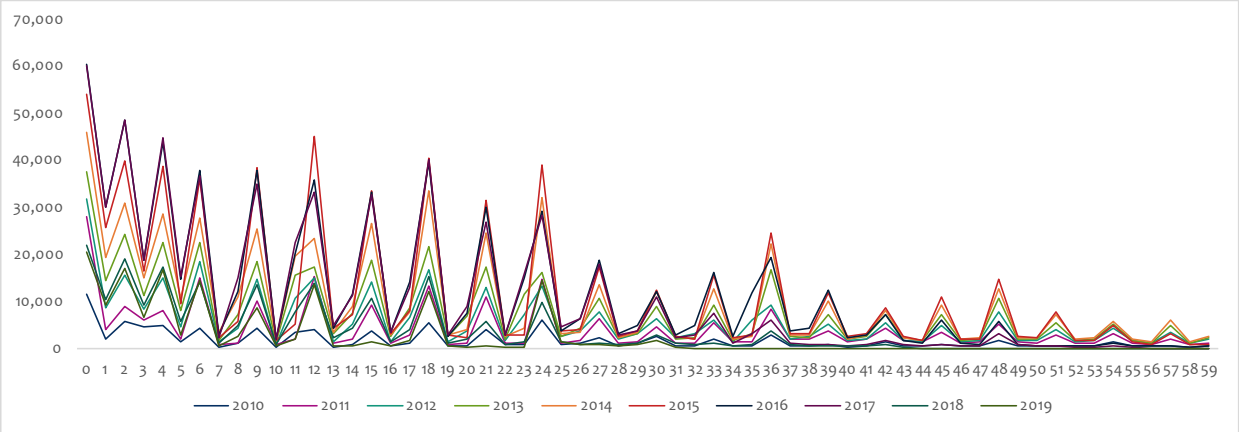
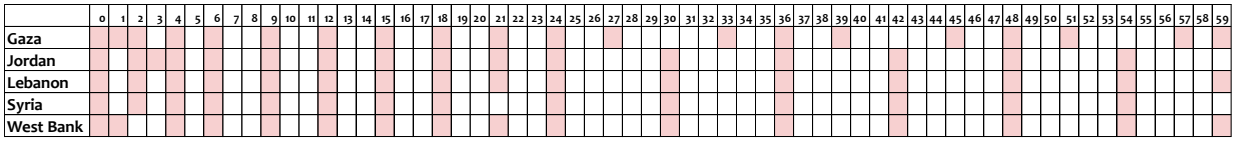


Figure S.3.3- Peaks by age and setting



Supplementary material 4- Quality of covariate data

The models adjust for sex and maternal education.

Sex of the child

The sex ratio ranged from 1.06-1.07 males per female, similar to previously published results from settings where sex-selective abortion is not widespread. The sex ratio is more skewed towards males as compared to the general population (for example Gaza 1.03 in 2022). However, ratio levels remain below 1.07 (levels indicating sex imbalances) (58).

Maternal education

The table below shows the distribution of maternal education by setting of children included in the cohort. The maternal education levels varied across the setting. In Gaza, a significant portion of mothers have completed secondary education (40.2%) or attained university and higher education (34.9%). However, in Lebanon and Syria, a higher proportion of mothers have completed only illiterate/basic/elementary education, with percentages reaching 60.9% and 64.6% respectively. For external validation, when available we compared the prevalence in the dataset with external sources. In general, the proportions in our dataset follow the proportions reported in external reports for Gaza, Lebanon and West Bank (59, 60).

Table S.4.1- Maternal education.

Palestinian refugees	Education level	E-health data	External reports of	Reference
Gaza	Illiterate/basic/elementary	19.25	19.0	(59)
	Diploma	5.69		
	Secondary	40.20	35.1	
	University and higher	34.86	45.9	
Jordan	Illiterate/basic/elementary	41.23		
	Diploma	9.33		
	Secondary	41.05		
	University and higher	8.38		
Lebanon	Illiterate/basic/elementary	60.9	69.9	(60)
	Diploma	8.02	5.0	
	Secondary	14.98	16.6	
	University and higher	16.09	8.4	
Syria	Illiterate/basic/elementary	64.61		
	Diploma	7.30		
	Secondary	18.12		
	University and higher	9.96		
West Bank	Illiterate/basic/elementary	27.75	19.0	(59)
	Diploma	6.82		
	Secondary	38.40	35.1	
	University and higher	27.03	45.9	

Supplementary material 5- Sensitivity analysis

Table S.5.1 The association between size at birth and gestational age with A) rapid weight gain starting at 40 weeks of gestational age, B) repeated overweight/obesity and C) overweight/obesity as measured using BMI Z score (24 months-59 months).

	A		**B**		**C**	
Model 1	**Rapid weight gain at 12 months starting at 40 weeks of gestational age**		**Repeated overweight/obesity**		**Overweight/obesity using BMI z score**	
N children	aOR* N=285,724	95% CI	aOR* N=386,288	95% CI	aOR* N=379,495	95% CI
SGA	2.32	(2.26-2.39)	0.68	(0.63-0.74)	0.58	(0.53-0.63)
AGA (reference)	1.00		1.00		1.00	
LGA	0.37	(0.36-0.39)	1.73	(1.85-1.81)	2.20	(2.07-2.33)
Preterm	0.82	(0.78-0.85)	1.04	(0.98-1.12)	1.11	(1.03-1.21)
Term (reference)	1.00		1.00		1.00	
Post-term	0.72	(0.68-0.77)	1.10	(0.97-1.23)	1.17	(1.01-1.34)
Model 2	**Rapid weight gain at 12 months**		**Repeated overweight/obesity**		**Overweight/obesity using BMI z score**	
Preterm-SGA	2.16	(1.93-2.41)	0.62	(0.45-0.85)	0.36	(0.24-0.52)
Preterm-AGA	0.80	(0.76-0.83)	1.13	(1.04-1.23)	1.27	(1.16-1.40)
Preterm-LGA	0.32	(0.30-0.37)	1.60	(1.42-1.80)	2.00	(1.73-2.32)
Term-SGA	2.31	(2.25-2.39)	0.68	(0.63-0.74)	0.59	(0.54-0.64)
Term-AGA (reference)	1.00		1.00		1.00	
Term-LGA	0.37	(0.36-0.39)	1.76	(1.67-1.85)	2.26	(2.12-2.41)
Post-term-SGA	1.55	(1.39-1.72)	0.87	(0.68-1.13)	0.87	(0.65-1.17)
Post-term-AGA	0.76	(0.70-0.81)	0.97	(0.84-1.13)	1.00	(0.85-1.18)
Post-term-LGA	0.22	(0.15-0.32)	2.78	(2.11-3.69)	4.13	(2.87-5.95)

*aOR= adjusted odds ratio

Table S.5.2 Association between rapid weight gain (measured starting gestational age starting at 40 weeks of gestational age till 12 months) with overweight/obesity (24 months-59 months) stratified by size at birth groups. Multilevel mixed effect logistic regression models adjusted for setting and child age.

				Overweight/obesity after 24 months to 59 months	
Exposure			N=	aOR*	95CI
Rapid weight gain starting 40 weeks		Total	282,421	6.14	(5.7-76.55)
Rapid weight gain	Stratified by				
		SGA	23,795	4.4	(3.50-5.52)
		AGA	224,834	7.58	(7.05-8.16)
		LGA	33,124	9.75	(8.28-11.50)
Rapid weight gain	Stratified by				
		Preterm	19,126	4.04	(3.24-5.02)
		Term	255,975	6.48	(6.05-6.93)
		Post-term	7,320	4.44	(2.93-6.72)
Rapid weight gain	Stratified by				
		Preterm-SGA	1,293	2.44	(1.06-5.63)
		Preterm-AGA	13,660	5.15	(3.97-6.67)
		Preterm-LGA	4,124	6.31	(3.83-10.38)
		Term-SGA	20,891	4.52	(3.54-5.74)
		Term-AGA	206,108	7.92	(7.33-8.56)
		Term-LGA	28,456	10.5	(8.80-12.52)
		Post-term-SGA	1,675	4.69	(1.76-12.47)
		Post-term-AGA	5,032	5.41	(3.32-8.82)
		Post-term-LGA	535	7.54	(1.87-30.26)
Rapid weight gain	Stratified by				
		Not exclusive breastfeeding	174,512	6.32	(5.82-6.86)
		Exclusive breastfeeding	119,223	5.73	(5.22-6.31)

*aOR= adjusted odds ratio

Table S.5.3- The association of size at birth phenotypes and overweight/obesity (24-59 months) adjusted for exclusive breastfeeding at 6 months, rapid weight at 12 months, setting and child age.

	Overweight/obesity 24-59 months		**Overweight/obesity 24-59 months**		**Overweight/obesity 24-59 months**		**Overweight/obesity 24-59 months**	
	aOR**	95% CI	aOR**	95% CI	aOR**	95% CI	aOR**	95% CI
Size at birth phenotypes								
Preterm-SGA	0.36	(0.24-0.55)	0.35	(0.22-0.53)	0.20	(0.13-0.32)	0.20	(0.12-0.31)
Preterm-AGA	1.28	(1.14-1.42)	1.26	(1.12-1.41)	1.19	(1.06-1.33)	1.17	(1.04-1.32)
Preterm-LGA	2.39	(2.02-2.83)	2.36	(1.98-2.82)	3.72	(3.10-4.46)	3.71	(3.09-4.46)
Term-SGA	0.51	(0.46-0.57)	0.50	(0.45-0.55)	0.31	(0.28-0.35)	0.31	(0.27-0.35)
Term-AGA (reference)	1.00	--	1.00	--	1.00	--	1.00	--
Term-LGA	2.85	(2.66-3.06)	2.90	(2.69-3.12)	4.44	(4.10-4.80)	4.45	(4.11-4.81)
Post-term-SGA	0.74	(0.52-1.04)	0.71	(0.49-1.02)	0.60	(0.41-0.89)	0.61	(0.41-0.91)
Post-term-AGA	0.89	(0.73-1.08)	0.92	(0.75-1.13)	1.07	(0.87-1.32)	1.08	(0.88-1.34)
Post-term-LGA	5.58	(3.72-8.36)	5.10	(3.32-7.83)	9.94	(6.38-15.48)	9.74	(6.22-15.25)
Exclusive breastfeeding 6 months								
No (reference)			1.00	--			1.00	--
Yes			0.82	(0.78-0.87)			0.92	(0.87-0.97)
Rapid weight gain 12 months								
No (reference)					1.00	--	1.00	--
Yes					8.16	(7.68-8.68)	8.13	(7.64-8.65)

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Chapter 6- Discussion of themes covered in the project

The overall aim of this thesis was to investigate the effects of nine different size-at-birth phenotypes on child well-being, including mortality, rapid weight gain and overweight/obesity outcomes, and to establish a Palestinian refugee birth cohort to analyse these effects in urban LMICs.

The key findings can be summarized as follows:

1) The umbrella review highlighted significant gaps and inconsistencies in the evidence on birth size and childhood overweight/obesity. It emphasized the importance of examining nine size-at-birth phenotypes and considering appropriate reference (comparison) categories and noted the inconclusive results regarding the effect of size at birth on overweight/obesity. The review identified four reviews which included eight meta-analyses on the effect of small size at birth on overweight/obesity in childhood highlighted that 3/8 meta-analyses found no effect, 1/8 found an increased risk of, and 4/8 showed a reduced risk of overweigh/obesity. Inconsistency with our study in Chapter 5 was due to the fact that early studies primarily focused on low birthweight rather than SGA.
2) A large birth cohort of Palestinian refugees was successfully established by linking obstetric, child health, and education records, achieving an overall linkage rate of 83%, which improved overtime from 71% in 2010 to 86% in 2020.
3) Expanded size-at-birth classifications revealed that post-term babies had an increased risk of being SGA (aRR= (RR=3.0 95% CI: 3.0-3.1) and post-term SGA, a previously under-researched group, had a two-fold increased risk of infant mortality (aRR=2.1, 95%CI 1.7-2.6).
4) Large-for-gestational age was associated with higher odds of childhood overweight/obesity, with rapid weight gain in the first year of life linked to childhood overweight/obesity, regardless of size at birth. Exclusive breastfeeding reduced the odds of rapid weight gain.

Moving beyond the discussions in individual papers, this final Chapter aims to synthesize the overarching themes and implications that emerged across the studies. By consolidating insights from each Chapter, it seeks to provide an understanding of the study's contributions and implications for public health practice and policy in Palestinian communities. I discuss the key contributions of the thesis related to measurement (section 6.1.1), the creation of a unique data resource: the Palestinian refugee birth cohort electronic health record (section 6.1.2), and the co-existence of extremes in the study population (section 6.1.3). I then highlight the strengths and limitations of the research. Finally, I explore the significance of these findings for UNRWA's electronic health records and for overweight and obesity in the Arab region and conclude by outlining the future research directions.

6.1. Key discussion themes emerging from this project

6.1.1. Using electronic health records to establish a large-scale Palestinian refugee birth cohort for epidemiological research

This thesis used clear definitions to determine associations based on proper measurements for 1) the nine sizes at birth phenotypes, 2) rapid weight gain, and 3) overweight/obesity. In this section, I focus on issues related to measurements and definitions and comparison groups.

Nine sizes at birth phenotypes

The concepts of small size at birth, LBW, SGA and preterm often overlap, making it difficult to discern the specific effects of early-life exposures on outcomes and elucidate aetiologic mechanisms. Previous literature has primarily focused on LBW as a catch-all and easily measurable entity (14, 73, 74). However, this approach is problematic because LBW usually encompasses both preterm birth and SGA, which reflect different intrauterine growth conditions influenced by distinct factors. This concept also overlooks SGA birth among post-term infants who might not be LBW. Table 2 indicates the different in utero factors influencing preterm birth and SGA (75). This thesis reinforces the argument in the existing literature for the need to move away from using LBW because it is insufficient granular in distinguishing vulnerabilities with potentially different aetiologies.

Table 2.Selected examples of the factors affecting preterm birth and SGA summarized from (75).

	Preterm	SGA
Hormones	Progesterone insufficiency or a shortened cervix increases the risk of preterm birth. Vaginal progesterone supplementation has been shown to reduce preterm birth in women with a previous preterm birth or a short cervix.	
Malnutrition		Deficiencies in nutrients like iron, zinc, and calcium and in calories, can limit the provision of nutrients and energy to the foetus, leading to growth restriction IUGR/FGR. Multiple micronutrient supplements can lower the risk of SGA births, particularly in underweight and anaemic women.
Psychological and physical stress	High levels of maternal cortisol caused by psychological or physical stress can trigger premature onset of labour.	Chronic maternal stress and elevated cortisol levels can suppress foetal growth by interfering with growth hormone and insulin-like growth factors.
Infection	Infection can trigger the expression of cyclooxygenase-2 in the placenta or foetal membranes, leading to the production of prostaglandins that initiate labour. Microbes like Ureaplasma species can ascend the cervix, causing membrane rupture and chorioamnionitis, without inflammation or labour initiation.	Infection and inflammation can impair placental function and nutrient transfer to the foetus, resulting in SGA birth. In addition, systemic inflammation suppresses foetal growth by interfering with the growth hormone and insulin-like growth factor axis.
Environmental	Exposures to air pollution, heat waves, and endocrine disruptors (phthalates) are associated with preterm birth.	Exposures to toxins (aflatoxins), endocrine disruptors (phthalates, BPA), and air pollution contribute to SGA by interfering with hormone signalling

To better understand the relative importance of preterm and SGA (IUGR/FGR) in the aetiology of adverse outcomes in children, it was crucial to distinguish between the nine phenotypes using a combination of gestational age and birthweight categories. It was also important to avoid grouping AGA and LGA as a single comparator when examining associations of SGA and different outcomes. This recommendation stems from the potential for underestimating the relative risk of SGA when using a combined AGA and LGA group as the reference. Such grouping could inadvertently combine low-risk AGA infants with potentially higher-risk LGA infants, potentially skewing the results and leading to an inaccurate assessment of the true relative risk of SGA. Distinguishing the phenotypes allowed us to determine that size-for-gestational-age, rather than prematurity, is associated with overweight/obesity (Chapter 5). Additionally, it enabled us to identify the role of post-term SGA versus preterm SGA and term SGA. This was a key focus in Chapter 4, where introducing a nine-category classification revealed that post-term SGA neonates had a two-fold increased risk of infant mortality compared to term AGA infants, even though most were not LBW (among the post-term SGA, 5.5% are LBW).

The measurement of gestational age has significantly improved over the past few decades. This includes the combination of multiple parameters (LMP, early ultrasound, maternal factors) to estimate gestational age more accurately and allowed for the use of global foetal/newborn size charts like INTERGROWTH-21st to identify SGA/LGA newborns (11). However, the accuracy of gestational age measurement, specifically compared to birthweight, remains a challenge, as noted in Chapters 3, 4, and 5. Variability in menstrual cycles can make it difficult to determine the date of conception based on the LMP, and reliance on the mother's memory of her LMP introduces recall bias. Women who seek prenatal care later in their pregnancy may miss the opportunity for more accurate early ultrasound dating (76). Inconsistent use of ultrasound due to varying access to high-quality equipment and trained personnel further complicates gestational age assessment (77-80). Technological limitations of ultrasound can lead to small errors that translate into discrepancies in gestational age, especially later in pregnancy (77-80). Medical conditions such as oligohydramnios or polyhydramnios, and multiple pregnancies, can also complicate measurements (77-80).

Proper assessment of gestational age is essential not only for evaluating foetal growth but also for guiding clinical decisions such as the timing of elective caesarean sections and post-term induction. Table 3 presents strategies linked to measurement improvement for gestational age and birthweight.

Table 3. Proper measurement of gestational age and birthweight.

Measurement	Strategies and issues
Gestational Age (77-80)	- Early ultrasound scanning (USS) is the gold standard for measuring gestational age, but coverage is low in LMICs - New technologies like portable USS machines and telemedicine support could increase access in LMICs - Where USS unavailable, prospective LMP data collection using home calendars can improve reliability for preterm birth classification - After birth, simplified newborn algorithms, skin/lens assessment, smartphone metrics for assessing gestational age show promise but need development.
Birthweight (81-83)	- Ensuring availability of functional, suitable weighing devices at facilities is challenging due to cost and durability issues - Improving accuracy through staff training, standardized guidelines/protocols, job aids - Exact recording of birthweight per gram.

Rapid Weight Gain

In our study, I operationalize rapid weight gain as an accelerated rate of weight gain over time, instead of the expected growth trajectory after a period of catchup growth due to preterm birth. To do this I defined rapid weight gain as an increase of weight for age z score by 0.67 or more between birth and 1 year of age indicating the infant crossed major percentile line on the standard growth chart (i.e., 2nd, 9th, 25th, 50th, 75th, 91st, and 98th percentile lines) (41, 84).

The identification of rapid weight gain in infants is complicated by the lack of a standardized definition and consistent time frame assessment (other measured rapid weight gain from birth till 2 years of age). I relied on the most common definition used in the paediatric literature. Alternative methods to measure rapid weight gain include, examining weight gain velocity or conditional weight gain. Weight gain velocity may provide a more continuous measure of rapid weight gain. Velocity is expressed as a

percentage deviation from mean velocity, with higher values representing faster growth than average (85-87). This can be done using the WHO weight velocity standard (87) or the Sitar package (88). Another approach is to use conditional relative weight gain, which accounts for present weight, and all previous weight measures, providing a measure of relative weight gain adjusted for weight and previous growth patterns (28). The varying definitions and approaches in the literature highlight the lack of a universally accepted standard for measuring rapid weight gain. The variety of methods used in the literature to measure rapid weight gain can make it challenging to compare findings across studies and populations. Table 4 compares the different methods used in the literature for measuring rapid weight gain. I opted for the first method which allowed me to compare our results with the existing literature. A systematic review found that rapid weight gains up to 1 year of age, was associated with overweight/obesity (pooled OR = 4.12, 95% CI: 1.83-9.28). This review reported high heterogeneity (I^2 = 89.5%, P < 0.001) among the included studies (50). The range of odds ratios in the review was similar to our study's findings (OR = 6.53, 95% CI: 6.15-6.94). Our results fall within the expected range, albeit at the higher end. The observed heterogeneity might be due to differences in when the outcome was measured and variations in covariate adjustments across studies.

Table 4. Different methods in the literature for rapid weight gain

Method	Description	Advantages	Disadvantages
Weight-for-Age Z-score Increase ***(method used)***	Increase in weight-for-age z-score by ≥0.67 between two time points (e.g., birth to 1 year)	- Commonly used in paediatric literature - Easy comparison with growth charts - Intuitive for clinicians and parents - Accounts for age and sex differences	- Lacks standardized definition/timeframe (birth to 1 year vs birth to 2 years) - May not capture subtle growth changes - Does not account for length/height changes
Weight Gain Velocity	Expressed as percentage deviation from mean velocity, using WHO	- Continuous measure of rapid weight gain - Can detect subtle changes in growth	- Complex calculation (SITAR is does not work well with large data) - May not capture relative growth accurately in all

	weight velocity standard or SITAR package	patterns - Accounts for age-specific expected growth rates	situations - May require complex statistical modelling - Requires large computational power (was not able to run it on large dataset) - Less practical to use in routine clinical settings
Conditional Relative Weight Gain	Accounts for present weight and all previous weight measures, providing relative weight gain adjusted for previous growth patterns	- Accounts for previous weight and growth patterns - Provides a more comprehensive view of growth trajectory - Reduces the impact of regression to the mean	- Depends on historical data availability - May be difficult for non-specialists to interpret - Requires multiple measurements over time
Absolute Weight Gain	Simple measurement of weight gain over a specific period	- Easy to measure and understand - No complex calculations required - Useful for short-term growth monitoring	- Does not account for initial size or expected growth patterns - Does not consider age or sex differences - May overestimate rapid growth in larger infants
Body Mass Index (BMI) Change	Calculation of change in BMI over time	- Accounts for both weight and height changes - Useful for assessing adiposity changes - Widely used in older children and adults	- Less accurate in infants and young children - Does not distinguish between fat and lean mass May not accurately reflect body composition changes

Overweight or obesity

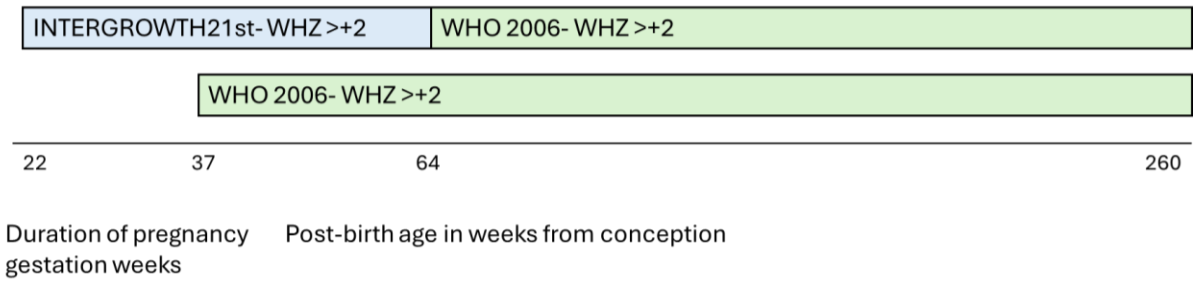

Figure 5- Overweight or obesity classification based on gestational age and growth charts.

The WHO growth standards are well-established for defining overweight/obesity in children. In this study, I used a weight-for-height z-score (WHZ) >+2 to define overweight/obesity, as recommended by WHO for children under 5 years of age (89). However, it is important to use the appropriate growth references based on gestational age at birth. The WHO growth standards are not suitable for assessing the growth of preterm infants due to several key factors. Preterm infants exhibit distinct growth patterns, portrayed by initial growth faltering followed by catch-up growth, which differ significantly from term-born infants (90). The WHO growth standard reference population excluded preterm infants, leading to inaccurate z-scores and potential misclassification of growth status when applied to this group. The biological implausibility thresholds in the WHO growth standard are based on term-born children, failing to account for the smaller size and slower initial growth of preterm infants (90). Clinical guidelines recommend using corrected age for preterm infants, a practice not directly compatible with the WHO growth standard. To address these challenges, alternative growth standards specifically designed for preterm infants, such as the Fenton curves and the INTERGROWTH-21st newborn size standards, should be used (90). In this study, for preterm infants, I used the INTERGROWTH-21st standards for weight-for-height z-scores (WHZ) up to 64 weeks since conception (gestational age equivalent) , after which the WHO growth standards were applied (91). This approach was chosen because correcting the age of preterm infants to 40 weeks would lead to missing data for these vulnerable infants during their early weeks of life. Using the WHO international standards for term

infants to assess preterm infants can lead to errors in classifying their weight status, an issue that is common in the literature (90).

We defined overweight/obesity in children under 59 months old according to the WHO standards, which are widely used in paediatric/nutrition research (89). Recent research suggests that these standards may not accurately reflect body fatness in young children, particularly those under 5 years of age. A study by Wright et analysed body composition data from a large sample of children aged 6 weeks to 20 years, measuring fat mass and lean mass (92). The researchers found that:

1. Before age 6, variability in fat mass index, lean mass index, and BMI was much lower compared to older ages.
2. Young children (under 6 years) with high BMI centiles had lower fat mass index than older children with the same BMI centile.
3. Raised fat levels were much less common in younger children compared to older age groups.

These findings suggest that current BMI centile cutoffs may over diagnose obesity in children under 6 years old (92). The researchers concluded that more stringent cutoffs are needed for this age group.

6.1.2. Using electronic health records to establish a large-scale Palestinian refugee birth cohort for epidemiological research

Electronic health records are increasingly being used in observational epidemiological research, offering invaluable insights into population health trends and outcomes. Most of the research using large scale electronic health records datasets has been conducted in higher-income nations, with limited application in studying marginalized demographics, like refugees or urban, marginalized groups, in LMICs although there are some notable exceptions, such as Brazil's 100-million cohort (53, 54). In particular, the Arab region currently lacks sizeable longitudinal cohorts. Previous regional cohorts include three labour-force panel surveys in Egypt, Tunisia, and Jordan (93-96), and four very small Egyptian pregnancy, birth, or contraceptive-use cohorts with short follow-up periods (97), and a Syrian refugee cohort focusing on non-communicable diseases

during COVID-19 (98). As far as I am aware, this is the first study, using UNRWA's electronic health records, to establish a birth cohort of refugees in the region. This cohort can serve as a resource for addressing critical knowledge gaps and informing policies and interventions to improve health and well-being in humanitarian settings but also among urban poor populations.

Advantages of electronic health data

Large scale electronic health records provide several advantages over traditional data collection methods.

1) Electronic health records offer readily available, pre-collected data, resulting in unparalleled gains in efficiency (with no need for participant recruitment and data collection effort). As with other cohorts, electronic health records mitigate recall issues through prospective data collection. During the period covered by the established cohort (2010-2020), a limited number of cross-sectional nationally representative health/nutrition related surveys were conducted in the region, including three Multiple Indicator Cluster Surveys (MICS) in the West Bank and Gaza (2010, 2014, 2019-2020) (99), two Demographic and Health Surveys (DHS) in Jordan (including Palestinian refugees, 2012, 2017-2018) (100), and two socioeconomic surveys including health outcomes for Palestinian refugees in Lebanon (2010, 2015) (101). Notably there were no national surveys of Palestinian refugees in Syria conducted during this period. The use of electronic health records provides opportunities to study health over time without the need for extensive survey efforts for example to determine indicators of vaccination rates, child growth, or caesarean section prevalence, allowing for continuous and non-cross-sectional data collection.
2) The large dataset size facilitated by use of routine electronic health records enabled me to discern associations between rare exposures or outcomes that would be difficult to study in smaller cohorts. For instance, the combination of post-term birth and SGA, accounts for 0.6% of the population, could be analysed due to the large sample size (Chapter 4). Additionally, the large dataset allowed me to examine nine distinct phenotypes, combining gestational age categories

(preterm, term, and post-term) with birthweight categories (SGA, AGA, LGA), with sufficient sample size in each phenotype (Chapter 5).

3) The longitudinal nature of electronic health records data allows for the cost-effective generation of cohorts, enabling us to study the long-term impacts of early-life exposures, such as size at birth, rapid weight gain, and feeding practices, on later health outcomes. Notably, this longitudinal dataset presents opportunities to examine associations between these early-life factors and repeated growth monitoring data over time, as well as educational attainment, areas that are significantly lacking in the existing literature, as highlighted in the umbrella review (Chapter 2).
4) The electronic health records system provides opportunities for signalling the need for additional interventions and highlighting areas that require improvement, informing interventions within UNRWA's health system. For instance, the data on rapid weight changes in children could be integrated into the system, enabling real-time flagging and intervention for cases of concerning weight loss or failure to thrive (Chapter 5). Similarly, the caesarean section data could be used to identify facilities or providers with higher-than-expected rates, prompting a clinical review of indications and feedback to optimize care (as reference to an analysis I first conducted using these data see Thesis Appendix 3)
5) A potential strength of the electronic health records system is its ability to facilitate data tracking and collection even amidst conflicts and crises in some cases where some of the primary health care centres are still functioning. This is evidenced by the availability of mortality data during the 2014 Gaza war, where I was able to capture information on conflict-related deaths, referred to as "shahid" شهيد (martyr) cases (identified when cleaning the mortality data in Chapter 4). Despite the challenging circumstances, the electronic health system included data from Palestinian refugees in Syria from 2012 onward, during the active years of the Syrian war providing data on maternal and newborn health, while previous studies noted very limited and fragmented data available in from Syria during the conflict (102). The potential capacity to maintain data collection and monitoring during conflicts and emergencies is a significant advantage in some context where electronic health records system is established. This could help identify

people who are displaced, and those who have missed vaccinations or antenatal care appointments. Of course, this is dependent on people being able to reach primary health centres and the continued functionality of the health system. It could help ensures the continuity of essential health information, which is crucial for informing humanitarian responses, providing insight into affected populations, allocating resources effectively, and addressing the unique needs of affected populations.

Internal and external validity of the electronic health data

The quality and completeness of electronic health data are essential for ensuring the validity of research findings. Throughout this project, I have demonstrated the internal and external validity of the data.

In terms of internal validity, I note that there were very few missing data and implausible values, with a very minimal percentage of weight and height measurements being missing or implausible, indicating high data validity and completeness. Additionally, some well-established associations, such as the increased likelihood of low birth weight within preterm births, were observed, lending credibility to the results and aligning with established knowledge. Furthermore, sensitivity analyses comparing data from pre-2013 and post-2013 periods, when efforts were made to improve data quality, when assessing associations between size at birth and overweight/obesity yielded consistent results, reinforcing the internal reliability and robustness of the observed associations. Finally, the ability to observe relatively consistent associations across the five settings within the UNRWA system further strengthens the validity and reliability of the data collected. This was observed in Chapters 4 and 5 as I see similar associations when I pool the data or when I present the data by country.

By triangulating our data with other external population-level indicators and established references, this study provides some evidence of the external validity and representativeness of the data.

1) The associations observed in the Palestinian dataset were consistent with those seen in the Brazilian and Mexican cohorts when examining post-term births and SGA infants in middle income countries.
2) Key indicators derived from the electronic health data, such as maternal education prevalence, size for gestational age prevalence, and other measures, aligned well with reported figures in the literature, indicating the representativeness of the data.
3) The infant mortality rate in the e-health system was compared to external estimates, with external sources (IGME/ MICS) showing comparable numbers to UNRWA's e-health system) (see Table 5 below)
4) The growth standards derived from our data fit well with the WHO growth curves. The growth curves among Palestinian refugees closely followed the median of the WHO curves, further demonstrating the plausibility of the data and its alignment with the general population.

Table 5. compares e-health calculated Infant Mortality Rate (IMR) (per 1000 livebirth) to modelled estimates from UN IGME and from MICS.

Palestinian refugees	UNRWA e-health 2010-2019 IMR (95% CI)	IMR IGME (37). 2010	IMR IGME (103) MICS (99) 2019
Gaza	12.9 (12.5-13.2)		12.7
Jordan	15.8 (15.3- 16.3)	17.2	13.4
Lebanon	12.7 (11.7-13.7)	9.7 (Lebanese)	7.4 (Lebanese)
Syria	15.1 (14.2-16.7)	16.2-(Syrian)	18.8 (Syrian)
West Bank	9.3 (8.8-9.9)		11.7
Palestine (West Bank & Gaza)	12.0 (11.7-12.3)	18.8	13.7

6.1.3. Co-existence of double burdens among Palestinian refugees

The Palestinian refugee population is undergoing an epidemiological transition characterized by the co-existence of a double burden of malnutrition. In this context, the establishment of this birth cohort can provide a better understanding of the contribution of birth outcomes and growth trajectories to this dual burden (both under and over-nutrition) in childhood. The separation of data into 9 distinct phenotypes of birthweight

and gestational age (and not lumping the AGA with LGA) allows for the distinction of patterns and extremes, including preterm/post-term, SGA, and LGA.

SGA and LGA

The spectrum of birth weights, ranging from SGA to LGA, reflects diverse intrauterine growth patterns among Palestinian refugee infants. In this population, I find that 9.3% are classified as SGA and 10.7% as LGA, highlighting the need to address and intervene on both ends of the spectrum of birthweight for gestational age in this setting.

Maternal nutritional status and gestational exposures influence foetal growth and development. Inadequate gestational weight gain can lead to FGR/IUGR and SGA infants. SGA is associated with an increased risk of rapid postnatal weight gain. The rapid weight gain trajectory during early life can lead to higher odds of overweight/obesity later in childhood and adulthood through metabolic programming pathways. As first noted in the Dutch Famine studies (29, 30), exposure to severe food insecurity during conflicts, can lead to a significant increase in the incidence of SGA. This is of relevance for those born in our cohort in Syria during the Syrian conflict and currently in Gaza. On the other end of the spectrum, maternal factors like excessive weight gain, pre-existing diabetes, obesity, multiparity, and advanced maternal age heighten the likelihood of delivering LGA infants. Notably, in 2023, the prevalence of diabetes during pregnancy (pre-existing and gestational) among Palestinian refugees was 7.8% (71). In our study and others in the literature, LGA infants have an increased risk of subsequent overweight/obesity, obesity, and metabolic complications (104, 105).

Preterm and post-term

While the prevalence of preterm births in the region is not the highest globally (106), it remains high compared to Northern America, Australia, Europe and Eastern Asia. Post-term births also occur due to a lack of clear national policies regarding induction. The literature indicates that refugees may potentially be more likely to experience preterm births in some cases, and exposure to conflict also contributes to preterm births, although this relationship has not been well established (69). Conversely, post-term births with prolonged gestation periods can lead to challenges in optimal nutrition

transfer. The lack of proper follow-up, policies, and gestational age measurement in the region means that post-term births still occur.

Overweight/Obesity, stunting, and anaemia

Amidst the social and political challenges faced in the Arab region in recent decades, particularly in areas where Palestinian refugees reside, a rapid shift in nutritional patterns has taken place. This transition, driven by accelerated urbanization and transformations in food systems, has consistently led to a rise in the prevalence of overweight/obesity among children and adolescents. This trend is driven by various factors, including changes in dietary habits, increased exposure to food advertising, and a more sedentary lifestyle. Concurrently, Palestinian refugees face significant levels of food insecurity, often relying on food or cash assistance for sustenance. Consequently, a dual burden of malnutrition persists among Palestinian refugee children, characterized by the coexistence of overweight/obesity and undernutrition (such as stunting, wasting, and micronutrient deficiencies like anaemia) within the same population or household or person (107, 108). Notably, the prevalence of individual-level double burden, where stunting and overweight/obesity coexist in individual children, is twice as high in the MENA compared to other global regions, exceeding statistical expectations (109, 110).

6.2. Strengths and limitations

6.2.1. Building on the literature

Our umbrella review builds on the most recent literature and serves as a comprehensive synthesis of a large body of evidence, related to the association between size at birth and child and adolescent outcomes. This synthesis not only facilitates the avoidance of redundant research endeavours, thereby conserving valuable time and resources but also enables the identification of gaps in our current understanding. Nevertheless, it is crucial to recognize the inherent limitations of umbrella reviews, including their reliance on the reporting of included meta-analyses and their potential inability to address omissions or overlaps in original studies.

6.2.2. First cohort of Palestinian refugees of high quality

This study establishes the first large birth cohort of Palestinian refugee using electronic health and education records from UNRWA. This cohort is also one of the first cohorts that includes a refugee population from the Arab region. The cohort includes data on 972,743 live births between January 1, 2010, and December 31, 2020, across five settings: Jordan, Lebanon, Syria, West Bank, and Gaza Strip. It provides extensive insights into maternal and child outcomes, encompassing aspects such as birth, growth, vaccination, and education. The utilization of high-quality data and robust methods ensures the reliability of the findings, which can effectively be used to guide policies and interventions aimed at improving refugee health. Given the unique challenges and vulnerabilities faced by refugee populations, there is a significant lack of longitudinal research focusing on their health issues. This cohort addresses this gap and focuses on birth and growth outcomes in refugees in the Arab region. This cohort not only fills a substantial knowledge void in this field but also opens avenues for further investigation. Potential future research could examine the effect of birth size on growth in older children and their health outcomes, and their educational achievements, as well as exploring the correlation between health of children (e.g. recurrent infections) and school attendance and educational achievement.

6.2.3. Robust methods

We used a variety of robust methods for each paper. These include a large umbrella review search, deterministic data linkage, classification, and regression decision tree approach (CART), mixed-effect logistic regression, and structural equation models. The use of appropriate methods and sensitivity analysis, strengthens the study's findings and conclusions.

6.1.1. Limitations of an electronic health records-based cohort

Electronic Health Records can be susceptible to various types of errors and biases when used for research purposes. I outline here some of those that are relevant to this thesis.

1) Information bias

Similar to survey data electronic health records are subject to information and recall bias. Variability in the classification of variables, such as exclusive breastfeeding in electronic health records, can stem from differences in data collection methods, including variations in how nurses pose questions, and cultural practices. For instance, among Palestinian refugees, providing liquids to infants under six months might not always be recognized as introducing other liquids, leading to inaccuracies in recalling exclusive breastfeeding duration. Another instance of information bias occurs in gestational age calculations based on the LMP, which may not always be precise, resulting in inaccuracies in determining birth timing. Moreover, incorrect recording of mortality events, such as intra-uterine foetal deaths (IUFD) mistakenly noted as live births, introduces ambiguity in classification. Despite attempts to harmonize with external estimates, variations in recording practices can undermine the accuracy and reliability of mortality data. These are all likely to result in non-differential misclassification. In addition, I was constrained by the available data on mortality from conducting separate analysis for early neonatal, late neonatal, and infant mortality in Chapter 4.

Measurements also are susceptible to various sources of error, impacting the reliability of collected data. In this thesis, I rely on weight (at birth and as the child grows) and height measurements. Errors can arise from techniques used in the measurement; for instance, if the child is not positioned correctly or if the measuring device lacks proper calibration. Measurements taken with shoes and heavy clothing can also distort both height and weight readings. Another significant source of measurement error stems from the use of different measurement devices across clinics or over time. Inconsistencies in the calibration or quality of scales and stadiometers used for weight and height measurements can introduce systematic biases into the dataset. This becomes particularly problematic when attempting to analyse trends over time or make comparisons across diverse populations.

Some variables that are important for research may not be pre-collected by the system, leading to their absence in the dataset. Examples include specific types of

malpresentation, induction, or complementary feeding types. The lack of these variables can limit the scope and depth of the analysis.

2) Selection bias

Identifying and distinguishing duplicate records or multiples (twins, triplets, quadruplets, etc.) records poses considerable challenges and can introduce inaccuracies into the dataset, as extensively discussed in Chapter 3. The inability to properly link multiple records resulted in the exclusion of this group from the analysis in Chapter 5, inadvertently overlooking the potential effects of multiples. Another critical consideration is underreporting of infant mortality. This is particularly true within high-risk groups such as preterm and multiple births. This underreporting, especially among such vulnerable populations, has the potential to skew the results and should be carefully considered in the analysis. Potential consequences of underreporting include selection bias, inaccurate mortality estimates and biased associations.

Loss to follow-up is a common and important issue to investigate in electronic health records. In the case of overweight/obesity outcomes measured at 23 months onward, follow-up challenges raise questions about tracking lost subjects. The loss to follow up could lead to selection bias. To assess loss to follow-up, I estimated the proportion of subjects lost by cohort year and age of last observation. This analysis allowed us to quantify the extent of loss to follow-up and identify any patterns or trends over time.

Selection bias may also arise if there is a lack of linkage of children with obstetric non-users, as they may have different characteristics compared to those who use UNRWA services. Given that UNRWA is the main service provider for Palestinian refugees in Gaza, Syria, and Lebanon, the chances of this bias are lower in these settings but more probable in Jordan and the West Bank.

6.2. Implication of the research

6.2.1. Adjustments to the electronic health records

The data analysis identified areas for improvement in the data collection process. Specific recommendations made to UNRWA and adopted by the agency include: 1) capturing more detailed information for caesarean sections on specific malpresentation or induction (paper in Thesis Appendix 3), 2) changing the way infant mortality is recorded from open text to a clear format with dates and 3) improving the recording of twins or multiple births.

The findings also highlighted the need for interventions and flagging mechanisms within the electronic health record system. For example, flagging gestational age that goes beyond 42 weeks (for induction), or identifying SGA or detecting rapid weight gain are just a few instances where such mechanisms can significantly enhance clinical decision-making and patient safety.

Several studies in the literature provide examples of how electronic health record systems can leverage lagging mechanisms for intervention to improve the quality of patient care. A study exploring staff expectations for implementing electronic health records highlighted the need to prioritize interventions (111). This involves setting up alerts or notifications within the electronic health record system to flag potential issues or deviations from established guidelines, prompting healthcare providers to take appropriate actions (similar to what was proposed in this thesis for gestational age that exceeds 42 weeks for example as an effort to avert post-term). A scoping review found limited evidence on the overall impact of electronic health records in improving patient outcomes but identified some benefits, such as enhanced decision support for medication prescribing, improved communication between teams, and better infection prevention alerts (112). Additionally, the Commonwealth Fund discusses how electronic health records can facilitate patient safety through checklists, alerts, predictive tools, and embedded clinical guidelines that promote standardized practices (113).

6.2.2. Overweight and obesity in the Arab region and refugee context

In this section, I adopt a life-course perspective that integrates insights from the thesis and discusses these in the context of existing literature (Figure 6) (114). I consider how the following factors contribute to or modify the risk of overweight in Palestinian refugee children:1) antenatal care and gestational health in the preconception and pregnancy period, 2) breastfeeding practices in infancy 3) rapid weight gain in infancy and childhood.

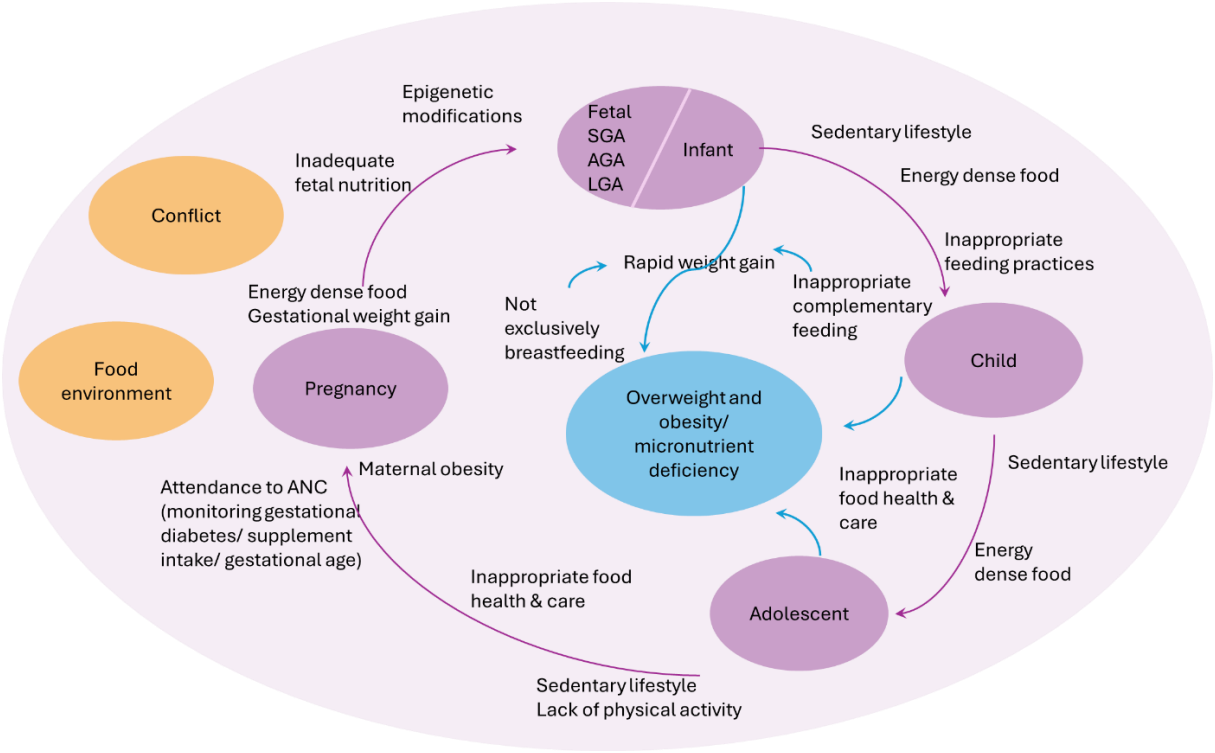

Figure 6- Life course: proposed conceptual framework (adapted from (114)).

Preconception and pregnancy period – inadequate foetal nutrition.

Antenatal care (ANC) plays a pivotal role in managing maternal and foetal health during pregnancy, including monitoring aspects of relevance to this thesis such as gestational weight gain for mother and foetus, gestational diabetes, and accurately determining gestational age.

Interventions aimed at optimizing maternal nutritional status and appropriate maternal weight gain play an important role in promoting appropriate foetal growth and mitigating intergenerational health risks. As part of routine antenatal care visits, it is desirable to

measure the woman's weight and plot it on a gestational weight gain (GWG) chart tailored to her pre-pregnancy BMI category. This allows for continuous monitoring to ensure that her weight gain aligning with the recommended range outlined by the Institute of Medicine (IOM) guidelines (115). However, the IOM guidelines were primarily developed based on observational studies conducted in high-income countries (HIC), leaving a gap in evidence-based public health tools for monitoring GWG across different geographic locations (115). To address this issue, WHO is currently developing global GWG standards (116). These standards aim to provide a comprehensive tool for dynamic monitoring of gestational weight gain in diverse antenatal care settings, ensuring optimal maternal and foetal health outcomes worldwide. Importantly a comprehensive meta-analyses examining 23 cohort studies, encompassing 1,309,136 women from diverse regions, revealed a significant association between excessive gestational weight gain (identified as women who gained weight above IOM guidelines) and LGA births, with an odds ratio of 1.85 (95% CI: 1.76-1.95) (117).

On the other hand, inadequate foetal nutrition can lead to adverse outcomes such as SGA and birth defects. Pregnant women need to ensure a balanced intake of essential nutrients, including folic acid, iron, calcium, protein, and omega-3 fatty acids. Moreover, addressing specific nutritional deficiencies through iron, folic acid, and multiple micronutrient supplements, as well as fortified foods, is crucial, particularly among Palestinian refugee who experience a high prevalence of micronutrient deficiencies among pregnant women (118, 119). Data from the 2013 Palestinian Micronutrient Survey revealed widespread micronutrient deficiencies among pregnant women in the first trimester in the Gaza Strip, including anaemia (20.7%), zinc (67.9%), vitamins A (11.4%), B12 (27.9%), D (78.6%), and E (18.0%) deficiencies (120, 121). These deficiencies coexist and can have severe consequences for maternal and foetal health. Recent evidence supports the use of maternal multiple micronutrient supplementation in LMIC as a more effective approach to improving birth outcomes compared to iron-folic acid supplementation alone. A systematic review found that micronutrient supplementation reduced the risk of SGA births by 7% (95% CI: 2-12) as compared to iron-folic acid supplementation alone (118, 119).

Among Palestinian refugees, access to quality ANC remains a concern. While ANC coverage (4+ visits) was relatively high in 2017 - 86% in Jordan, 94% in Lebanon, 64% in Syria, 95% in Gaza, 92% in West Bank - early ANC access in the first trimester was lower at 82%, 92%, 61%, 89%, and 75% respectively (70).

Conflicts and emergencies can further decrease access to and utilization of ANC services, exacerbating these maternal health issues. In future work, I plan to further explore the association between conflict exposure and various health outcomes (including birthweight typologies), using different methods to operationalize conflict exposure. This analysis will primarily utilize Armed Conflict Location & Event Data (ACLED) and Uppsala Conflict Data Program (UCDP) data to quantify exposure to conflict.

Thesis Appendix 4 includes slides of preliminary analyses conducted using electronic health records, highlighting the effect of conflict on delayed access to ANC services and its implications for foetal health including preterm and stillbirth. Women exposed to conflict events during the first trimester were 37% less likely to use UNRWA antenatal care services, those using them delayed timing of the first visit by 11.9 days (CI 11.3-12.5) (Thesis Appendix 4). Women exposed to conflict were less likely to report taking folic acid supplementation (OR=0.9,95%CI: 0.9-0.9) (Thesis Appendix 4) Exposure to conflict before birth also increased the odds of stillbirth (OR=1.4, CI=1.2-1.5), and of extremely preterm (OR=1.2, CI 1.0-1.4), very preterm (OR=1.1;CI 1.0-1.2) and preterm (OR=1.0, CI 1.0- 1.1) deliveries (using multinomial model with term delivery as the reference and conflict exposure).

The anticipated impact of conflict-related stress on maternal and foetal health is further supported by research on the effects of maternal stress and elevated cortisol levels during pregnancy (68, 122, 123). Research has shown that maternal cortisol levels above 17.66 µg/L are associated with a 2.28-fold increased risk of low birth weight and a 2.16-fold increased risk of lower weight-for-length in infants (122).

Infancy - breastfeeding practices

Our findings contribute to the body of literature on the protective effects of breastfeeding against childhood overweight/obesity, primarily by mitigating rapid weight gain.

Additionally, our research highlights that infants who are SGA or preterm are less likely to be breastfed, which amplifies their nutritional vulnerabilities and increases the risk of adverse health outcomes.

The low and declining prevalence of exclusive breastfeeding for the first six months is a significant concern in the Arab region, particularly in areas hosting Palestinian refugees (124). The MENA region has the lowest prevalence of exclusive breastfeeding at 6 months at 35% compared to other regions (124). Key issues linked to this low prevalence in the region are linked to sociocultural attributes of mothers and beliefs regarding infant feeding practices and to policy environments, including a low number of baby-friendly hospitals, unregulated marketing of breastmilk substitutes, limited maternity leave (125, 126). This video depicts these challenges in the Arab region, highlighting the complexities surrounding breastfeeding practices (link). A study in West Bank indicated that the main raison for interruption of exclusive breastfeeding was returning to work (127). A study in Lebanon, mapping policies in the region, found discrepancies between policy endorsements and their translation into practice on the ground, citing weak engagement of professional associations and governmental institutions, undue influence by the breastmilk substitute industry, and competing priorities (98).

Conflicts and emergencies exacerbate the declining trend in breastfeeding rates, leading to lower rates of breastfeeding initiation and continuation.

Conflict leads to a decrease in breastfeeding mainly by:

1) Disrupting access to health services and antenatal care that promote and support breastfeeding practices,

2) Creating environments of displacement and insecurity that are not conducive to initiating and continuing breastfeeding (due to stress, overcrowding, and lack of support systems),

3) Increasing influxes of donated breastmilk substitutes, which can undermine breastfeeding practices when distributed inappropriately (125).

Infancy and childhood - rapid weight gain and food environment

A concerning aspect of the nutrition transition among Palestinian refugees is that of inappropriate complementary feeding practices and subsequent rapid weight gain in infants and young children. Complementary feeding practices among children aged 6–23 months in countries hosting Palestinian refugees often fall short of recommendations, the percentage meeting minimum dietary diversity was 42% in Lebanon, 32% in Jordan and 50% in Palestine (128). Factors related to complementary feeding such as early introduction of solid foods, provision of energy-dense, nutrient-poor foods, failure to recognize hunger cues, and inappropriate feeding practices contribute to rapid weight gain (129-131). A systematic review indicated that the introduction of complementary foods in the Middle East and North Africa region occurs early, with studies indicating that up to 80% of infants receive these foods before the recommended age of six months in the region (132). The early introduction of non-milk fluids, such as sweetened water and herbal teas, is a widespread practice in the region, often driven by cultural beliefs and practices, including the perception that breast milk alone is nutritionally insufficient for infants after a few months. Inappropriate early feeding practices have been associated with increased risks of overweight/obesity and cardiovascular diseases later in life, highlighting the potential long-term health implications of these regional dietary habits. Addressing these factors is crucial to ensure optimal growth and development in infants and young children and mitigate the risk of childhood overweight/obesity.

Beyond infancy, child food insecurity remains a significant challenge among Palestinian refugees, characterized by low dietary diversity, high consumption of calorie-dense but nutrient-poor foods (133-135). In a study in four schools in Lebanon, around 20% of Palestinian refugees reported being food insecure, impacting not only diet diversity but also school attendance (135).

Moreover, school aged children in the MENA region grapple with alarmingly high rates of physical inactivity among children, with percentages as high as 75.8% in Gaza, 81.7% in the West Bank, 65.4% in Lebanon, and 84.9% in Syria, defined as engaging in less than 60 minutes of physical activity per day on five or more days per week (136). The prevalence of inactivity was consistently higher among girls across all these settings,

potentially contributing to higher rates of maternal overweight/obesity in adulthood (136). In addition, food environments have been documented to foster unhealthy dietary habits (137-139) and food assistance in Palestine has been criticized for being high in energy (140). This combination of factors in adolescent girls and beyond may in turn, increase the risk of LGA births (141) childhood overweight/obesity, perpetuating the cycle of obesity across generations.

Table 6 outlines these factors at different stages of the life-course, how they manifest in Palestinian refugee populations, and potential interventions to curb this intergenerational cycle.

Table 6- Summary of Life Stages and Factors Influencing Overweight or Obesity

Life Stage	Influences	Context-Specific Factors (Palestinian Refugees)	Potential Interventions
Preconception & Pregnancy	- Foetal nutrition - Gestational weight gain - Gestational diabetes	- High prevalence of micronutrient deficiencies - Conflict and emergencies reducing ANC access - Delayed ANC access in first trimester	- Optimize maternal nutrition - Monitor gestational weight gain - Provide micronutrient supplements
Infancy	- Breastfeeding practices - Rapid weight gain	- Low and declining prevalence of exclusive breastfeeding - Sociocultural barriers - Policy environment and unregulated marketing	- Promote exclusive breastfeeding - Strengthen baby-friendly hospital initiatives - Extend maternity leave
Infancy & Childhood	- Rapid weight gain - Complementary feeding practices - Food environment - Physical activity	- Early introduction of complementary foods - High consumption of nutrient-poor foods - Food insecurity - High rates of physical inactivity	- Educate on appropriate complementary feeding - Promote physical activity - Improve food assistance programs
Adolescence	- Food environment - Dietary habits -Physical activity	- Advertising and availability of unhealthy food options in schools - High rates of overweight and obesity among school children - High rates of physical inactivity	- Regulate food advertising - Implement school feeding programs - Promote physical activity

6.3. Conclusion and future research directions

The body of work presented in this thesis has identified various future research directions. The umbrella review synthesized evidence, identified gaps, and highlighted inconsistencies in the associations. It identified that there is a need for meta-analyses on 13 subthemes identifies including for example seizures, age at menarche, feeding problems as discussed in Chapter 2. Chapter 3 identified the need to explore alternative methods for linking data, such as comparing deterministic versus probabilistic linkage methods. Further comparisons could be made to evaluate the reliability of key indicators derived from different data sources and survey data. Building on the post-term analysis in Chapter 4, future studies could investigate actions and policies to reduce post-term birth. Chapter 5 also suggests additional research that is needed on growth velocity when considering the early-life determinants of overweight and obesity. Future research could also explore strategies to address rapid weight gain in infants and young children. Studies on complementary feeding practices and their impact on child growth and development in different cultural contexts, particularly the MENA region, where no such studies exist, are needed.

The establishment of the Palestinian refugee birth cohort opens a wide array of future research avenues. I plan to continue to conduct research that:

- Explores the association between size at birth and other outcomes, including education, which are currently missing from the literature.
- Investigates interactions between health, nutrition, and education, which could provide insights into these complex relationships.
- Overlays external data sources, such as conflict and climate indicators, to assess the effect of these global crises on various birth and growth and development outcomes.

Overall, this rich cohort serves as a valuable resource for addressing critical knowledge gaps and informing policies in humanitarian settings.

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Thesis Appendix

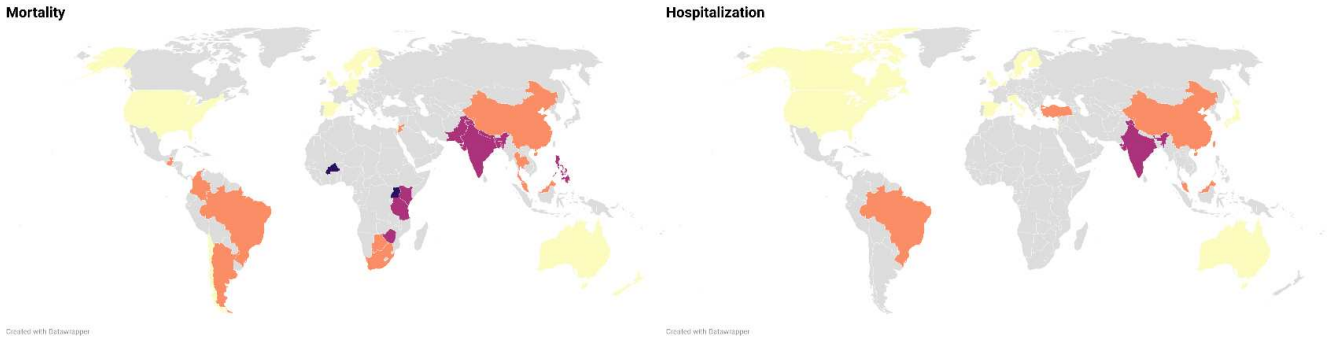
Thesis Appendix 1- Additional supplementary from umbrella review

Supplementary material 5 Figure 2- Countries in systematic reviews with metanalyses covering different themes/subthemes.

Maps legends

- High-income countries
- Upper middle countries
- Lower middle countries
- Low-income countries

Mortality and Hospitalization

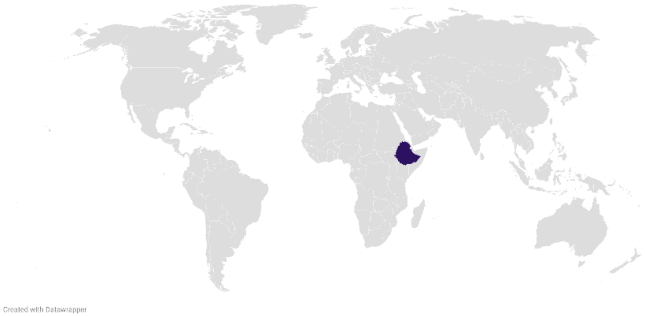


39

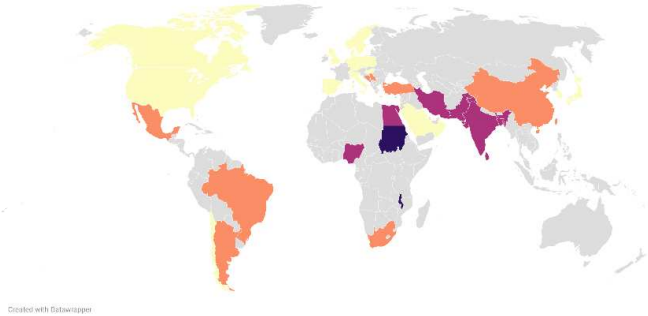
Jamaluddine Z, *et al*. *Arch Dis Child* 2023;0:1–14. doi: 10.1136/archdischild-2022-324884

Neonatal Early Childhood Health

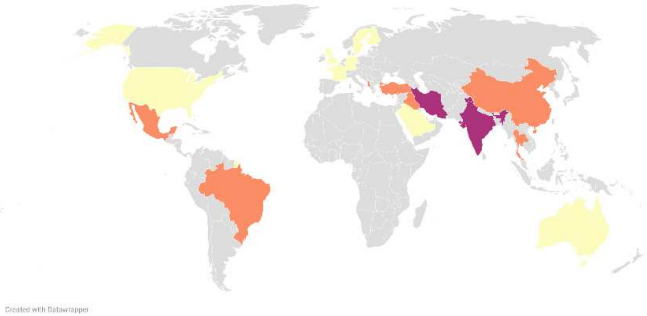
Asphyxia



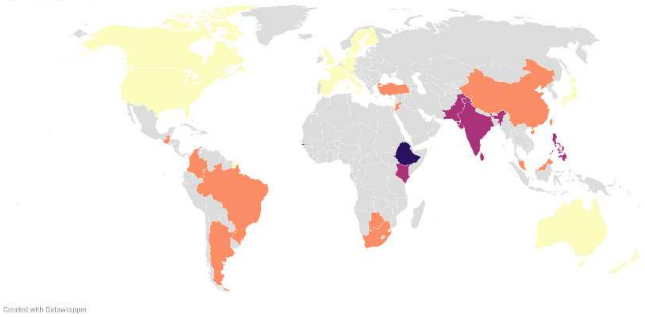
Retinopathy



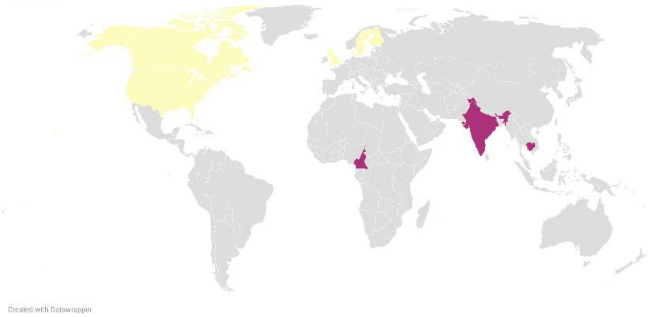
Caries/Oral Health



Infection/ Sepsis



Epilepsy



Quality of Life

40

Jamaluddine Z, *et al*. *Arch Dis Child* 2023;0:1–14. doi: 10.1136/archdischild-2022-324884

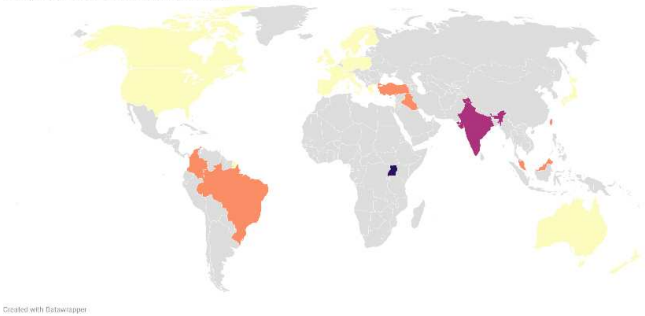
Lung

Atopic Dermatitis

Other Allergies

Lung Function

Lung Diseases (Asthma/Wheezing)



Other Lung Related Outcomes

41

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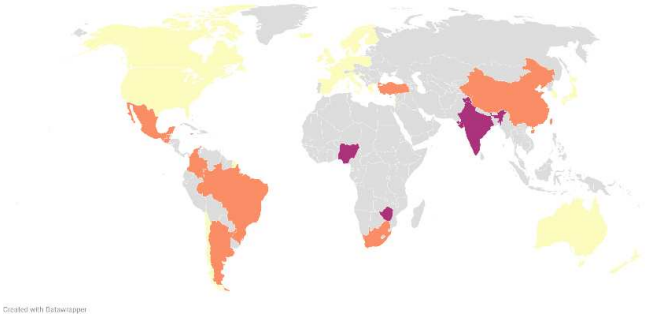
Chronic Diseases

Hypertension



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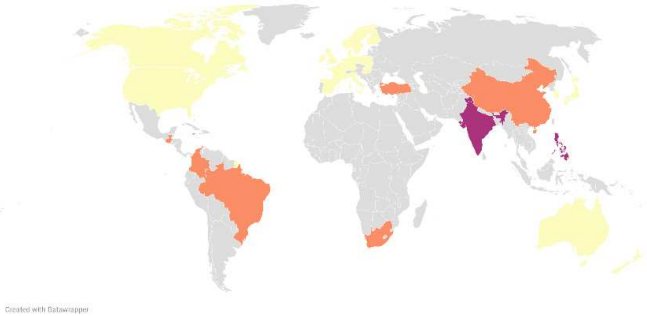
Hypercholesterolaemia



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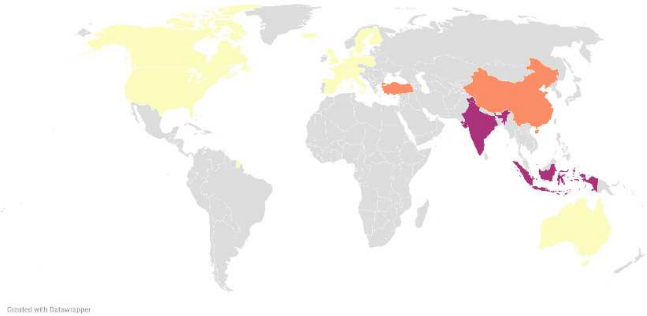
Coronary Heart Disease and Heart Function



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Kidney Related Diseases

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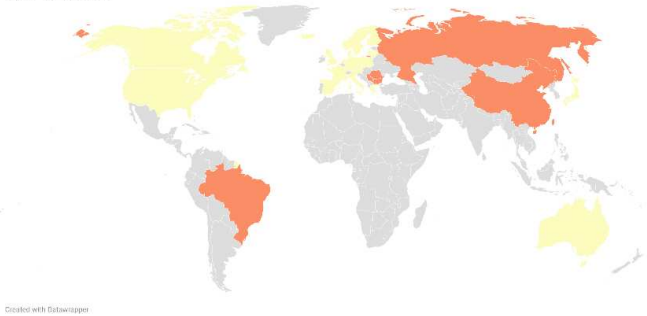
Type 1 Diabetes



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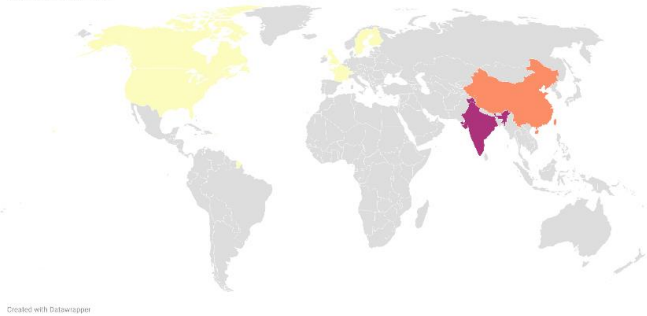
Type 2 Diabetes



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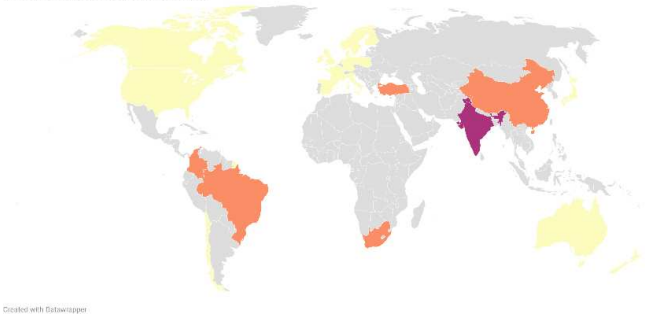
Diabetes Related Measurement



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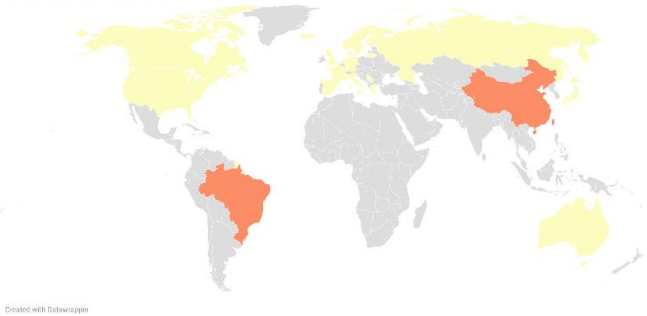
Paediatric CNS Tumours



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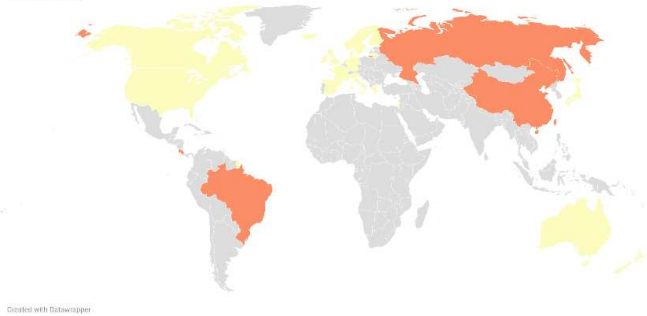
Leukaemia



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42

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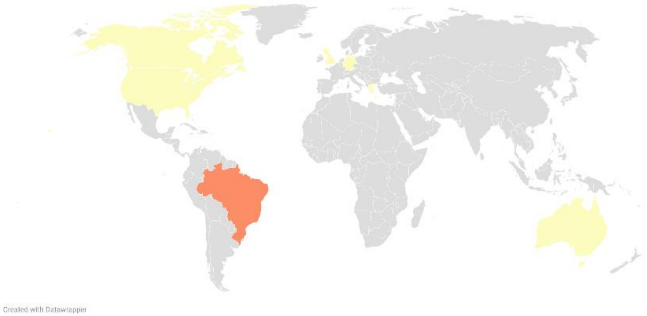
Lymphoma



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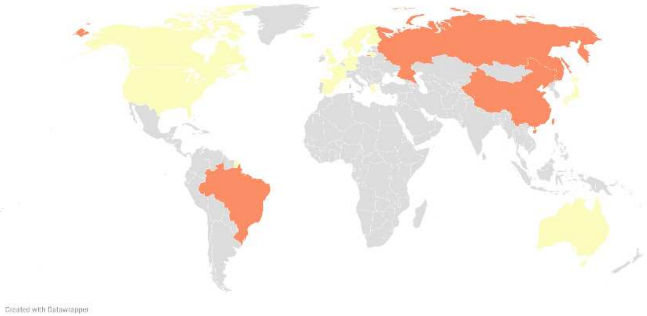
Wilm's Tumour (Nephroblastoma)



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Other Tumours

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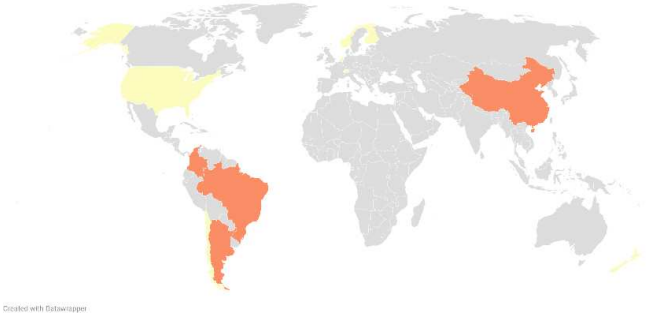
Metabolic Syndrome



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Metabolic Biomarkers

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Developmental

Brain Neurodevelopment

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Visuomotor

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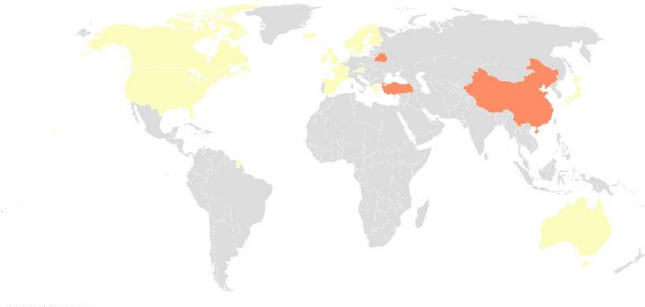
Cerebral Palsy



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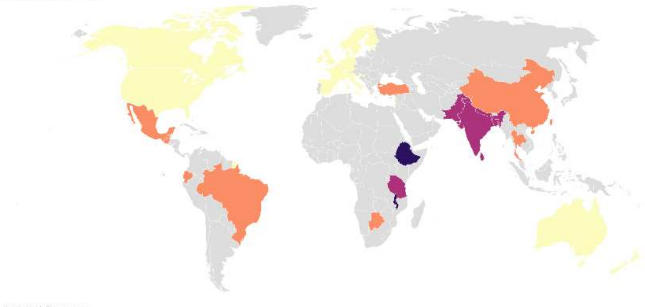
Physical Motor



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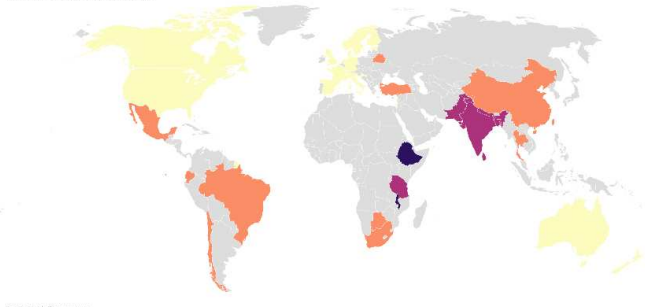
Intellectual Disabilities



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Memory

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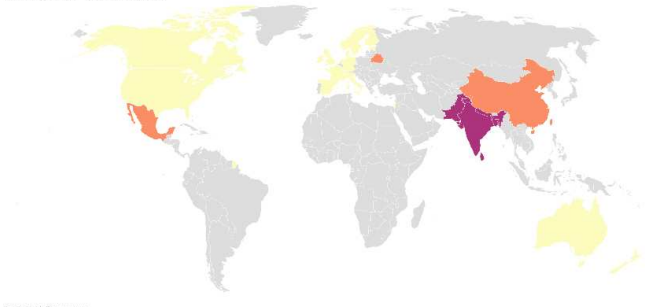
Intelligence Quotient (IQ)



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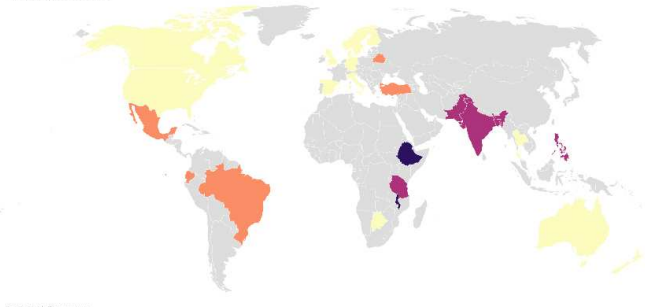
Communication



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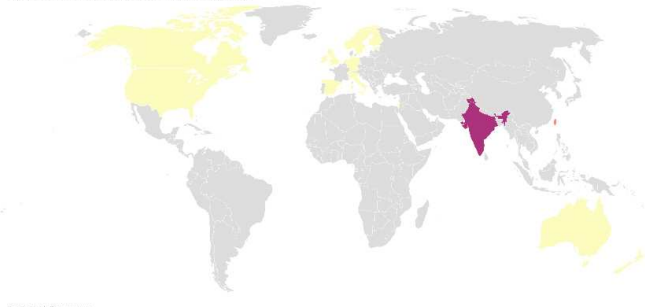
Specific Learning Disorder: Language



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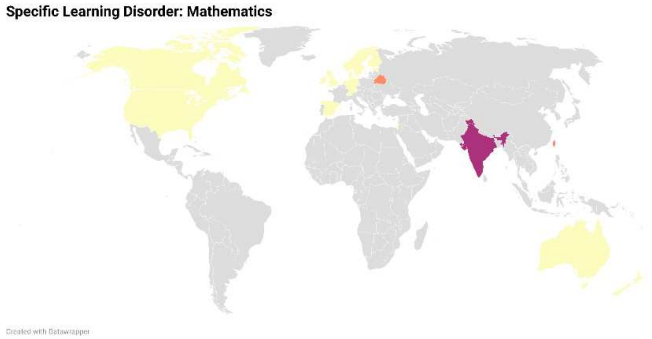
Specific Learning Disorder: Mathematics
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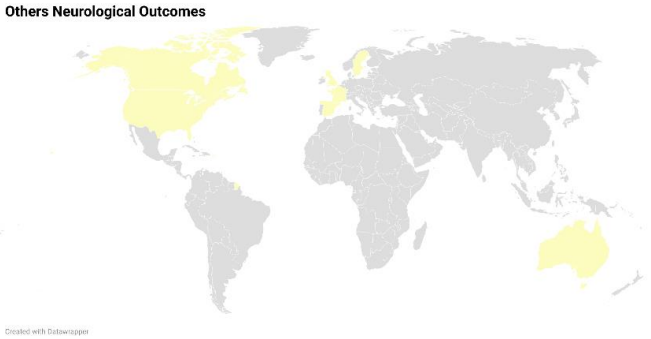
Others Neurological Outcomes
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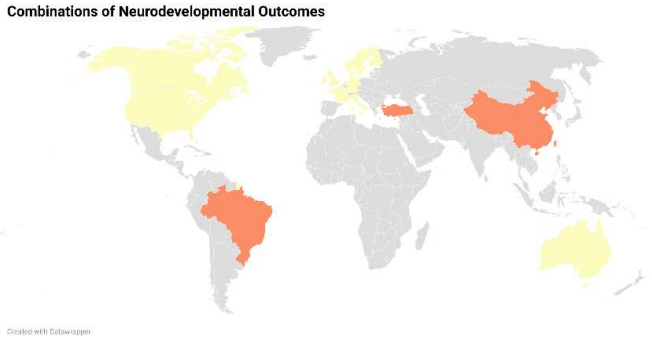
Combinations of Neurodevelopmental Outcomes
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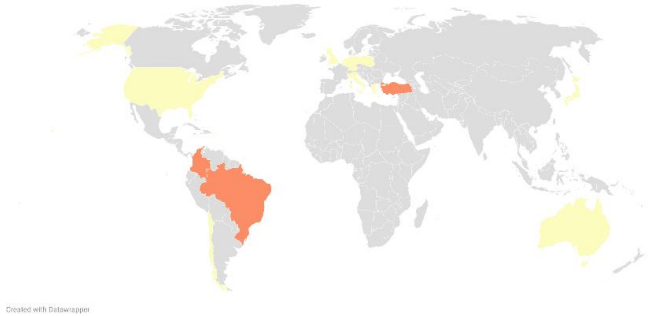
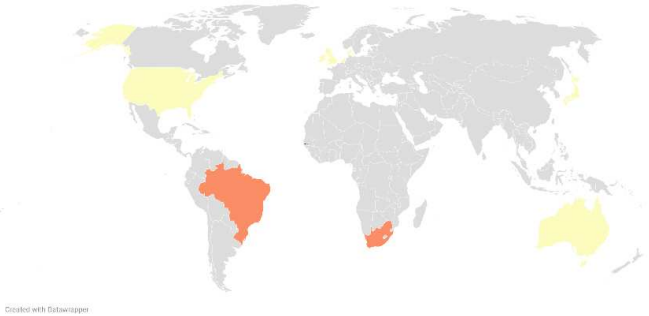
Growth and Nutrition

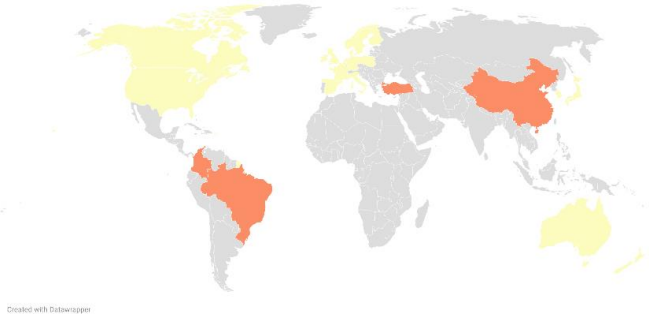
Body Composition



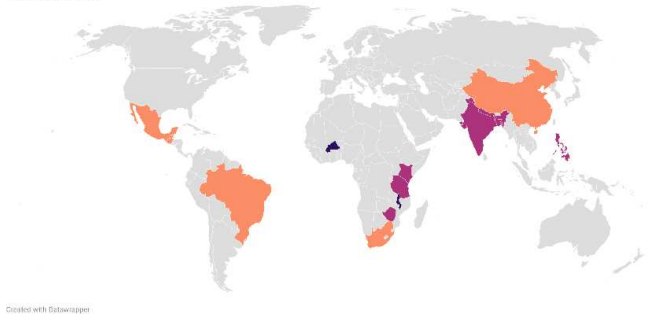
Bone Mineralization



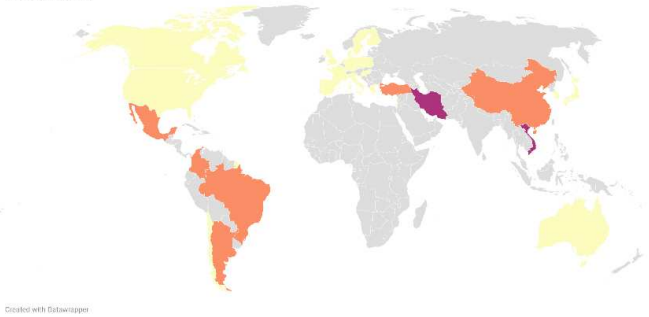
BMI



Undernutrition



Overnutrition

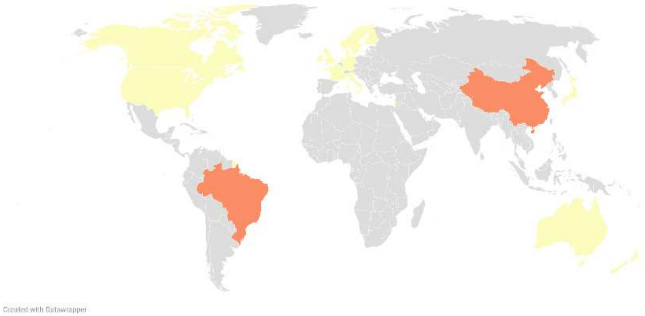


46

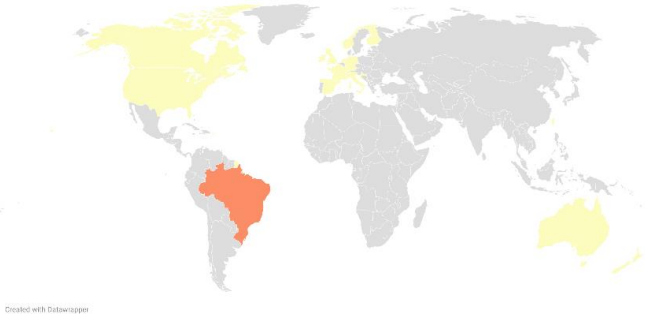
Jamaluddine Z, *et al*. *Arch Dis Child* 2023;0:1–14. doi: 10.1136/archdischild-2022-324884

Behavioural and Mental Health

Depressive/ Anxiety Disorders

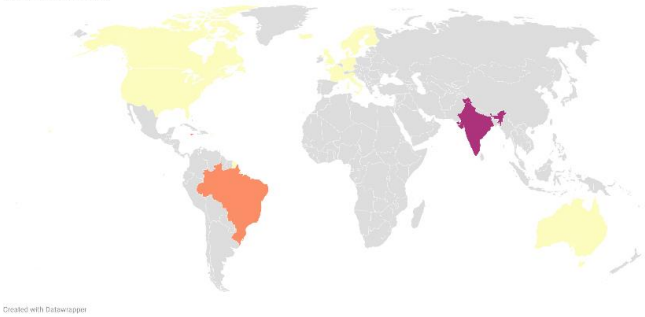


Other Psychological



Behavioural

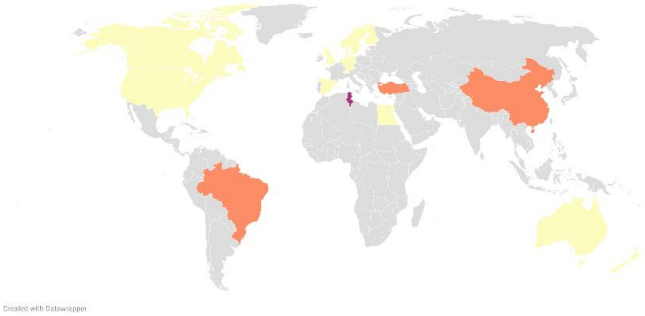
Physical Activity



Attention

Attention-Deficit/Hyperactivity Disorder

Autism Spectrum Disorder



Suicidal Behaviour

Supplementary material 7- Prisma checklist 2020

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title page
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Background paragraph 3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Background paragraph 4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Methods paragraph 4, 6, 7
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Methods: paragraph 3
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supplementary material 2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Methods: paragraphs 4 and 7
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Methods: paragraph 5-7 No data were sought from investigators
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	No outcomes were pre-specified. Figure 2 and Table 1 show the range of outcomes identified.
	10b	List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions	Methods: paragraph 5

Section and Topic	Item #	Checklist item	Location where item is reported
		made about any missing or unclear information.	
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Methods: paragraph 6 describes quality assessment and c approach; results are in Supplementary material 3
Effect measures	12	Specify for each outcome the effect measure(s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results.	Tables 1 and 2
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Not applicable
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Tables 1-3
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g., subgroup analysis, meta-regression).	None conducted
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	None conducted
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	None conducted
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Narrative synthesis, use of colour coding
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	
Study	17	Cite each included study and present its characteristics.	Tables 1 and 2

Section and Topic	Item #	Checklist item	Location where item is reported
characteristics			
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g., confidence/credible interval), ideally using structured tables or plots.	Tables 1 and 2
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	None conducted
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	None conducted
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	None conducted
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Discussion paragraphs 1-5
	23b	Discuss any limitations of the evidence included in the review.	Discussion paragraph 6
	23c	Discuss any limitations of the review processes used.	Discussion paragraph 6
	23d	Discuss implications of the results for practice, policy, and future research.	Recommendations paragraph 1-4
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	PROSPERO CRD42021268843w
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	LSHTM Data Compass
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	

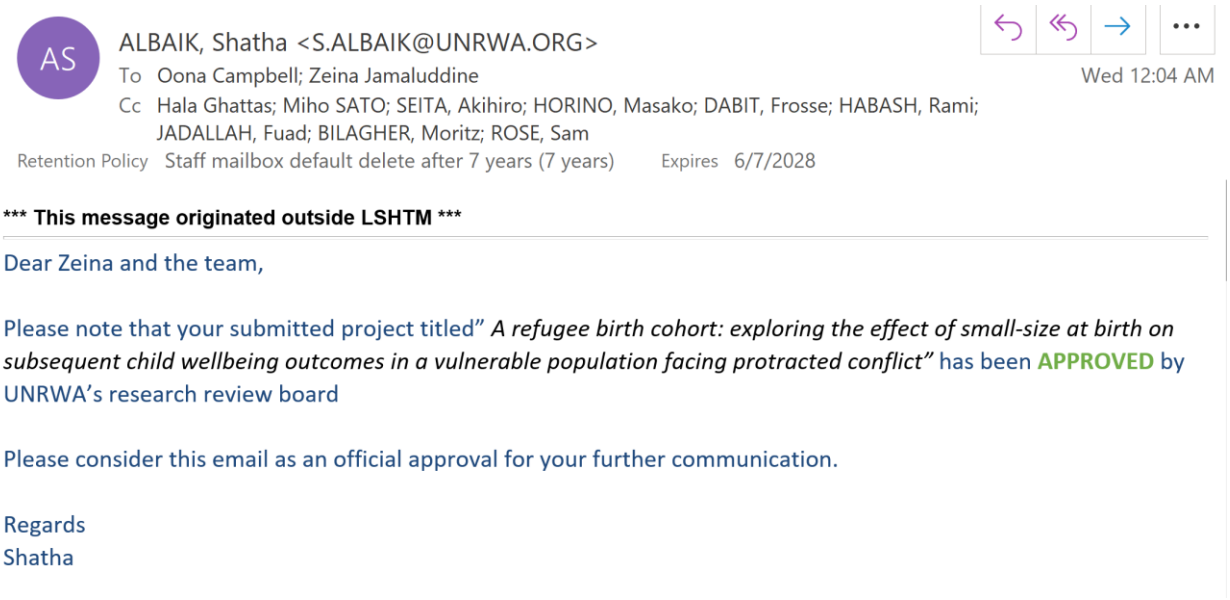
55

Jamaluddine Z, *et al*. *Arch Dis Child* 2023;0:1–14. doi: 10.1136/archdischild-2022-324884

Section and Topic	Item #	Checklist item	Location where item is reported
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	This research was supported by the Nagasaki University "Doctoral Program for World-leading Innovative and Smart Education" for Global Health, KYOIKU KENKYU SHIEN KEIHI ("the Stipend"). Ministry of Education, Culture, Sports, Science and Technology (MEXT). The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript.
Competing interests	26	Declare any competing interests of review authors.	No competing interests
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	All materials used are in Appendices and LSHTM Data Compass https://datacompass.lshtm.ac.uk/

Thesis Appendix 2- LSHTM and URNWA ethical approval letters

UNRWA Ethics approval



AS

ALBAIK, Shatha <S.ALBAIK@UNRWA.ORG>

To Oona Campbell; Zeina Jamaluddine

Cc Hala Ghattas; Miho SATO; SEITA, Akihiro; HORINO, Masako; DABIT, Frosse; HABASH, Rami; JADALLAH, Fuad; BILAGHER, Moritz; ROSE, Sam

Wed 12:04 AM

Retention Policy Staff mailbox default delete after 7 years (7 years) Expires 6/7/2028

***** This message originated outside LSHTM *****

Dear Zeina and the team,

Please note that your submitted project titled" *A refugee birth cohort: exploring the effect of small-size at birth on subsequent child wellbeing outcomes in a vulnerable population facing protracted conflict"* has been **APPROVED** by UNRWA's research review board

Please consider this email as an official approval for your further communication.

Regards
Shatha

Thesis Appendix 3-Example of analysis using the e-health data on increasing caesarean section

BMC Pregnancy and Childbirth

RESEARCH

Open Access

Classifying caesarean section to understand rising rates among Palestinian refugees: results from 290,047 electronic medical records across five settings

Zeina Jamaluddine[1,2*†], Gloria Paolucci[3†], Ghada Ballout[3], Hussam Al-Fudoli[3], Louise T. Day[1], Akihiro Seita[3] and Oona M. R. Campbell[1]

Abstract

Background: Rising caesarean-section rates worldwide are driven by non-medically indicated caesarean-sections. A systematic review concluded that the ten-group classification system (Robson) is the most appropriate for assessing drivers of caesarean deliveries. Evidence on the drivers of caesarean-section rates from conflict-affected settings is scarce. This study examines caesareans-section rates among Palestinian refugees by seven-group classification, compares to WHO guidelines, and to rates in the host settings, and estimates the costs of high rates.

Methods: Electronic medical records of 290,047 Palestinian refugee women using UNRWA's (United Nations Relief and Works Agency for Palestine Refugees in the Near East) antenatal service from 2017–2020 in five settings (Jordan, Lebanon, Syria, West Bank, Gaza) were used. We modified Robson criteria to compare rates within each group with WHO guidelines. The host setting data were extracted from publicly available reports. Data on costs came from UNRWA's accounts.

Findings: Palestinian refugees in Gaza had the lowest caesarean-section rates (22%), followed by those residing in Jordan (28%), West Bank (30%), Lebanon (50%) and Syria (64%). The seven groups caesarean section classification showed women with previous caesarean-sections contributed the most to overall rates. Caesarean-section rates were substantially higher than the WHO guidelines, and excess caesarean-sections (2017–2020) were modelled to cost up to 6.8 million USD. We documented a steady increase in caesarean-section rates in all five settings for refugee and host communities; refugee rates paralleled or were below those in their host country.

Interpretation: Caesarean-section rates exceed recommended guidance within most groups. The high rates in the nulliparous groups will drive future increases as they become multiparous women with a previous caesarean-section and in turn, face high caesarean rates. Our analysis helps suggest targeted and tailored strategies to reduce caesarean-section rates in priority groups (among low-risk women) organized by those aimed at national governments, and UNRWA, and those aimed at health-care providers.

†Zeina Jamaluddine and Gloria Paolucci contributed equally to this work.

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Keywords: Caesarean-section, Delivery, Refugees, Obstetrics, Electronic Medical Records, Routinely Collected Health Data

Introduction

Medically-indicated caesarean-section is effective in reducing maternal and neonatal mortality and morbidity and stillbirths. However, the World Health Organization (WHO) suggests rates above 10% do not confer additional maternal or perinatal benefits [1, 2], while a review of ecological studies suggests that the optimal proposed caesarean-section threshold is 9–19% [3, 4]. The rising global caesarean-section rate, from 7 to 21% between 1990–2020 [5], is driven by non-medically indicated caesarean-sections [6], the latter are caesarean-sections in absence of any maternal or fetal indications such as specific pre-existent maternal health condition, low-lying placenta, placenta previa, labour dystocia, abnormal or indeterminate fetal heart rate tracing, fetal malpresentation fetal macrosomia and multiple gestations.

Non-medically indicated caesarean-sections pose unnecessary risks to mothers and children, and add financial costs. Maternal risks include haemorrhage, infections, anaesthetic and thromboembolic events, and surgical/urological complications, e.g. fistula [7, 8]. Longer term, women with caesarean delivery face increased risks of infertility, ectopic pregnancy, placental abnormalities, uterine rupture, stillbirth, preterm birth, and abdominal adhesions [9]. Children born by caesarean-section have increased risks of neonatal respiratory complications, reduced breastfeeding, and iatrogenic prematurity if gestational assessment is inaccurate. Longer-term effects on children include increased risk of mortality, asthma, and allergies, and reduced intestinal-microbiome diversity [10–13]. Hospitals in the five settings where UNRWA works charge more for caesarean sections than for vaginal births, and this pattern holds in many settings. Caesarean section also require longer hospital lengths-of-stay and recovery periods [14]. Reducing unnecessary caesarean-sections will protect women and children, improve quality of care, and reduce costs to those insuring/financing childbirth services, including women and families.

Limiting unnecessary caesarean-section requires understanding its drivers. WHO recommends the Robson classification to monitor and prioritize where caesarean-section rates should be reduced [15]. Robson categorises all women into ten mutually exclusive groups via routinely-collected clinical data on: parity, previous caesarean-section, onset of labour (spontaneous vs induced), single vs multiple pregnancy, gestational age, and fetal lie or presentation. Using ten-groups classification system (Robson) moves away from whether a caesarean-section is indicated for a specific woman, towards examining groups where rates are excessive or too low [16]. Betran and colleagues, also provide a WHO conceptual framework of drivers of high rates [17], which we used to structure our discussion.

Caesarean-section rates among Palestinian refugees have doubled from 15 to 31% between 2006–2020 [18, 19]. Refugees' access to health services is based on their country of residence. UNRWA, the United Nations Relief and Works Agency for Palestine Refugees in the Near East, provides free primary health care services to Palestinian refugees in Jordan, Lebanon, Syria, West Bank, and Gaza, including free antenatal care services [19]. Pregnant Palestinian refugees can also access low-cost or free national public antenatal services in Jordan, West Bank, Gaza, and Syria, while in Lebanon, those not using UNRWA services must pay for private care. Except for one hospital in West Bank, UNRWA does not directly provide childbirth care– rather it used partial reimbursement co-payment schemes to accredited non-UNRWA facilities, including for childbirth.

This study examines and contextualizes caesarean-section rates among Palestinian refugees residing in the five settings where UNRWA operates, from 2017 to 2020. We examined caesareans-section rates among Palestinian refugees by using a seven groups caesarean section classification modelled on the Robson classification, compared these to WHO guidelines and to rates in the host settings, and estimated the costs of rates above the guidelines.

Methods

We relied UNRWA electronic medical records (EMR) and cost data, and on desk reviews of annual health reports.

The setting and UNRWA's electronic medical records

The percentage of pregnant Palestinian refugees using UNRWA's antenatal care services is estimated at around 35% in Jordan**,** 49% in West Bank, 73% in Gaza, 34% in Syria; it is difficult to estimate in Lebanon [19]. In Syria, many UNRWA clinics reduced services or were destroyed in the war in 2011–2014, and many Palestinian refugees left the country, making the denominator unreliable.

UNRWA's EMR is a web-based patient-centred digital system capturing every primary healthcare clinic visit recorded by the doctor, nurse, or midwife caring for women. It includes contemporaneous modules on

antenatal care, and antenatal referrals, and records pregnancy outcomes retrospectively during postnatal care, the child's first vaccination visit, or by telephone follow-up. In 2017, the EMR system was updated to record information on the mother (place of residence, date of birth, marital status, and education level), obstetric history (parity, previous caesarean-section, previous pregnancy risk score), and more detailed current pregnancy outcomes (gestational at delivery, mode of delivery, malpresentation, number of neonates).

We extracted anonymized electronic medical records data for pregnancies ending between January 1, 2017, to December 31, 2020. Data analysis was performed in accordance with the ethics guidelines and regulations. UNRWA is the main custodian of the electronic health system and maintains the system following ethical, legal privacy and confidentiality requirements. We obtained ethics approval from UNRWA's research review board and the London School of Health & Tropical Medicine Research Ethics Committee (LSHTM Ethics Ref: 22,801) (Date: 12 November 2020). Participant consent was not required as the study used de-identified registry based secondary data. As long as the work does not violate the rights of individuals and does not include identifiable information, UNRWA permit researchers to access EMR without obtaining prior consent from participants to pursue research for the common good of Palestinian refugees. Informed consent was waived by UNRWA's research review board.

Seven groups caesarean section classification

UNRWA's EMR dataset included some variables required for the Robson classification: parity (nulliparous (nullip)/multiparous (multip)), previous caesarean-section (yes/no), number of fetuses (1/2+), gestational age (preterm (defined as less than 37 weeks completed)/term) and fetal lie/presentation (normal/abnormal lie, malpresentation) (Appendix S1) [20], but not the specific type of malpresentation or abnormal lie (breech/transverse/oblique) or onset of labour (spontaneous/induced) or pre-labour caesarean-section. We generated a 7-groups caesarean section classification based on the Robson classification and will be refer to it as the " 7-groups caesarean-section classification". Therefore, we modified the Robson classification from 10 to 7 groups, collapsing group 1 (nulliparous, spontaneous labour) with group 2 (nulliparous, induced labour or caesarean-section before labour) in one group (1+2) and group 3 (multiparous, spontaneous labour) with group 4 (multiparous, induced labour or caesarean-section before labour) in one group (3+4). Hereafter these are called groups 1+2 (nullip, term) and groups 3+4 (multip, term, no prev caesarean-section). We refer to malpresentation as including both abnormal lie and malpresentation and collapsed nulliparous women in group 9 (transverse or oblique) with group 6 (breech) hereafter called groups 6/9 (nullip, malpresentation). We did the same for multiparous women group 7 (breech) with group 9 (transverse or oblique), hereafter called groups 7/9 (multip, malpresentation). Group 5 (multip, term, previous caesarean-section), group 8 (multiple pregnancy), and group 10 (preterm) were not modified. In the text the symbol "/" refers to "or" while the symbol "+" refers to "addition".

Based on the Robson group-specific caesarean-section rates guidelines proposed by WHO [20], we generated a modified weighted guidelines for groups 1+2 (nullip, term) and groups 3+4 (multip, term, no previous caesarean-section) (Appendix S1).

Desk review

Trend data from 2006 till 2020 were extracted for Palestinian refugees from UNRWA annual health reports [21], and for host settings from country national annual health reports, Palestinian Ministry of Health Annual reports (2016–2020), [22] Lebanon Ministry of Public Health (MOPH), Vital Data Observatory statistics (2015–2018) [23]. In Palestine (West Bank and Gaza), around 41% of the population are classified as refugees [24]. We also used population-based household surveys including Demographic Health Surveys (DHS) (Jordan 2007, 2012, 2017/2018) [25], Multiple Indicator Cluster Surveys (MICS) (Palestine 2010, 2014, 2019/2020, Palestinian refugees in Lebanon 2011) [26] and Pan Arab Project for Family Health (PapFam) (Syria 2009) [27]. We reviewed Health Resources Availability Monitoring System (HeRAMS) reports for facility-level data in Syria (2014 till 2018) [28].

Cost data

Cost data from UNRWA were available to two authors (GP and AS) in their capacity as hospitalisation consultant and Director of Health Department at UNRWA.

Analysis

We calculated frequencies and cross-tabulations to assess data quality and investigated missing data. Because the EMR reports women's current age and parity status, we adjusted these to reflect the values when the index delivery occurred. To assess external validity, we compared our data to population surveys and national statistics.

We restricted the analysis to women who delivered a live birth at any gestation or a stillbirth at 28 completed weeks of gestation or beyond (i.e., removing early fetal deaths) [20]. Data collected in UNRWA was recorded per birth, where twins and triplets had 2 and 3 entries respectively. We collapsed twins and triplets to generate

one record per delivery event (with the mother as unit of analysis) and calculated caesarean-section rates among live births, stillbirths and total births [29]. We calculated the relative size of each group among the obstetric population in each of the five settings, and the caesarean-section rates by setting, and within each group. We then calculated the absolute and relative contribution of groups to caesarean-section rates and examined the change in caesarean-section rates from 2017 to 2020. We compared caesarean-section rates within each group with WHO guidance to identify priorities for action. We then compared caesarean-section rates of refugees and host communities. All data were analysed using Stata, version 16 (StataCorp, College Station, USA).

To understand the financial impact of the caesarean section performed, we costed all deliveries as if they were performed in UNRWA contracted hospitals.

Results

From January 1, 2017, to December 31, 2020, UNRWA EMR included data on 294,184 live births and 1,401 stillbirths which occurred in a total of 291,704 delivery events. Missing data ranged from 0.2% in Gaza to 1.5% in Syria; the final analysis data included 290,047 births (99.5%).

Most women who delivered were 20–29 years old, with Syria and Jordan having the highest prevalence of women under 20 years of age (Table 1). Gaza contributed the most deliveries (48%). Palestinian refugees residing in Jordan, Lebanon, and Syria had lower educational attainments compared to those in West Bank and Gaza (Table 1).

Caesarean-section rates were highest for refugees in Syria (64%), followed by Lebanon (50%), West Bank (30%), and Jordan (28%) (Fig. 1). Gaza had the lowest (22%) (Fig. 1). In all five settings, caesarean-section rates among stillbirths were only slightly lower than among liveborn infants (Jordan liveborn 28% vs stillborn 25%, Lebanon liveborn 50% vs stillborn 44%, Syria liveborn 64% vs stillborn 56%, West Bank liveborn 30% vs stillborn 21%, Gaza liveborn 22% vs stillborn 19%.

Between 2017 and 2020, caesarean-section rates increased by 1% in the West Bank 3% in Jordan, Syria, and Gaza, and 5% in Lebanon, with average annual rates of increase ranging from 0.42% to 1.94%. The largest increase in caesarean-section rates was among nulliparous women (Fig. 2).

Most pregnant women were multiparous, with a singleton pregnancy and cephalic presentation at birth. Preterm births were highest in Syria (15.2%) (Table 1). Appendix S2 includes detailed groups by setting, including total births and caesarean-sections numbers, relative group size, group caesarean-section rates, and absolute and relative contribution to the overall caesarean-section rate. The proportion of group 8 (multiple pregnancy) ranged from 1.2% in Jordan to 1.6% in West Bank (Appendix S2). The size of the multiparous groups (group 3+4 (multip, no prev caesarean-section) and group 5 (multip, term, prev caesarean-section)) was 64% in Jordan, 59% in Lebanon, 56% in Syria, 65% in West Bank, and 67% in Gaza, and reflected the relatively-high fertility rates in these settings (Appendix S2). Appendix S3 includes the quality of the data using 7-groups caesarean section classification.

We also examined the group contributions to the caesarean-section rate by setting. In all five settings, group 5 (multip, term, prev caesarean-section) was the highest contributor to the overall caesarean-section rate (Fig. 3). A sub-analysis on group 5 for parity one is available in Appendix S4. Caesarean-section rates in 1+2 groups (nullip, term), were above weighted WHO guidance of 16% in all setting (See appendix for details of weighting): Syria (65%), Lebanon (46%), Jordan (26%), West Bank (26%) and Gaza (18%) (Fig. 3).

Caesarean-section rates for group groups 3+4 (multip, term, no previous caesarean-section) also exceeded guidance of below 6% (guideline Appendix S1) in Jordan, Lebanon, Syria, and West Bank. Within group 5 (multip, term, previous caesarean-section), women in Lebanon and Syria had rates of 94% or over; other settings were also substantially above the 50–60% guideline (Fig. 3). All five settings had over double the recommended 30% caesarean-section rates within Robson group 10 (preterm) (Fig. 3). In groups 6/9 (nullip, malpresentation) and 7/9 (multip, malpresentation), caesarean-section rates were lower than the expected prevalence of 80–100% in most settings (Fig. 3).

Figure 4 compares trends in refugees to nationals (from 2006–2020) and shows increasing caesarean section rates among both Palestinian refugees and host settings. In Jordan, Lebanon, and Syria, nationals' caesarean-section rates were higher than those of residing Palestinian refugees (Fig. 4). In the West Bank and Gaza, refugees and non-refugees had similar rates.

Table 2 shows reimbursement policies in all five settings, and results of our cost modelling of caesarean-sections that exceed the guidelines.

Discussion

We evaluated Palestinian refugee caesarean-section rates among 290,047 deliveries resulting in live birth or stillbirth from 2017–2020 in five settings. The overall caesarean rate was 28%, with considerable variability by settings. We found: (1) evidence for the need to add missing data elements in UNRWA EMR to be able to implement the ten group classification system (Robson) (2)

Table 1 Characteristics of Palestinian refugee women delivering in the five settings, 2017–2020

Palestinian refugees in	Jordan	Lebanon	Syria	West Bank	Gaza
Number of women delivering	72,472	15,962	15,760	47,446	140,064
Pregnancy outcome, n (%)					
Livebirth	71,979 (99.3)	15,874(99.5)	15,608(99.0)	47,275(99.6)	139,147(99.5)
Stillbirth	389 (0.5)	65(0.4)	136(0.9)	126(0.2)	667(0.5)
Unknown	104 (0.1)	23(0.1)	16(0.1)	45(0.1)	250(0.2)
Maternal age, n (%)					
< 20 years old	6219(8.6)	901(5.6)	1433(9.1)	2329(4.9)	7914(5.7)
20–24 years old	22,977(31.7)	4218(26.4)	4491(28.5)	14,662(30.9)	42,020(30.0)
25–29 years old	20,226(27.9)	5071(31.8)	4044(25.7)	15,796(33.3)	47,075(33.6)
30–34 years old	13,037(18.0)	3444(21.6)	3299(20.9)	8843(18.6)	26,819(19.1)
35–39 years old	7540(10.4)	1834(11.5)	1867(11.8)	4414(9.3)	12,674(9.0)
40–44 years old	2312(3.2)	469(2.9)	590(3.7)	1317(2.8)	3336(2.4)
> 45 years old	158(0.2)	24(0.2)	36(0.2)	82(0.2)	225(0.2)
Missing	3(0.0)	1(0.0)	0(0.0)	3(0.0)	1(0.0)
Education level, n (%)					
Illiterate/Basic	32,869(45.4)	9656(60.5)	10,169(64.5)	9576(20.2)	23,716(16.9)
Secondary	26,866(37.1)	2391(15.0)	2329(14.8)	17,593(37.1)	55,203(39.4)
Diploma	5671(7.8)	1156(7.2)	1162(7.4)	3203(6.8)	7716(5.5)
University/Higher	7066(9.7)	2759(17.3)	2100(13.3)	17,074(36.0)	53,429(38.1)
Parity, n (%)					
Nulliparous	19,386(26.7)	4828(30.2)	4923(31.2)	13,121(27.7)	33,242(23.7)
Multiparous	53,005(73.1)	11,117(69.6)	10,828(68.7)	34,289(72.3)	106,624(76.1)
Missing	81(0.1)	17(0.1)	9(0.1)	36(0.1)	198(0.1)
Previous CS, n (%)					
Nulliparous	19,386 (26.7)	4828 (30.2)	4923 (31.2)	13,121 (27.7)	33,242 (23.7)
No previous CS	39,209 (54.1)	6570 (41.2)	5095 (32.3)	25,201 (53.1)	85,127 (60.8)
Yes previous CS	13,877 (19.1)	4564 (28.6)	5742 (36.4)	9124 (19.2)	21,695 (15.5)
Number of neonates, n (%)					
Singleton	71,608(98.8)	15,715(98.5)	15,521(98.5)	46,664(98.4)	138,007(98.5)
Multiples	864(1.2)	247(1.5)	239(1.5)	782(1.6)	2057(1.5)
Foetal malpresentation, n (%)					
No	71,999(99.3)	15,897(99.6)	15,633(99.2)	46,943(98.9)	136,420(97.4)
Yes	473(0.7)	65(0.4)	127(0.8)	503(1.1)	3644(2.6)
Gestational age at delivery, n (%)					
Preterm	7929(10.9)	2023(12.7)	2400(15.2)	3852(8.1)	12,840(9.2)
Term	64,224(88.6)	13,876(86.9)	13,130(83.3)	42,949(90.5)	127,074(90.7)
Missing	319(0.4)	63(0.4)	230(1.5)	645(1.4)	150(0.1)

high and increasing caesarean section rates (3) caesarean section rates within most groups exceeding guidelines, (4) a built-in momentum caused by high caesarean section rates among nulliparous women, who will likely have subsequent caesareans, (5) a powerful correlation with host country caesarean section rates, which are also increasing, (6) a considerable financial cost associated with potentially unindicated caesarean section, and (7) sub-optimal clinical management.

This study showcases the need to ensure routine EMR capture all the data necessary to fully implement the ten-groups classification system (Robson) as recommended by WHO. Our study was limited by the absence of data elements on onset of labour (spontaneous/induced) or pre-labour caesarean-section and the type of fetal abnormal lie/malpresentation type and so could not benefit from the full extent of Robson group classification, size of the group (for proper quality check) and the WHO recommendation for

Fig. 1 Mode of delivery in each of the five settings where Palestinian refugees reside with absolute contribution of groups to overall caesarean section rate (n = 290,047 births) (2017-2020)

monitoring rates. A direct consequence of our study, is that UNRWA already added the types of presentation and onset of labour variables to its EMR, an example of collaborative research informing practice. A remaining concern however is whether this data will be captured accurately by the recently delivered women's' reports. This is a challenge in EMR that are collected in primary health care facilities on births which occurred elsewhere. One suggestion is that hospitals would provide all ten-group classification systems data elements in the discharge summary sheets linked to reimbursement. The EMR should also capture the number of previous cesarean-section to subdivide analysis in group 5 into group 5.1 (one previous caesarean section) and group 5.2 (the two or more previous caesarean section).

Caesarean-section rates in all five settings (22%-64%) were higher than the rates associated with improvements in maternal or neonatal outcomes or stillbirths (9–19%) [3, 4], suggesting many were not medically indicated. Over a four-year period starting in 2017, caesarean-section rates rose with an average annual increase of 0.4%-1.9%, tracking increases in host countries (average annual increases: 0.6%-1.4%).

Groups with low indication for caesarean-section, specifically the nulliparous women group (1 + 2) and the multiparous women without a previous caesarean-section group (3 + 4), had rates that were higher than WHO guidelines.

The rapid rise in caesarean-section rates over time stems partly from the increase in rates of first caesarean-section among the nulliparous group (group 1 + 2), combined with high fertility, whereby these women go on to have multiple subsequent births. Palestinian refugees have relatively high total fertility rates, around 3.6 births per women in West Bank and Gaza in 2020, 3.3 in Jordan in 2010, 2.7 in Lebanon in 2017, 2.5 in Syria in 2011 [30]. Reflecting this high fertility, the multiparous obstetric population in our study is 69%-76%, a relatively high percentage compared to other countries, and higher than WHO expectations of approximately 58%-65% [31]. High fertility rates, combined with increases in unnecessary caesarean birth among nulliparous women, have a built-in momentum and lead to future increases in caesarean births as these women subsequently enter group 5 (multip, term, prev caesarean-section) who in turn have high caesarean section rates. This group contributed the most to the high caesarean-section rates (8–27%).

Fig. 2 Change in caesarean section rates within caesarean section groups, in the five settings (2017–2020)

Fig. 3 Caesarean-section group rate in five settings ($n = 290{,}047$ births). Shaded areas indicate percent exceeding the recommended guidelines (guidelines defines in Appendix S1)

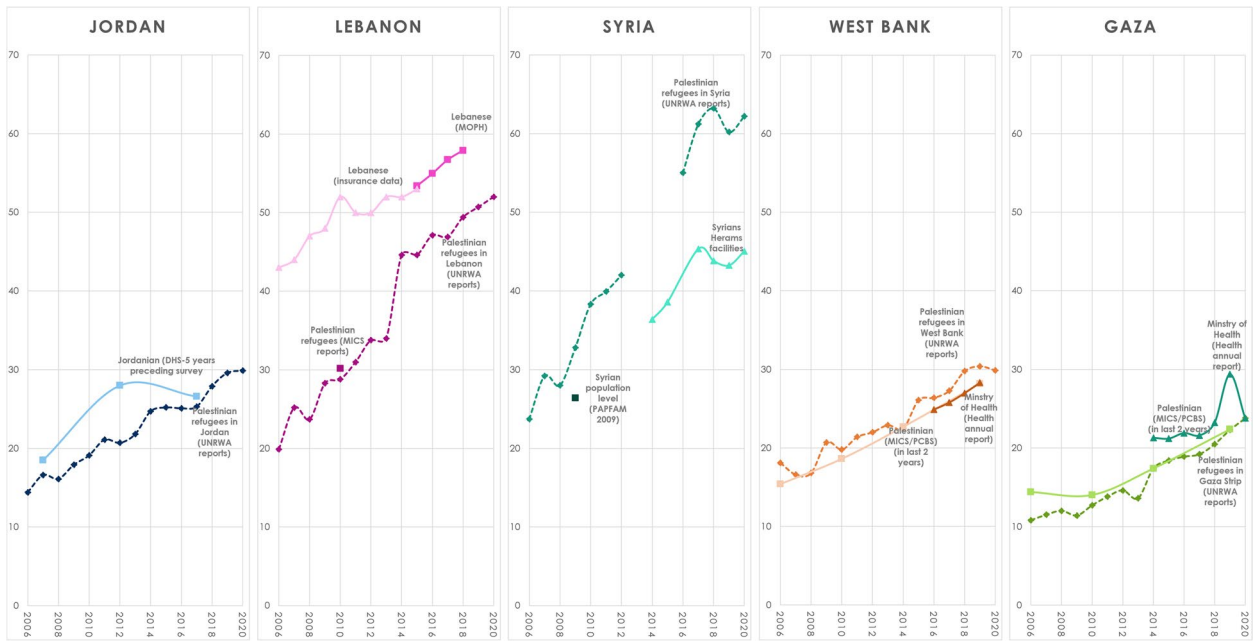

Fig. 4 Caesarean section rates in Jordan, Lebanon, Syria among nationals and refugees and in Palestinian (West Bank and Gaza) among non-refugees and refugees from 2006 till 2020

Table 2 Reimbursement policies and cost of caesarean sections exceeding WHO guidelines. Vaginal and caesarean-section deliveries are covered differently in the five settings as per policies shown in the table below

Average costs paid by UNRWA per patient delivery and current childbirth policy reimbursements by setting					
	Jordan	**Lebanon**	**Syria**	**West Bank**	**Gaza**
Vaginal delivery	Average USD 74 UNRWA covers 75% of the cost up to 100 JOD (equivalent to 140 USD in 2020)	Average USD 230 UNRWA covers 275,000 Lebanese Lira (Equivalent to USD 183 in 2017 and USD 15 in 2020)	Average USD 50 UNRWA covers 75% of the cost	Average USD 150 UNRWA covers 50% of the cost	Average USD 87
Caesarean section delivery	Average USD 300	Average USD 580 UNRWA covers 100% of the cost in Palestinian Red Crescent Society hospitals, 90% in Secondary hospitals, 60% in Tertiary hospitals	Average USD 100 UNRWA covers 75% of the cost	Average USD 510 UNRWA covers 75% of the cost	Average USD 430
SSN/ poor hardship	UNRWA covers 95% of the cost up to 150 JOD (equivalent to 211 USD)		UNRWA covers 95% of the cost	UNRWA covers 90% of the cost	Average 90 USD for vaginal; 445 USD for caesarean

The unit cost for deliveries that UNRWA has agreed with service providers differs according to the contract in place in the five settings. UNRWA only covers deliveries submitted within the Hospitalization Support Program and not all the deliveries recorded in its health centers. Palestinian Refugees might choose alternative solutions (governmental or private insurance scheme where available). Under the assumption that all deliveries would have cost as per UNRWA agreements, a total of USD 52.3 million would have been spent in 2017–2020: USD 20.3 million for vaginal deliveries and almost USD 32 million for caesarean-sections. USD 6.8 million of the latter amount could have been saved had guidance been adhered to (USD 1.9 million by exceeding guidance in group 1 + 2 (nullip, term), almost USD 1.4 million in group 3 + 4 (multip, term, no prev caesarean-section), USD 2 million in group 5 (multip, term, prev caesarean-section), and USD 1.5 million in group 10 (preterm))

The findings from previous studies in Lebanon and Gaza using Robson to classify caesarean-section, are comparable to our results [32, 33]. However, the former analyses were restricted to Lebanese women using a tertiary hospital in Lebanon and Palestinian women in three hospitals in Gaza, while our study is population based [32, 33].

In the Palestinian refugee context, there is an urgent need to develop strategies targeting low-risk women to optimise vaginal delivery and limit an even more rapid

rise in caesarean-section rates, as well as a need to improve quality of care. We use the framework of Betran and colleagues, which identifies interventions and strategies at different levels to discuss potential approaches: namely those linked to national governments and healthcare organizations and those linked to health professionals [17].

Drivers and interventions linked to national systems and healthcare organisations

The high rates and increasing trends in caesarean-section seen in the refugee population do not occur in a vacuum – rather they reflect rates and trends in the national host populations. In West Bank and Gaza, rates among Palestinian refugees and non-refugees are comparable, suggesting there are not major differences in these populations. In Jordan, Lebanon and Syria, the lower rates seen among refugees compared to nationals probably reflect the lower socio-economic status and greater marginalization of refugees, or possibly the rates in the hospitals which UNRWA contracts out.

The high and increasing national trends in all five settings also reflect the structure of national health systems. There are low and declining percentages of births attended by midwives. For example, 23.8% of deliveries in Jordan in the 2012 DHS were with midwives, declining to 10.6% in the 2017–18 DHS. The most recent survey data suggest births attended by doctors (largely obstetricians) are 89.1% in Jordan (2017–18), 86.7% in Lebanon (2011), around 80% in Syria (2009 pre-conflict), 70.8% in West Bank (2019–20) and 87.5% in Gaza (2019–20) [27, 34–36]. The high rates we observed among refugees and Syrians in Syria might stem from the conflict, which reduced access and availability of obstetricians [37], and shifted to delivery by general surgeons, who only conduct caesarean deliveries.

Health systems in the five settings also have substantial and growing doctor-led private sectors (33.4% Jordan (2017–18), 29.1% Lebanon (2011), 46.3% Syria (2009), 46.3% West Bank (2019–20) and 15.7% Gaza (2019–20)) [27, 34–36].Private providers earn more from caesarean deliveries, and find them more manageable to schedule because women expect to be delivered by "their" doctor [38].

Costs associated with unindicated caesarean sections are substantial, particularly in the context of large and ever-growing numbers of refugees and donor fatigue. Unnecessary costs also burden national governments and women and their families, irrespective of refugee/national status.

Our results highlight the need to intervene with a unified national effort/policy to decrease caesarean-section for both refugees and women in the national host settings, particularly where donors do not fund their own services, but rather contract them out to national providers. Refugee agencies, namely UNRWA and UNHCR, may also have opportunities to use their financial clout in contracting and negotiating with hospitals. Strategies proposed in the literature at national level include removing perverse financial incentives or changing the percentage coverage of caesarean-sections to avoid privileging these over vaginal births [17].

Interventions targeting health professionals and facility managers

In addition to the excessive rates within most of the categories which were discussed above, we also found evidence of likely suboptimal clinical decisions by healthcare providers, including high rates of caesarean-section among stillbirths and low rates of vaginal birth after caesarean (VBAC).

There were high, and increasing, caesarean-section rates among stillbirths (19%-56%). This is higher than rates observed in some high income countries (United State of America (15% in 2014)) and low middle income countries (7% in 2015) [39, 40]. Timely emergency caesarean-section is indicated when fetal distress is diagnosed. However unless there is a maternal medical indication, vaginal birth is the recommended mode of delivery when the baby is known to have died in utero [41]. Women's preferences should also be taken into account with a discussion of the risk–benefit balance for subsequent pregnancies after caesarean-section and reassurance of support during vaginal birth including adequate analgesia.

Trial of labour after caesarean (TOLAC) and VBAC are uncommon among Palestinian refugees and in the host countries, where "once a caesarean always a caesarean", is embraced. In our study, 3.2%-30.4% of multiparous women with previous caesarean section had a vaginal birth, and VBAC was particularly low in Lebanon (3.2%) and Syria (5.9%). Some of the benefits of VBAC documented included lower rates of maternal morbidity and mortality and shorter recovery compared to repeated caesarean-sections [42]. Repeated caesarean-sections in the context of high parity pose complications including abnormal placental adherence, bowel, and bladder injury and may require emergency hysterectomy [43], in the index pregnancy [44], and have serious implications for future pregnancies [43].

Both aspects of suboptimal care require support to health providers to improve clinical management. Currently recommended interventions include: educational training, exploring improving adherence to evidence-based practices, caesarean-section decision second opinions policies, clinical audit, and feedback [17]. In terms

of education, addressing safety concerns, misinformation, convenience, and peer group norms among clinicians in the decision-making related to vaginal delivery of stillbirths and to TOLAC and VBAC could help in reducing caesarean-section rates [17]. In different countries, including Lebanon, a policy for a mandatory second opinion along with audit system and feedback has been implemented to reduce unnecessary caesarean-section, including by UNHCR which supports Syrian refugees in Lebanon. This second opinion approach by UNCHR led to a flattening in the rates of caesarean-section increase [45]. In Lebanon, Médecins Sans Frontières provides childbirth services directly, attempting to model more evidence-based, less interventionist childbirth practices via a midwifery-led birthing centre in Lebanon, adjacent to the largest public hospital in Beirut.

The literature also suggests provider feedback, showcasing caesarean-section rates using Robson groups in a standardised, and action-oriented manner helps health professional staff see their institutional rates and could also be used as an audit tool [17]. Facility managers and accrediting bodies can also be approached with such data, as there is evidence that facilities may be encouraging high caesarean-section rates [46].

The conceptual framework we used assessed drivers and interventions at the community/family/woman level and gave options to target women with information to address concerns about safety, misinformation, or mode of delivery choices. Our study did not gather evidence from women or communities, but there is no evidence that substantial proportions of refugee women are requesting unnecessary caesarean-sections; moreover, women are at a relative disadvantage in the power dynamics of decision making vis-à-vis health providers [47]. A recommendation for future research would be to collect data on this dimension of caesarean-section.

Despite most Robson categories having excessive rates, we were surprised to find caesarean-section rates in the malpresentation groups were lower than the Robson guideline. This might be due to misclassification of malpresentation which was captured at the last antenatal visit not labour, or because of our merging of transverse lie with breech.

Conclusion

The most successful caesarean-section reduction strategies are multi-faceted. We show that Palestinian refugees caesarean-section rates in five settings were higher than the recommended levels in the group where caesarean-section is unindicated. The analysis indicates the need to collect further information on malpresentation and induction to conduct the 10 groups caesarean classifications (Robson). Our analysis suggests areas where targeted and tailored strategies can be applied to reduce caesarean-section rates in priority groups (among low-risk women) organized by those aimed at national governments, and UNRWA, and those aimed at health-care providers.

Authors' contributors

OC and AS conceived the study. GP, GB, HA extracted the data. ZJ and HA cleaned the data. ZJ and GP analysed the data, with guidance from OC. ZJ, GP, OC wrote the first draft of the manuscript. LTD supported in interpreting the findings and writing the analysis. All authors read and approved the final version.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12884-022-05264-z.

Additional file 1.

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Author contributions
OC and AS conceived the study. GP, GB, HA extracted the data. ZJ and HA cleaned the data. ZJ and GP analysed the data, with guidance from OC. ZJ, GP, OC wrote the first draft of the manuscript. LTD supported in interpreting the findings and writing the analysis. ZJ prepared the figures and tables. All authors have seen and approved the final version of manuscript.

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Availability of data and materials
Data for this study, including individual participant data and variables in the dataset, may be shared, depending on specific requests. Refugees are in a vulnerable position and their information is highly sensitive. UNRWA, as the main collector of personal data of Palestinian refugees, has a system in place to ensure respect for data protection principles. De-identified participant data, and the statistical analysis plan, may be shared for specific analyses within an agreed-upon collaboration under the terms of a signed access agreement with the two joint senior authors (AS, OC). The request for data will be reviewed by an independent research review board at UNRWA.

Declarations

Ethics statement in the declaration
We extracted anonymized electronic medical records data for pregnancies ending between January 1, 2017, to December 31, 2020. Data analysis was performed in accordance with the ethics guidelines and regulations. UNRWA is the main custodian of the electronic health system and maintains the system following ethical, legal privacy and confidentiality requirements. We obtained ethics approval from UNRWA's research review board and the London School of Health & Tropical Medicine Research Ethics Committee (LSHTM Ethics Ref: 22801) (Date: 12 November 2020). Participant consent was not required as the study used de-identified registry based secondary data. As long as the work does not violate the rights of individuals and does not include identifiable information, UNRWA permit researchers to access EMR without obtaining prior consent from participants to pursue research for the common good of Palestinian refugees. Informed consent was waived by UNRWA's research review board.

Consent for publication
Not applicable.

Competing interests
AS, GP, GB, HA are funded by UNRWA. The other authors (ZJ, LD, OC) declare no competing interests.

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Publisher's Note

Thesis Appendix 4- Example of analysis using the e-health data on effect of conflict exposure on healthcare access

International Maternal Newborn Health Conference

TOGETHER 2023

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

長崎大学 NAGASAKI UNIVERSITY

Effects of Acute Exposure to Conflict Events on Health Service Use and Quality Provided to Palestinian Refugees

Findings from Electronic Health Records in Five Settings

Zeina Jamaluddine, Oona Campbell, Hala Ghattas, Akihiro Seita

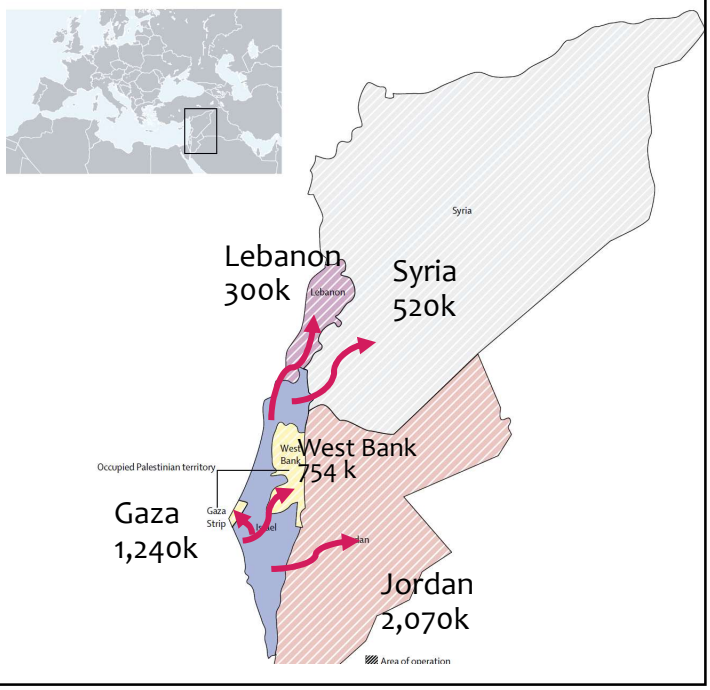
1

Palestinian refugees and UNRWA

1948 Nakba (creation of Israel) led to Palestinian refugees expelled to Jordan, Lebanon, Syria, West Bank and Gaza

United Nations Relief and Works Agency for Palestine Refugees

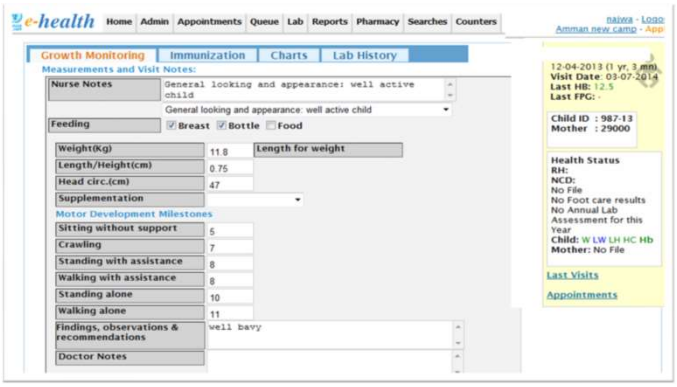
Health, education and social services



2

E-health

140 clinics in 5 settings: Jordan, Lebanon, Syria, West Bank, Gaza



3

The Armed Conflict Location & Event Data Project (ACLED)

Collects real-time data on:

- Locations
- Dates
- Actors
- Fatalities
- Types of all reported political violence and protest events around the world.

4

Rationale, Objectives and Population

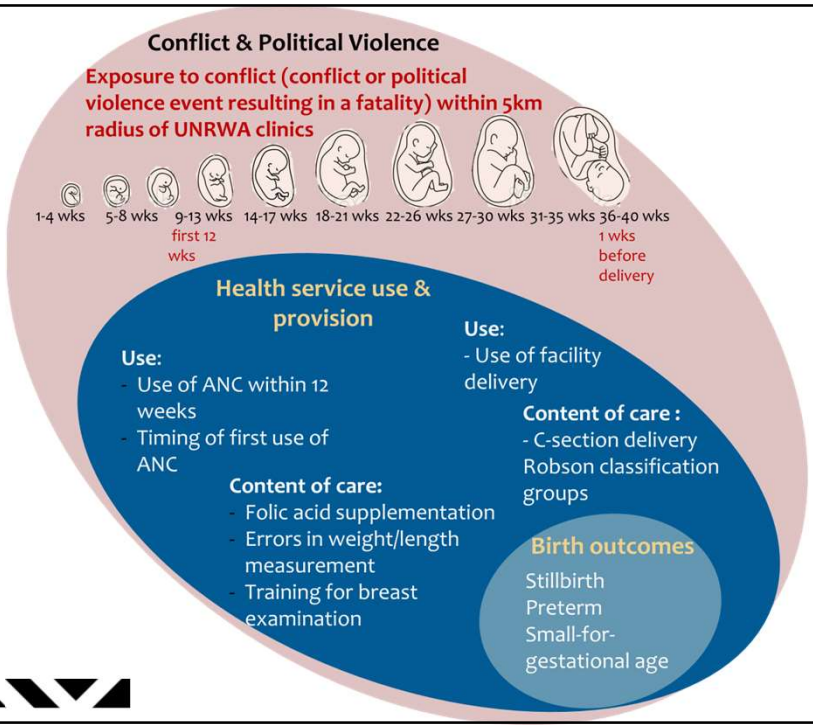
Exposure to violent conflict during pregnancy potentially threatens birth outcomes either directly or through changes in use of services.

Explore the effects of exposure to conflict on:
- Service-use patterns (use and timing of antenatal care and delivery location)
- Content of care (folic acid supplements, training in breast examination, errors in recording of weights and heights, caesarean section)

Among Palestinian refugees living in Jordan, Lebanon, Syria, West Bank and Gaza.
Women delivering 1 Jan 2017 to 31 Dec 2020

5

Our conceptual framework



6

Overlay two datasets

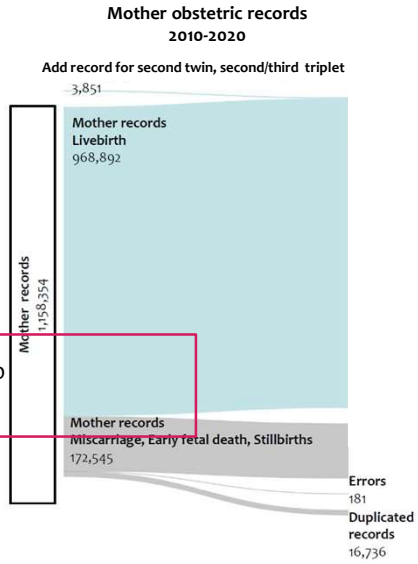
Location of clinic, the timing of pregnancy and birth, service/intervention use, and birth outcomes were obtained for 2017-2020 from UNRWA

Data on location and timing of armed conflict exposure:

- political violence resulting in one or more fatalities
- within 5 km of clinic

ACLED Bringing clarity to crisis

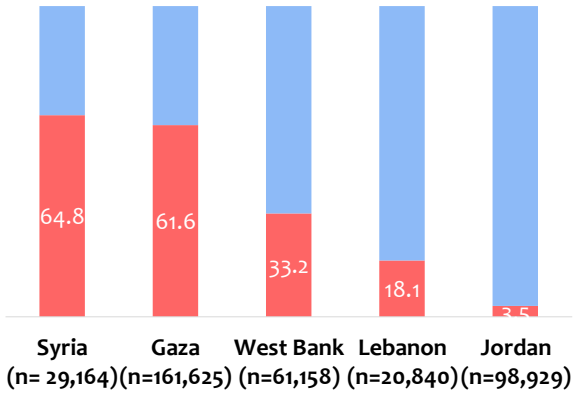
Pregnant records 2017-2020
N= 371,716

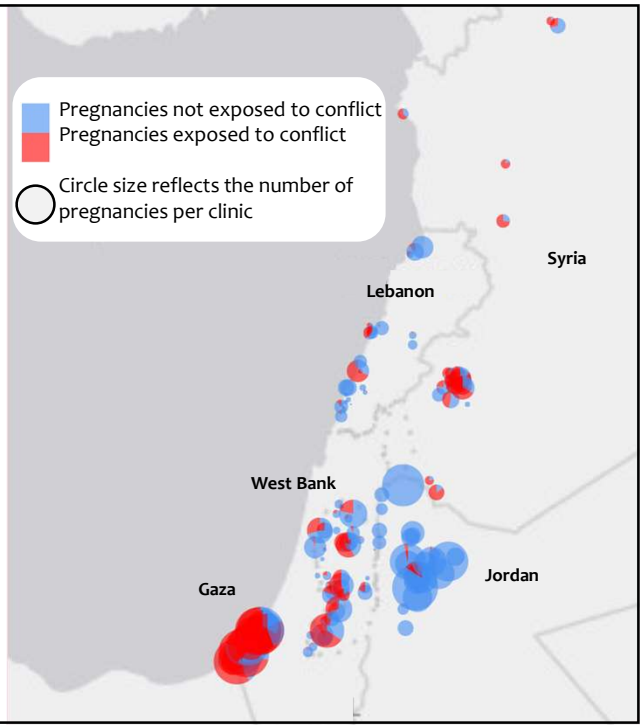


7

Proportions exposed to violence within first 12 weeks of pregnancy

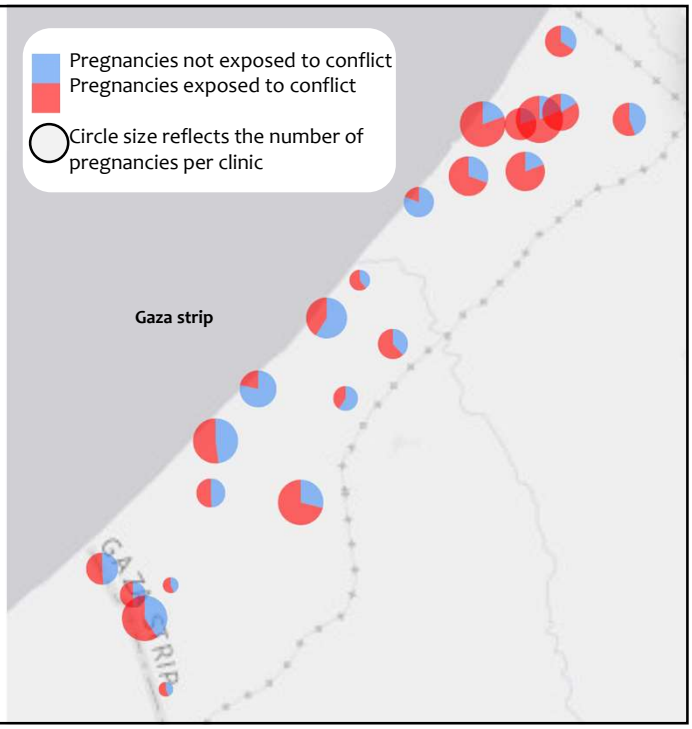
Pregnancies not exposed to conflict
Pregnancies exposed to conflict within 5km radius of the clinic





8

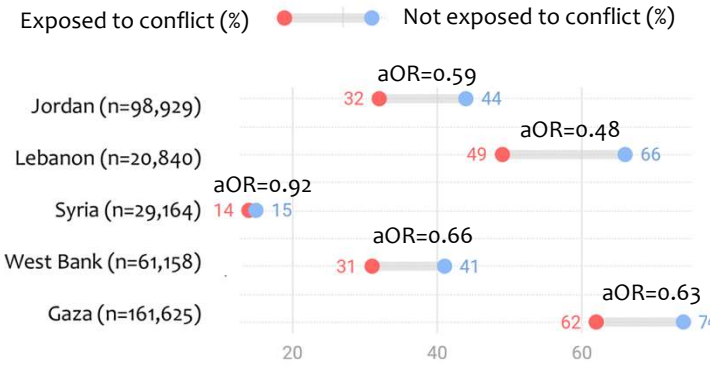
Zooming in: example of exposure in Gaza strip



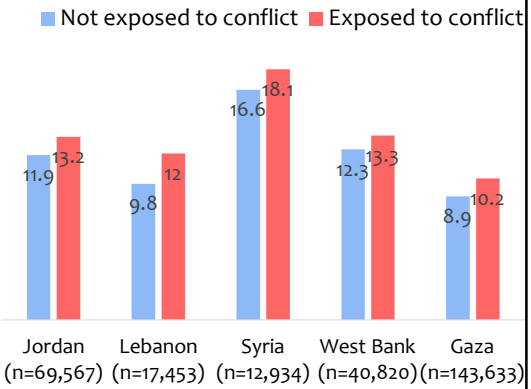
9

Women exposed to conflict during the first 12 weeks were 37% less likely to use UNRWA antenatal care services; timing of use was delayed

Use of UNRWA ANC services



Among those who used ANC, mean weeks of access

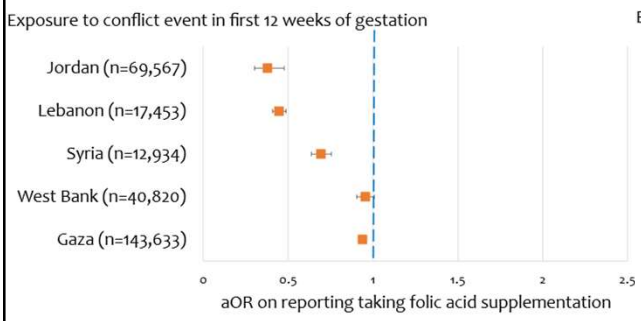


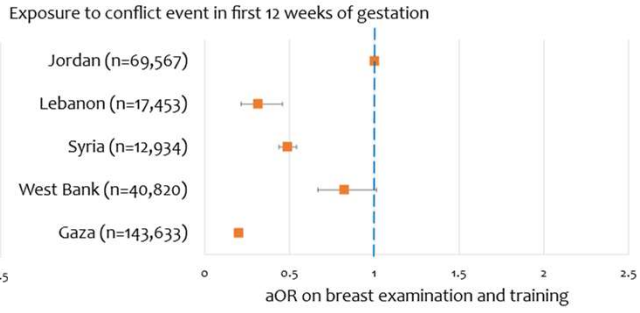
Models adjusted for women's age and education level

10

Women exposed to conflict during the first 12 weeks were

- Less likely to report taking folic acid supplementation aOR=0.88 [0.86-0.90]
- Less likely to have received training on breast examination aOR=0.39 [0.36-0.42]
- Expect for Jordan, no deterioration in recording of measurements





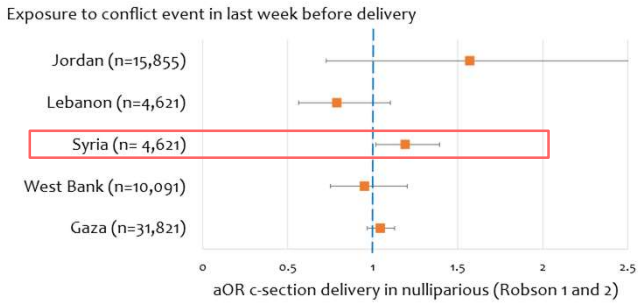
Models adjusted for women's age and education level and parity

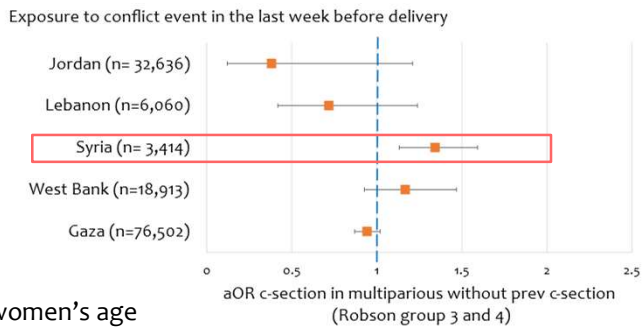
11

Women exposed to conflict during the last week of pregnancy

- No effect on the place of delivery
- No effect on increase overall c-section delivery
- In Syria specifically increased c-sections in groups without indication for c-sections among nulliparous and multiparous women without a previous c-section

"Women would show up and say: 'I want a C-section now because I don't want to stay in hospital […] I am afraid it's going to get attacked, and so why would I sit here in labor for 20 hours and give 20 hours of vulnerability to an attack?'" . Akik Semaan et al 2020





Models adjusted for women's age and education level and parity

12

Work in progress

- Explore exposure in a different way (continuous exposure/ distance/time-varying exposure)
- Mediation analysis: direct effect on birth outcome or indirect effect via service use
- Sensitivity analysis (km of exposure/ date of delivery that might be wrongly recorded)
- Limitation: Unknown if women accessed other services

Conclusion

- Conflict leads to women missing ANC or delaying the first visit
- Appropriate attention given to catchup content
- Post-conflict recovery potentially avoid ever-increasing c-sections. Reverse the rates by increasing VBA, reducing c-section among nulliparous women, retraining
- Prepare support services for women

13

Thank you!

IMNCH 2023 Scholarship
UNRWA clinic doctors, midwives, nurses, staff clerks, and IT team.
UNRWA health department Ghada Ballout, Hussam Al Fudoli, Shatha Albaik, Gloria Paolucci

14