THE RISK OF METABOLIC CONSEQUENCES IN ADULTHOOD FROM RAPID WEIGHT GAIN AND CATCH-UP GROWTH IN THE FIRST TWO YEARS OF LIFE: A SYSTEMATIC REVIEW

A THESIS SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF CLINICAL SCIENCE

NATALIE VAN DER HAAK
BND, BSC (HONS)
JBI
FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF ADELADE

FEBRUARY 2023

Table of Contents

Word count: 26,071

SUMMARY

Infants who experience faltering growth, are born preterm, or small for gestational age, often experience rapid weight gain in infancy. Poor growth during infancy is associated with children who are lighter and shorter later in life and have a lower Intelligence Quotient (IQ) and poorer neurocognitive outcomes. Catch-up growth in infants born small for gestational age is known to prevent gastrointestinal dysfunction, developmental delay, and improves survival rates in infants born preterm. In recent years, more attention has been given to the longer term risks of rapid weight gain in infancy, with studies showing increased rates of overweight and obesity and other metabolic outcomes later in life in infants who experienced rapid weight gain. The aim of this systematic review was to build on existing evidence and provide a more detailed analysis of the relationship between not only rapid weight gain and overweight status in adulthood, but also between changes in weight gain in infancy and adult Body Mass Index (BMI), with weight gain experienced at various time points in the first two years of life, across term, preterm and small for gestational age infants. This review aims to assist clinicians to better determine how to approach the management of infants with poor growth requiring weight gain.

Electronic bibliographic databases and trial registers were searched for all study types investigating infancy weight gain experienced from 0-2 years of age and metabolic outcomes experienced after 18 years of age, with no date or language restrictions. Two independent reviewers conducted the literature search, title, abstract and full text screen, assessed methodological quality using the QUIPS (Quality in Prognosis Studies) tool, and extracted the data using bespoke excel spreadsheets. Synthesis involved pooling for statistical meta-analysis with a random effects model where possible, and a narrative analysis with figures and tables where meta-analysis was not possible.

There were 23 studies with 24,531 subjects identified. Of the 23 studies, 16 reported a significant association between infancy weight gain and BMI or overweight in adulthood. The risk of overweight in adulthood from rapid weight gain experienced at any interval from 0-2 years was significant (pooled OR = 2.59, 95% CI 1.16, 5.75, p = 0.02; low certainty). The risk of overweight in adulthood from rapid weight gain experienced at the interval from

0-6 months was not significant (pooled OR 1.90, 95% CI 0.86, 4.19, p = 0.11; moderate certainty). Of 18 studies exploring the relationship between infancy weight gain and adult BMI, 12 reported a significant positive association. Overall, the weight of evidence supports a positive association between rapid weight gain or change in weight-for-age z-score or standard deviation score in infancy and BMI in adulthood.

This review demonstrates a risk of overweight in adulthood from rapid weight gain experienced in the first two years of life, which is stronger when experienced later in infancy. It is prudent to suggest that healthcare workers focus on modifiable determinants of rapid weight gain, such as promoting breastfeeding, are mindful of unnecessary weight gain in infancy, particularly after the neonatal stage, and educate families on the risks of rapid weight gain in infancy.

ACKNOWLEDGEMENTS

To Professor Zachary Munn, thank you sincerely for your support, guidance, motivation, feedback and input into this review. To Dr Merryn Netting, thank you for your expertise and feedback into this review. To Jana Bednarz, thank you for assistance and determination with statistical analyses, and feedback on this review.

To my secondary reviewers, Kate Wood and Annabel Comerford, thank you for your input into this review, and for taking on the screening, appraisal and extraction tasks with so much energy despite the busyness of your work and personal lives.

To the Women's and Children's Hospital Nutrition Department team, thank you for supporting me to undertake this project in addition to my leadership role, and to take study leave over the project duration.

To Natalie Dempster, thank you for your assistance with the search strategy for this review, and for your support in sourcing journal articles and in using Endnote.

To Cam, thank you for your support, understanding, encouragement and care.

DECLARATION OF ORIGINALITY

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint award of this degree.

I give permission for the digital version of my thesis to be made available on the web, via the University's digital research repository, the Library Search and also through web search engines, unless permission has been granted by the University to restrict access for a period of time.

I acknowledge the support I have received for my research through the provision of an Australian Government Research Training Program Scholarship.

Natalie van der Haak

8th February 2024

LIST OF FIGURES

LIST OF TABLES

LIST OF APPENDICIES

LIST OF ABBREVIATIONS

BMI – Body mass index

CHD – Coronary heart disease

CUG – Catch up growth

CVD – Cardiovascular disease

GRADE – Grading of Recommendations, Assessment, Development and Evaluations

HDL – High density lipoprotein

JBI – Joanna Briggs Institute (Formerly)

OR – Odds ratio

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-analyses

RWG – Rapid weight gain

SD – Standard deviation

SDS – Standard deviation score

WAZ – weight-for-age z-score

CHAPTER 1: INTRODUCTION

INFANT GROWTH

Normal infant growth is characterised by progressive changes in height, weight and head circumferences that are compatible with established standards for a given population, and are dependent on genetic, nutritional and environmental factors.[1]

Failure to thrive or faltering growth refers to infant growth that does not meet these expected growth standards, and results from an imbalance in energy intake versus energy expenditure. This can arise from insufficient calorie intake such as during periods of intercurrent illness, an insufficient intake of calories to meet the increased requirements associated with illness, or insufficient calorie provision by caregivers. Faltering growth can also occur due to a loss of calories through malabsorption associated with a number of medical conditions such as coeliac disease or cystic fibrosis.[2] Faltering growth is a symptom of under nutrition rather than a diagnosis,[2] and there is a lack of consensus in the current literature as to the definition of faltering growth with a number of definitions described (table 1).[3] Children who experience faltering growth in infancy are lighter and shorter[4] and can have a lower IQ[5] than their age matched counterparts.

Children born small for gestational age or preterm have often experienced a period of growth restriction in utero,[6 7] while infants born preterm are at risk of poor growth in the neonatal phase due to difficulties in achieving the same nutrient accretion as would be experienced in utero as a result of the infant's immature digestive system.[8] Infants born small for gestational age or preterm are also more likely to be shorter[9] and thinner later in life,[10] with reduced intellectual capacity[11] and poorer neurodevelopmental outcomes[12] compared to their age matched counterparts. Treatment of poor growth across all infant populations is therefore paramount to promote optimal physical and neurocognitive development.

RAPID WEIGHT GAIN AND CATCH-UP GROWTH

Catch-up growth refers to growth at a rate that is faster and beyond normal expectations for age which occurs after a period of impaired growth (table 1).[13] Children who experience

faltering growth benefit from catch-up growth to prevent the detrimental effects of poor growth such as muscle wasting, infection, gastrointestinal dysfunction, developmental delay, and deficits in cognition and social and emotional competence.[14] In infants born small for gestational age, catch-up growth can prevent deficits in final adult height[9] as well as suboptimal intellectual and psychological performance.[15] In the preterm population, survival rates for extremely low birthweight infants have increased considerably over the past 30 years, with the 50% survival rate standard increasing from 25-26 weeks in the 1990s to 23-24 weeks by the mid-2000s.[16] This is in part due to improved growth in this population, with a landmark study in 2006 demonstrating catch-up weight gain was associated with a significantly reduced occurrence of cerebral and neurodevelopmental impairment.[12]

Table 1: Infant population or growth parameter, definition and prevalence

Population/Growth Parameter	Definition(s)	Prevalence
Faltering Growth	BMI <5th percentile[17] Weight-for-age <3rd or 5th percentile[18] Weight-for-length <10th percentile[18] Weight falling over two or more percentile bands*[17]	5-10% of infants in primary care settings[19] 3-5% of infants and toddlers in hospital settings[20]
Small for Gestational Age	Born at <-2 standard deviations from the mean[21] Weight <10th percentile for age*[22]	27% of all live births in low and middle income countries[22]
Preterm Birth	Birth occurring before 37 weeks of gestation[23]	9.6% globally[23]
Catch-up Growth/ Rapid Weight Gain	Weight gain to above 90th percentile between time points[24] Change in WAZ between time points[25] Increase in WAZ ≥0.67[26]	

Abbreviations: WAZ, weight-for-age z-score; BMI, body mass index

MANAGEMENT OF INFANTS REQUIRING CATCH UP GROWTH

Nutritional intervention is the mainstay in management of infants requiring catch-up growth in the first two years of life, as it is during this period of rapid growth that nutritional intake is the primary determinant of growth.[27] Once a child is over around two years of age, growth hormone and insulin-like growth factor primarily regulate growth, while later pubertal growth is regulated by the sex hormones.[27] Interventions employed to facilitate this catch-up growth in infancy depend on the age of the child, method of feeding and severity of growth impairment. Common interventions can include more frequent breastfeeding and lactation support, formula to supplement breastmilk intake, concentrated formula, with or without the addition of a carbohydrate supplement, and food fortification with energy dense foods.[3]

LATER ADVERSE OUTCOMES OF RAPID WEIGHT GAIN AND CATCH-UP GROWTH

While catch-up growth and achieving an adequate growth rate is recognised as an important determinant of health, recent attention has focussed on the longer term consequences of catch-up growth and rapid weight gain in infancy.[28] While it is widely accepted that lifestyle factors such as smoking, a sedentary lifestyle and a poor diet can contribute to metabolic syndrome (defined by the National Institute of Health as having at least three of the following conditions: central obesity, elevated triglycerides, low HDL cholesterol, hypertension or elevated fasting plasma glucose),[29] a significant body of research supports the role of early life exposures such as birthweight and pre and postnatal nutrition in the aetiology of metabolic syndrome and related disorders. Historical observations, such as the Dutch famine of 1944-1945, led to the epidemiologic observation in the 1970s that children born to mothers who were at early stages of pregnancy during the famine were at a significantly increased risk of cardiometabolic disorders in adulthood.[30]

In 1989, Barker presented evidence from a large scale epidemiological study in England, demonstrating a correlation between low birthweight and risk of CVD in adulthood.[31] This seminal paper challenged the notion at the time that heart disease was primarily linked to adult and lifestyle factors such as diet and exercise. Barker then proposed the “thrifty gene” hypothesis positing that malnutrition during pregnancy resulted in irreversible adaptive

changes in the body's physiology geared towards conserving energy.[32] This would increase the individual's chances of survival in an environment where food availability is limited, but is not well suited to environments where food is in abundance and may therefore increase the risk of metabolic disorders.[32] Barker went on to question whether it was simply low birthweight or poor nutrition in utero that lead to this increased risk of cardiovascular disease (CVD) or whether postnatal growth played a role and in 1999 demonstrated that for every unit increase (kg/m^2) in body mass index (BMI) from birth to 11 years, the hazard ratio for death from coronary heart disease (CHD) increased by 22%.[33] Since then numerous studies have replicated the finding that low birthweight, growth in utero and postnatal growth confer an increased risk for metabolic disease, commonly known as the "Barker Hypothesis" or more recently the "Developmental Origins of Adult Disease" hypothesis.[34]

The association between rapid weight gain in the first year of life and the development of overweight and obesity later in life has now been further established,[35] and it has been reported that those born small for gestational age are at an increased risk for higher fat mass and other metabolic consequences in later childhood and early adulthood.[21] In addition, there are reports of metabolic consequences of rapid weight gain or catch-up growth experienced in infancy such as CVD,[33] hypertension[36] and insulin resistance.[37]

WEIGHT GAIN IN INFANCY VS. LONG TERM ADVERSE HEALTH OUTCOMES

There is a dilemma for health care providers in that for infants with faltering growth and born preterm or small for gestational age, catch-up weight gain and rapid growth may result in both short-term benefits and long-term risks.[38] A study from the United States in 2013[39] showed that in 945 preterm infants born ≤37 weeks with low birthweight ≤2500g, those with a faster BMI z-score gain from 0-4 months were 19% less likely to have an IQ of <85 at 8 years of age, but 36% more likely to be overweight or obese at 8 years of age. It is therefore difficult to determine appropriate growth targets for infants requiring catch-up growth, that balance the metabolic risks of catch-up growth with the physical and neurodevelopmental benefits.

CONTEXT OF REVIEW QUESTION

The scope of this systematic review and meta-analysis is to assess the risk of adverse metabolic outcomes in adulthood from experiencing rapid weight gain in the first two years of life. A search of Medline, Embase, JBI and Cochrane databases in July 2021 did not identify any systematic reviews evaluating all metabolic outcomes. Four systematic reviews exploring the risk of overweight and obesity from rapid weight gain in the first two years of life were identified,[25 40-42] reporting an association between increase in overweight and obesity with rapid weight gain (table 2). Zheng et al.[40] and Ong et al.[41] were the only two studies to conduct a meta-analysis, with both reviews finding a significant association between rapid weight gain in infancy and later overweight and obesity. However, these reviews only included studies addressing the risk of being overweight in adulthood, expressed as odds ratios (OR), and did not include studies that explored the association between rapid weight gain in infancy and BMI in adulthood through regression analyses. Moreover, Zheng et al.[40] only included studies where the exposure of rapid weight gain was defined as a change in weight-for-age z-score of >0.67 (table 2). These reviews also explored the risk of childhood overweight and obesity from rapid weight gain experienced in infancy, however a limitation noted was the use of different criteria for defining childhood overweight and obesity, including the use of the World Health Organisation (WHO) growth standards,[43] International Obesity Task Force criteria[44] and the Centre for Disease Control and Prevention BMI percentile charts.[45] Furthermore, while it is known childhood obesity predicts risk of adulthood obesity, a systematic review highlighted that the relationship between childhood obesity and adulthood obesity is not a direct correlation, in that some children who were obese as adults were not obese as children and vice versa.[46] This review aims to provide an updated analysis on the data for risk of overweight and obesity in adulthood, from rapid weight gain and catch-up growth in infancy, defined by all measures, across those born term, preterm or small for gestational age.

It is hoped that the results of this review will provide clear information to direct practice when managing infants requiring catch-up growth, to achieve the appropriate balance of providing adequate growth in infancy to promote optimal development while also mitigating the risk of long term adverse metabolic outcomes.

Table 2: Existing reviews in the literature on risk of overweight from rapid weight gain in infancy

Author	Year published	Search Conducted	Protocol	Bias assessment	Types of studies	Meta-analysis	Studies included (subjects >18 years)	Comments
Baird	2005	2005	No	Yes	Observational	No	Stettler 2003 Stettler 2005	Did not conduct a meta-analysis
Ong	2006	2006	No	No	Observational	Yes	Stettler 2005 Euser 2005 Ekelund 2006 Stettler 2003 Law 2002 Ezzahir 2005	Included studies with outcomes measured in childhood. Not stratified by overweight risk /high BMI in adulthood
Monteiro	2005	?	No	Yes	Observational	No	Stettler 2003 Law 2002 Ong 2000 Eriksson 2003	Did not conduct a meta-analysis
Zheng	2018	2017	Yes	Yes	Observational	Yes	Demerath 2009 Odegaard 2013 Sutharsan 2015 Salgin 2015	Included only studies that defined rapid weight gain as a change in weight-for-age z-score of >0.67 only

STATEMENT OF REVIEW QUESTION

The specific review question to be addressed is: what is the risk of metabolic outcomes in adulthood for individuals who experienced rapid weight gain or catch-up growth during the first two years of life?

OVERVIEW OF EVIDENCE SYNTHESIS

Evidence-based healthcare has been described as an approach to health-care decision making that considers the feasibility, appropriateness, meaningfulness and effectiveness of healthcare practices that is informed by the best available research evidence, clinical expertise, patient values and preferences.[47] The term evidence-based medicine was first described in the early 1990s by Gordon Guyatt[48] with a key definition provided by David Sackett, who described evidence-based medicine as "the conscientious, explicit and judicious use of current best evidence in making decision about the care of individual patients,"[49] (p.71) calling for a move away from practice that was based on anecdotal experience and dogma.

Since the advent of evidence-based health care over 30 years ago, the publication of systematic reviews has increased. Systematic reviews are a structured way to summarise and synthesise existing literature relevant to a particular health care practice question, and now underpin evidence-based healthcare.[50] Meta-analyses are often included as a way to combine the result of many studies through the quantitative synthesis of primary data to yield an overall result.[51] Ultimately, systematic reviews are the gold standard to search for, collate, critique and summarise the best available evidence regarding a clinical question, with results providing the most valid evidence base to inform the development of trusted guidelines, recommendations and clinical decision making.[52]

The proliferation of published research and systematic reviews, at times of varying quality, has resulted in the development of several approaches to conducting reviews and reporting results. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[53] provides a checklist and guidance on reporting of systematic reviews and includes items such as inclusion and exclusion criteria, data sources, methods to assess risk

of bias and methods used to synthesise and present results. Methodological guidelines such as the Cochrane Handbook for Systematic Reviews of Interventions[54] and the JBI Manual for Evidence Synthesis[50] also exist to guide authors on the methodological conduct of their reviews.

JBI's approach to evidence-based healthcare was first conceptualised in 2005[55] and centres around five components of evidence generation, synthesis, transfer, implementation and global health to facilitate decision making that is informed by best available evidence, delivered contextually and considers client preference and practitioner judgement. Importantly, it is underpinned by accounting for evidence of feasibility, appropriateness, meaningfulness and effectiveness as outlined in figure 1.[47] In the JBI model, evidence synthesis is the evaluation and analysis of research evidence and ultimately collation into guidelines, evidence summaries and systematic reviews to aid decision making in healthcare.[47]

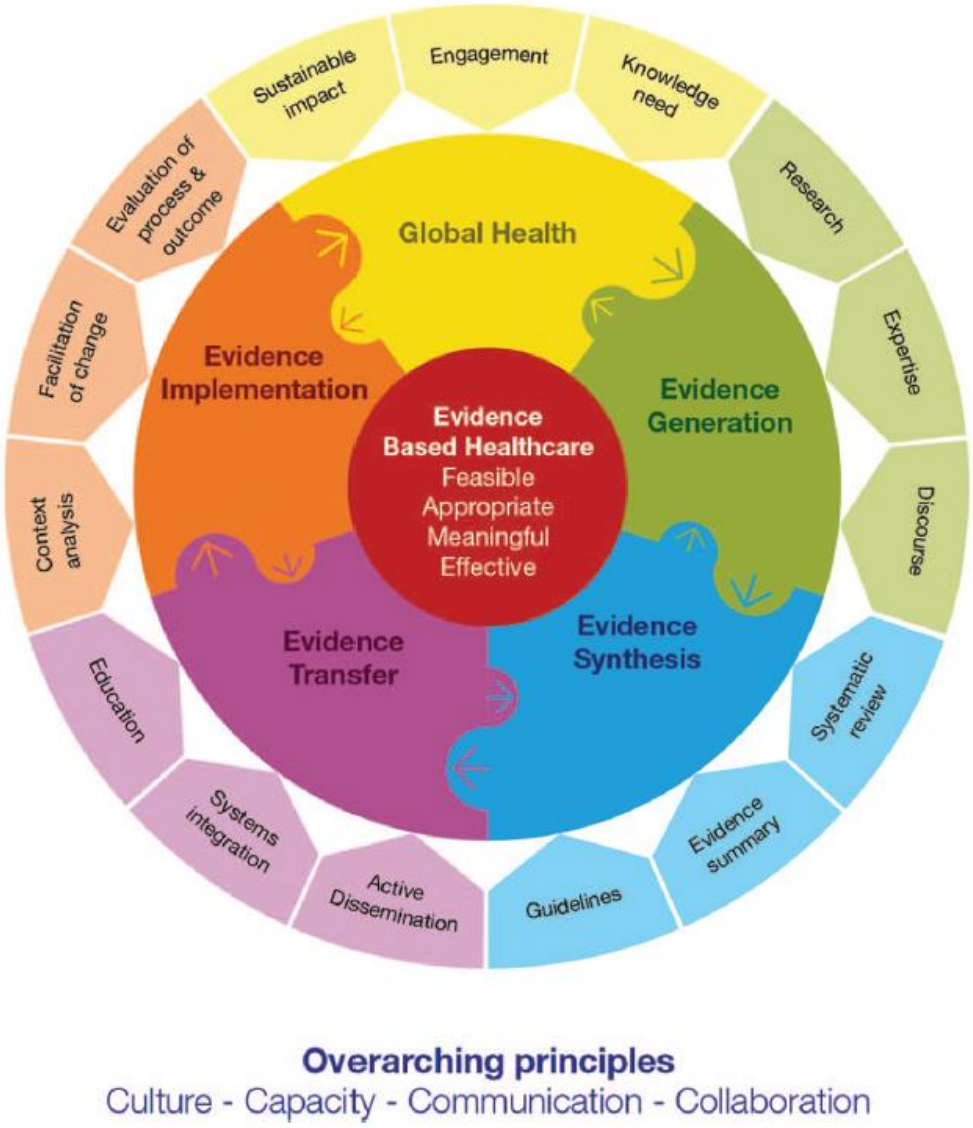


Figure 1: JBI Model of Evidence-Based Healthcare

DISCUSSION OF METHODOLOGICAL APPROACH TAKEN

The systematic review process is part of the evidence synthesis component of the JBI model and involves the evaluation, analysis and collation of research evidence.[47] In the JBI model, an *a priori* protocol must precede the review and predefine the methods of the systematic review. Any deviations from this should be discussed in the report. The systematic review should have an explicit and clear statement of the review question which specifies the focus of the review, the types of participants, interventions and comparators, and outcomes

considered. The review should provide clear inclusion and exclusion criteria and an explicit search strategy detailing all information sources searched and strategies for searching. The review requires independent dual reviewer title, abstract and full text screening, followed by dual reviewer quality appraisal of the studies using an appropriate tool, and finally data extraction. Statistical analysis should include meta-analyses where possible, otherwise narrative synthesis should be used. Statistical analyses should be appropriate, with details of statistical models, methods and effect estimates described and measures of statistical heterogeneity included. Reporting should follow PRISMA guidelines and the review should include a GRADE (Grading of Recommendations, Assessment, Development and Evaluations) summary of findings table of evidence to establish certainty in the evidence.[50]

CHAPTER 2: METHODS

The systematic review protocol was registered with PROSPERO (CRD42021274696). A protocol for this systematic review was published prior to commencement.[56] Prior to undertaking the review, the protocol was amended to include outcomes experienced only at age 18 or older (appendix 1). Deviations from this protocol are outlined in appendix 2.

STUDY TYPES

This review considered both experimental and quasi-experimental study designs including randomized controlled trials, non-randomized controlled trials, before and after studies and interrupted time-series studies. In addition, analytical observational studies including prospective and retrospective cohort studies, case-control studies and analytical cross-sectional studies were considered for inclusion. No language limits were applied. No date limits were stipulated in this review.

INCLUSION AND EXCLUSION CRITERIA

Participants

This review considered studies that included participants 18 years and older who experienced any type of rapid weight gain or catch-up growth in the first two years of life. Studies that included infants with a specific medical condition known to impair growth including but not limited to kidney disease, cardiac disease and coeliac disease were excluded.

EXPOSURE

For the purposes of this review, catch-up growth and rapid weight gain were defined as a change in weight above what is normally expected for age, including but not limited to an increase in weight-for-age z-score (WAZ) or weight-for-age standard deviation score (SDS) of ≥0.67, and studies that measured the relationship between change in weight in the first two years of life and later metabolic outcomes were included.

OUTCOMES

This review screened studies that assessed metabolic outcomes experienced at 18 years of age or later, including but not limited to:

- Overweight - measured by a body mass index (BMI) score ≥25kg/m^2
- Body Mass Index
- Hypertension – measured by blood pressure
- Hyperlipidemia – measured by serum cholesterol and triglycerides
- Cardiovascular disease – measured by presence of Coronary Heart Disease
- Type 2 diabetes and Insulin Resistance – measured by blood glucose levels
- Body composition – as measured by waist circumference, percentage fat mass, abdominal fat distribution and/or visceral adiposity

This review did not include studies that investigate non-metabolic outcomes including but not limited to cancer, type 1 diabetes mellitus, asthma and cognitive ability.

SEARCH STRATEGY

The search strategy was initially developed using the key terms or concepts of the review question in a logic grid.[57] An initial limited search of Medline and Embase was undertaken to identify articles on this topic, followed by analysis of the text words contained in the titles and abstracts, and of the index terms used to describe these articles. This informed the development of a search strategy including identified keywords and index terms which were tailored for each information source. The reference list of all studies considered for this review was screened for additional studies. The full search strategy is detailed in appendix 3. The search strategy aimed to find both published and unpublished studies.

Search terms used included:

- Infant* or toddler* or child* or babies or small for gestational age or neonat* or preterm or newborn*
- faltering growth or failure to thrive or malnourish* or intrauterine growth restriction or IUGR
- ((rapid* or catchup or catch-up or accelerat* or velocit* or fast or faster) adj6 (weight or growth or adipos*))

- (metaboli* or obesity or overweight or adiposity or blood pressure or hypertensi* or hyperlipidemia or type 2 diabetes or cvd or coronary heart disease or body composition or body mass index or percentage mass fat or abdominal fat distribution

Information Sources

The Ovid platform was used to conduct the literature search. The databases and trial registers searched included the following as suggested in the Cochrane Handbook for Systematic Reviews of Interventions: [54 58]

- Databases - Medline and Embase
- Trial Registers - Cochrane register of controlled trials

The systematic review was conducted in accordance with JBI methodology and the methodology for reviews of prognostic factors.[59]

STUDY SELECTION

Following the search, all identified citations were collated and uploaded into Endnote and duplicates removed. Titles and abstracts were screened by the main author and an independent reviewer for assessment against the inclusion criteria for the review. Studies that met the inclusion criteria were retrieved in full and their details imported into the Covidence Systematic Review Management software.[60] The full text of selected citations were retrieved and assessed in detail against the inclusion criteria by the main author and an independent reviewer. Full text studies that did not meet the inclusion criteria were excluded and reasons for exclusion are provided in table 3. The results of the search are presented in the PRISMA flow diagram (figure 2).

CRITICAL APPRAISAL

All included studies were critically appraised by the main author and an independent reviewer (AC or KW) at the study level for methodological quality using the Quality in Prognosis Studies (QUIPS) tool,[61] which asks questions related to study participation, attrition, prognostic factor and outcome measurements, confounders and statistical analysis, to assess the risk of bias as high, moderate or low for each issue. Prompts and

considerations listed in each domain allow the reviewer to determine a risk level for each domain. For example, in the study participation domain, a study would be considered as having a high risk of bias if the participation rate is low and the study sample has a different age and sex distribution from the source population.[61] Disagreements in assessments of level of risk within each domain were resolved through discussion and with a third reviewer (ZM) where required. The results of critical appraisal are reported in both narrative and tabular form (table 4).

DATA EXTRACTION

All studies, regardless of their methodological quality, underwent data extraction by two independent reviewers (KW and AC) using a bespoke excel spreadsheet. Data extracted included specific details about the exposures, populations, study methods and outcomes of significance to the review question and specific objectives. Any uncertainty with data extraction was discussed with a third reviewer (ZM). Direct contact with authors was sought for clarity regarding data as required.

DATA SYNTHESIS

Where appropriate, studies were pooled in statistical meta-analysis using Cochrane's Review Manager (RevMan 5.4). Effect sizes are expressed as odd ratios (for dichotomous outcomes) and 95% confidence intervals. For data that were combined, heterogeneity was assessed statistically using the standard chi squared and I^2 tests. Heterogeneity was classified as not important, moderate, substantial or considerable according to the criteria outlined in Dettori et al., 2021.[62] Statistical analysis were performed using a random effects model as per the guidance by Tufanaru et al., 2015.[63]

It was planned that a funnel plot would be generated using RevMan 5.4 to assess publication bias however there were no outcomes for which 10 or more studies were pooled. Similarly, statistical tests for funnel plot asymmetry (e.g. Egger's test, Begg's test, Harbord test) were not performed. Subgroup analyses were conducted where there were sufficient data to investigate the population and timing of exposure, including small for gestational age or preterm infants and rapid weight gain experienced at 0-3 months, 3-6

months, 0-6 months, 0-1 year, 0-2 years and 1-2 years. Studies were also stratified by age at outcome 18 to <30 years or ≥30 years of age. Where statistical pooling was not possible the findings were presented in narrative form including tables and figures to aid in data presentation where appropriate. Sensitivity analyses were conducted to determine the impact of decisions made by the authors, including the pooling of data that measured the exposure at different ages and the combining of adjusted estimates that had adjusted for different variables.

Results from studies that reported regression coefficients with a corresponding 95% confidence interval or standard error, that described the relationship between infancy weight gain and adult BMI, were summarised graphically in an albatross plot using the *albatross* add on in Stata 18 (StataCorp. 2023. *Stata Statistical Software: Release 18*. College Station, TX: StataCorp LLC.). The formula from Altman and Bland was used to derive *p* values if these were not reported.[64] Where results were reported separately for independent subgroups (e.g. for boys and girls separately), a combined effect estimate was calculated using the methods described by Nieminen.[65] Studies included in the albatross plot were categorised according to the measure of infancy weight gain used (rapid weight gain and change in WAZ/SDS) and are labelled in the plot by solid and hollow dots, respectively.

ASSESSING CERTAINTY IN THE FINDINGS

A 'Summary of Findings' table using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach for grading the quality of evidence for prognostic factors[66] was developed using GRADEPro GDT 2023 (McMaster University and Evidence Prime).

CHAPTER 3: RESULTS

This chapter presents the findings of the systematic review and results of meta-analyses conducted. In line with the study protocol and JBI methodology,[67] the search strategy and details, study selection process, critical appraisal, meta-analyses, albatross plot and the Summary of Findings table are presented below.

DESCRIPTION OF SEARCH STRATEGY AND STUDY SELECTION

After completion of the literature search in December 2022, 15,215 records were identified. After removal of 4,571 duplicates, the remaining 10,644 records were screened by title and abstract. Of these, 10,556 were excluded for not meeting the inclusion criteria and 78 articles were selected for full text screening. After full text review, 23 studies satisfied inclusion and exclusion criteria and proceeded to critical appraisal. No studies were excluded after critical appraisal. Reasons for exclusion after full text review are included below in the PRISMA diagram (figure 2) and in table 3.

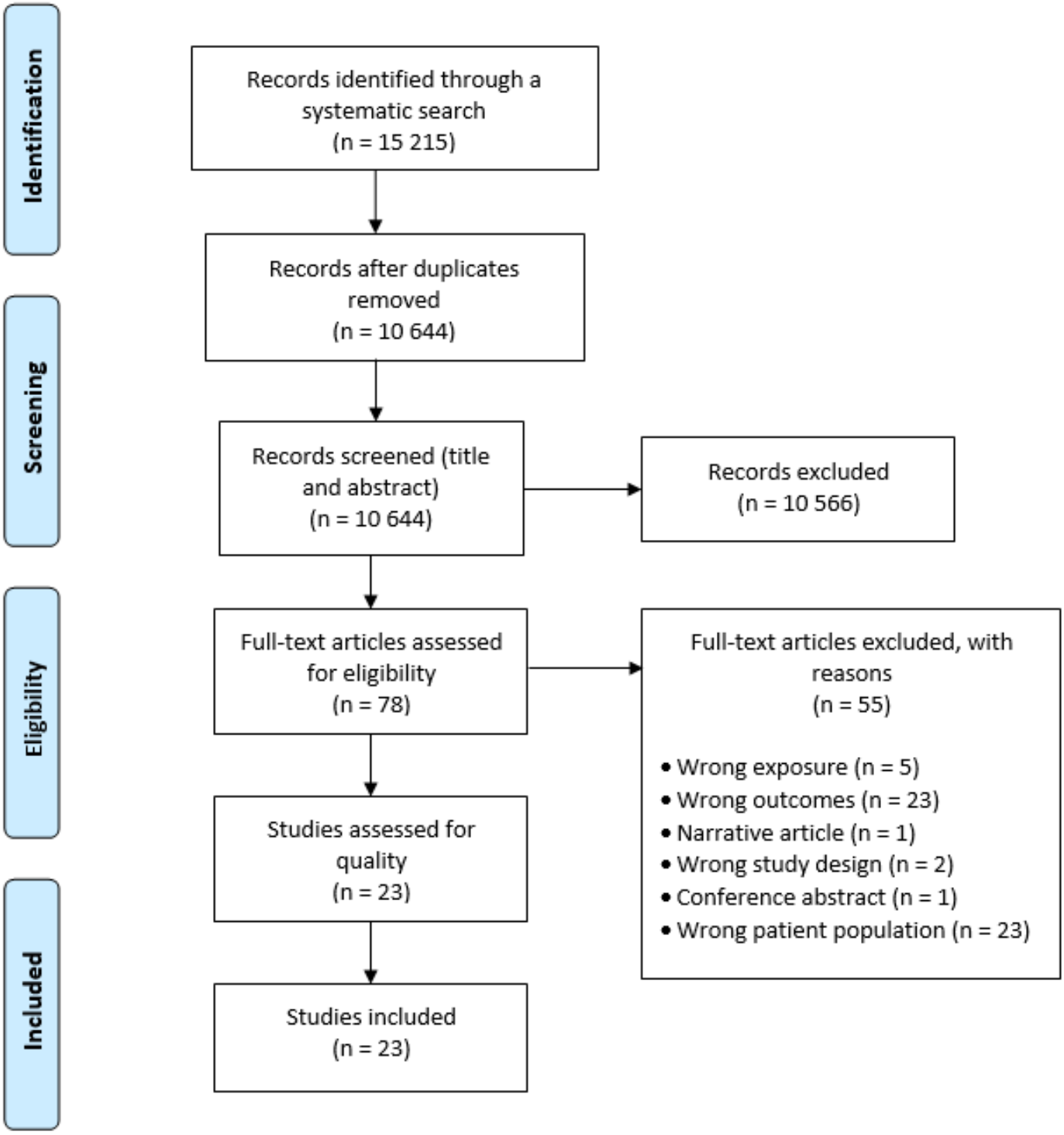


Figure 2: PRISMA Flow Diagram

DESCRIPTION OF INCLUDED STUDIES

The 23 studies included in this review were conducted across 13 countries; America,[68-72] Australia,[73] Belgium,[74] Brazil,[75 76] Denmark,[77] England,[78 79] Finland,[80 81] France,[82] Germany,[83] Japan,[84] The Netherlands,[85-88] South Africa,[89] and Wales.[90] Eleven studies were prospective cohort studies,[68-71 73 76 79 81-83 89] eight studies were a retrospective analyses of a prospective birth cohort[72 74 75 77 78 80 87 90] and four studies were retrospective cohort studies.[84-86 88] The total number of subjects with data on infancy weight gain and adult BMI was 24,531. The earliest study was published in 2002[78] and the latest in 2021.[79] The patient population age at outcome ranged between 18 and 46 years. A description of each study can be found in appendix 4 and information on each study can be found in the summary table of included studies in appendix 5.

The exposure of rapid weight gain was measured by an increase in weight-for-age/length z-score or SDS of ≥0.67 in seven studies,[68-71 73 85 86 88] change in weight-for-age or SDS in seven studies,[68-71 73 85 86 88] conditional weight gain (current weight and length accounting for previous weights and lengths) in three studies,[68 76 78] change in BMI z-score in one study,[80] increase in WAZ of >1 SD in one study,[71] increase in BMI SDS >1 in one study,[83] increase in BMI SDS >0.3 in one study,[82] peak weight velocity in one study[81] and a spline model of an increase above normal expectations converted to a z-score in one study.[90] Rapid weight gain was assessed by weight measurements taken at either birth for birthweight and clinic visits for weights taken between birth and two years in 14 studies,[68-73 75 80 82 83 85-88 90] at home or clinic visits in two studies,[77 79] home visits in three studies,[76 89 90] and existing records in four studies.[74 78 81 84] Infancy weight gain was assessed at a total of 28 time points (appendix 5).

The outcome of overweight was measured by BMI ≥ 25kg/m^2 in six studies,[68-73] and BMI >30kg/m^2 in one study.[80] BMI in adulthood was assessed as a continuous variable 16 studies,[74-79 81-90] and was measured as kg/m^2 in six studies,[75 78 79 81 84 90] SDS in six studies[76 77 82 83 87 89] and log transformed in four studies.[74 85 86 88] BMI was assessed by weight measurements taken in adulthood in follow up clinic visits in 17 studies,[68-72 74 79 81-90] home visits in two studies,[75 76] self-reported in three studies[72 77 80] and unclear in one study.[78] Overweight was measured between 18 to <30 years in 19 studies,[68 70-76 78 79 82-90] and ≥30 years of age in four studies[69 77 80 81] (appendix 5).

DESCRIPTION OF EXCLUDED STUDIES

55 studies were excluded after full text review. Details of the excluded studies are recorded in table 3.

Table 3: Excluded studies and reasons for exclusion

Author	Year	Reason for exclusion
Adair	2007	Wrong exposure
Adair	2009	Wrong outcomes
Anonymous	1999	Wrong study design
AraujodeFranca	2016	Wrong outcomes
Arroyo	2022	Wrong outcomes
Barker	2002	Wrong patient population
Barker	2002[a]	Wrong patient outcomes
Barker	2005	Wrong patient population
Beardsall	2009	Wrong patient population
Belsky	2012	Wrong patient population
Ben-Schlomo	2008	Wrong outcomes
Berkey	2017	Wrong patient population
Bjerregaard	2021	Conference abstract
Ceelen	2009	Wrong patient population
Cheng	2015	Wrong outcomes
Chomtho	2008	Wrong patient population
Das	2020	Wrong patient population
Davies	1972	Wrong outcomes
East	2020	Wrong outcomes
Ekelund	2007	Wrong outcomes
Eriksson	2001	Wrong patient population
Eriksson	2000	Wrong patient population
Eriksson	2002	Wrong patient population
Eriksson	2001[a]	Wrong outcomes
Eriksson	2015	Wrong exposure
Eriksson	1999	Wrong patient population
Eriksson	2006	Wrong outcomes
Fall	2008	Wrong outcomes
Fahraeus	2012	Wrong exposure
Ferguson	2017	Wrong outcomes
Finken	2006	Wrong outcomes
Forsen	1999	Wrong patient population
Goedegebuure	2022	Wrong exposure
Hollanders	2017	Wrong study design
Howe	2014	Wrong outcomes
Huang	2015	Wrong patient population
Jarvelin	2004	Wrong outcomes
Kerkhof	2012	Wrong outcomes
Kerkhof	2012[a]	Wrong outcomes
Leunissen	2012	Wrong patient population
Leunissen	2009	Wrong patient population
Lyons-Reid	2021	Narrative article

Meas	2008	Wrong exposure
Meer	2022	Wrong patient population
Nyati	2021	Wrong patient population
Ni	2020	Wrong patient population
Norris	2012	Wrong patient population
Olaiya	2020	Wrong patient population
Sabo	2017	Wrong patient population
Tarik	2019	Wrong outcomes
Tu	2013	Wrong outcomes
Tu	2010	Wrong outcomes
Thompson	2022	Wrong patient population
vanderSteen	2017	Wrong patient population
Workman	2015	Wrong outcomes

METHODOLOGICAL QUALITY OF INCLUDED STUDIES

The risk of bias assessment was conducted for the 23 included cohort studies. No studies were excluded based on their risk of bias score. A risk of bias assessment is presented in table 4 and the summary of findings table (table 5).

The overall risk of bias was determined as follows; low risk – all six domains scoring a low rating; moderate risk – one or more domains scoring a moderate rating and no domains scoring a high rating; and high risk – one or more domains scoring a high rating. Overall studies varied in scoring, with no studies returning an overall risk of bias score of “low”, 17 studies returning an overall risk of bias score of moderate[68-72 75-77 79 82-88 90] and six studies returning an overall risk of bias score of “high”.[73 74 78 80 81 89]

Table 4: Risk of bias assessment

	Study Participation	Study Attrition	Prognostic Factor Measurement	Outcome Measurement	Study Confounding	Statistical Analysis and Reporting	Overall risk
Adair 2013	Low	Moderate	Low	Low	Low	Low	Moderate
Bjerregaard 2014	Low	Moderate	Low	Moderate	Low	Low	Moderate
Breij 2014	Low	Moderate	Low	Moderate	Low	Low	Moderate
Breij 2015	Moderate	Moderate	Moderate	Low	Moderate	Low	Moderate
Buffarini 2018	Moderate	Moderate	Moderate	Low	Low	Low	Moderate
Demerath 2009	Moderate	Low	Low	Low	Low	Low	Moderate
Euser 2005	Low	Low	Low	Low	Moderate	Low	Moderate
Eriksson 2003	Low	Low	Moderate	High	Moderate	Low	High
Ezzahir 2005	Low	Moderate	Low	Low	Moderate	Low	Moderate
Law 2002	Low	Moderate	Moderate	Moderate	High	Moderate	High
Leunissen 2009	Low	Moderate	Moderate	Low	Moderate	Low	Moderate
McCarthy 2007	Low	Moderate	Low	Low	Moderate	Low	Moderate
Ni 2021	Low	Moderate	Moderate	Low	Low	Low	Moderate
Odegaard 2013	Low	Low	Moderate	Moderate	Low	Low	Moderate
Oyama 2010	Moderate	Moderate	Moderate	Low	Moderate	Low	Moderate
Rzehak 2017	Low	Moderate	Moderate	Moderate	Moderate	Low	Moderate
Salgin 2015	Moderate	High	Moderate	Low	Moderate	High	High
Stettler 2003	Low	Moderate	Low	Low	Low	Low	Moderate
Stettler 2005	Moderate	Moderate	Moderate	Moderate	Moderate	Low	Moderate
Sutharsan 2015	Low	High	Moderate	Low	Low	Low	High
Touwslager 2013	Moderate	High	High	Low	Moderate	Low	High
Tzoulaki 2010	Moderate	Moderate	High	Low	Low	Low	High
Victora 2007	Low	Moderate	Moderate	Low	Low	Low	Moderate

Table 5: Summary of Findings: Rapid weight gain compared to no rapid weight gain in infancy for risk of overweight in adulthood

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With no rapid weight gain	With rapid weight gain	Relative effect (95% CI)	Risk with no rapid weight gain	Risk difference with rapid weight gain
Overweight (RWG at any interval from 0-2 years) (assessed with: BMI ≥ 25kg/m^2)											
3032 (4 observational studies)	serious[a]	not serious[b]	not serious[c]	serious[d]	none	⨁⨁◯◯ Low	2031/3032 (67.0%)[i]	Not reported	**OR 2.59** (1.16 to 5.75)	670 per 1,000	**170 more per 1,000** (from 32 more to 251 more)
Overweight (RWG at interval from 0-2 years) (assessed with: BMI ≥ 25kg/m^2)											
655 (2 observational studies)	not serious[e]	not serious[b]	not serious[c]	serious[d]	none	⨁⨁⨁◯ Moderate	439/655 (67.0%)[i]	Not reported	**OR 3.03** (1.16 to 7.89)	670 per 1,000	**190 more per 1,000** (from 32 more to 271 more)
Overweight (RWG at interval from 0-6 months) (assessed with: BMI ≥ 25kg/m^2)											
2799 (3 observational studies)	serious[f]	serious[g]	not serious[c]	serious[h]	none	⨁◯◯◯ Very low	1875.33/2799 (67.0%)[1]	Not reported	**OR 1.90** (0.86 to 4.19)	670 per 1,000	**124 more per 1,000** (from 34 fewer to 225 more)

CI: confidence interval; **OR:** odds ratio; **RWG. rapid weight gain; BMI, body mass index**

Explanations

a. Risk of bias assessed using QUIPS tool. Of the four studies, three scored an overall ROB of moderate and 1 scored and overall ROB of high
b. Two studies have wide point estimates however CIs mostly overlap. Small number of studies
c. All studies include subjects from relevant populations
d. CIs do not cross the line of no effect, however, are wide and likely across important decision-making thresholds
e. Risk of bias in two studies moderate
f. One study scored a ROB of high, one study scored a ROB of moderate
g. Some CIs do not overlap. Small number of studies
h. CIs include null effect
i. Calculated on rates of overweight and obesity in the Australian general population[91]

FINDINGS OF THE REVIEW

Overall, 23 studies were included in this review[68-90] with 16 [68-72 75-78 81-83 86 87 89 90] reporting a significant positive association between infancy weight gain and BMI or overweight in adulthood. Six studies[73 74 79 84 85 88] reported a positive but not significant association, and one study did not report an effect.[80] A positive association refers to infancy weight gain being associated with an increase in BMI or overweight in adulthood while a negative association refers to infancy weight gain being associated with a decrease in BMI or no overweight in adulthood.

Results are described below by outcome, exposure type, timing of exposure, population, gender, feeding type and age. The exposure measurements were divided into two categories; rapid weight gain (includes increase in weight-for-age/length or BMI SDS ≥0.67, conditional weight gain, change in BMI SDS>0.3, peak weight velocity and spline model) and change in weight-for-age z-score or standard deviation score (expressed as change in WAZ/SDS). The rapid weight gain category includes all definitions that measure an *increase* in weight gain above normal expectations for age between time points while the change in weight-for-age z-score category includes definitions that measure the *change* in weight between time points.

OVERWEIGHT

Six studies[68-73] reported an OR for the outcome of overweight based on infancy weight gain with a total of 5,248 patients. Five of these studies[68-72] reported a significant association between infancy weight gain and overweight in adulthood and one reported a positive but not significant association.[73]

Exposure – rapid weight gain

Four studies[69-71 73] explored overweight in adulthood associated with rapid weight gain vs. no rapid weight gain in infancy in a combined total of 3,032 subjects. A pooled random effects model indicated an increased risk of overweight in adulthood with rapid weight gain relative to no rapid weight gain at any time point interval from 0-2 years (pooled OR = 2.59, 95% CI 1.16, 5.75, p = 0.02), however there was substantial heterogeneity between studies,

with a $T^2 = 0.49$, $I^2 = 81\%$, chi-squared test p = 0.001) (figure 3). One of the studies included in this meta-analysis[71] included on outcome of overweight-overfat defined as a BMI of ≥25kg/m^2 and a sum of skin folds thickness of ≥85th percentile rather than BMI alone as used in the other three studies. The authors were contacted to determine the number of subjects with a BMI of ≥25kg/m^2 not included in this category however no response was received. The risk of overweight remained positive but was no longer significant when this study was removed in a sensitivity analysis (pooled OR 2.02, 95% CI 0.93, 4.36, p=0.07) (appendix 6).

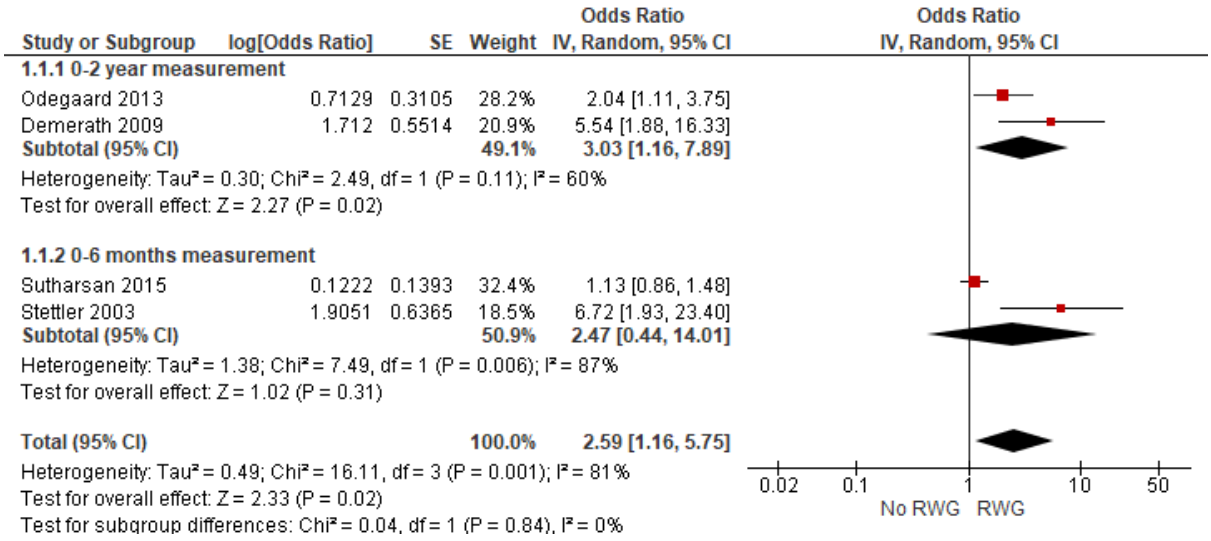


Figure 3: Forest plot for risk of overweight in adulthood after experiencing rapid weight gain in infancy

A sensitivity analysis was conducted for adjustment of birthweight (appendix 6). All studies included adjusted for other important variables such as maternal age, maternal BMI, adult age and gestational age. Sensitivity analyses were not conducted for breastfeeding or formula use, as two or fewer studies included in the meta-analysis adjusted for these variables. Appendix 7 shows which variables were adjusted for in each study. When adjusting for birthweight, rapid weight gain in infancy was significantly associated with an increased risk of overweight in adulthood (OR = 3.69, 95% CI 1.63, 8.34, p = 0.002). Compared to the main result, the effect size of the association is increased, and the association remains significant.

Adair et al[68] explored overweight in adulthood in 2,710 subjects based on an exposure of rapid weight gain in infancy defined by a conditional weight gain which corresponded to a

change in WAZ of slightly less than 0.67SD and found that for every 1SD increase in conditional relative weight gain at the interval from 0-2 years there was an increased risk of overweight (OR 1.51, 95% CI 1.43, 1.60). This study was not pooled in the meta-analysis as the effect estimate was expressed as an increase in SD.

The study by Odegaard[70] presented ORs for overweight status in adulthood at 23 time point intervals between 0-24 months. The OR was positive and significant at nine time points (table 6).

Table 6: Findings of Odegaard et al[70]

Age	OR (95% CI)
0-1	1.07 (0.27-4.25)
0-3	1.69 (0.84-3.41)
0-6	0.91 (0.84-3.41)
0-9	0.91 (0.5-1.68)
0-12	1.60 (0.9-2.84)
0-18	1.54 (0.88-2.71)
0-24	2.04 (1.11-3.74)*
1-3	NA
1-6	1.88 (0.93-3.77)
1-9	1.46 (0.82-2.58)
1-12	1.97 (1.12-3.46)*
1-18	1.55 (0.89-2.68)
1-24	1.8 (1.02-3.18)*
3-6	2.20 (1.12-4.33)*
3-9	1.59 (0.91-2.79)
3-12	1.65 (0.91-3.00)
3-18	2.01 (1.12-3.60)*
3-24	1.77 (1.04-3.04)*
6-9	4.71 (1.86-11.94)*
6-12	1.78 (1.03-3.11)*
6-18	2.15 (1.26-3.69)*
6-24	1.59 (0.91-2.78)
12-24	2.45 (0.53-11.27)

Abbreviations: OR, odds ratio
* significant association

Exposure – change in WAZ/SDS

One study[72] reported that change in WAZ from birth to 112 days was associated with overweight in adulthood (OR 1.41, 95% CI 1.09, 1.82).

Timing of exposure

The relationship between infancy weight gain and overweight in adulthood was measured across two main time point intervals: 0-2 years and 0-6 months. The data are presented below for the intervals that were measured in multiple studies. For the time point intervals only measured in one study, Odegaard et al,[70] the data are presented in table 6.

0-2 years

Exposure - rapid weight gain

Three studies[68-70] looked at rapid weight gain at the interval from 0-2 years. Two[69 70] were pooled and found rapid weight gain was significantly associated with an increased risk of overweight in adulthood (OR 3.03, 95% CI 1.16, 7.89, p = 0.02). There was substantial heterogeneity withT^2 = 0.3, I^2 = 60%, chi-squared test p = 0.11) (figure 3). The third study by Adair et al[68] has been described above.

Exposure – change in WAZ/SDS

No studies

0-6 months

Exposure - rapid weight gain

Odegaard et al[70] also reported an ORs for risk of overweight from rapid weight gain experienced at the interval from 0-6 months. The study by Stettler 2003[71] reported an OR for rapid weight gain experienced at the interval from 0-4 months. These were combined in a separate meta-analysis with the study by Suthersan[73] which also reported an OR for risk of overweight from rapid weight gain experienced at the interval from 0-6 months. This meta-analysis showed rapid weight gain at the interval from 0-6 months was not significantly associated with an increased risk of overweight in adulthood in 2,799 subjects (pooled OR 1.90, 95% CI 0.86, 4.19, p = 0.11) (figure 4). There was substantial heterogeneity with T^2 = 0.35, I^2 = 76%, chi-squared test p = 0.02).

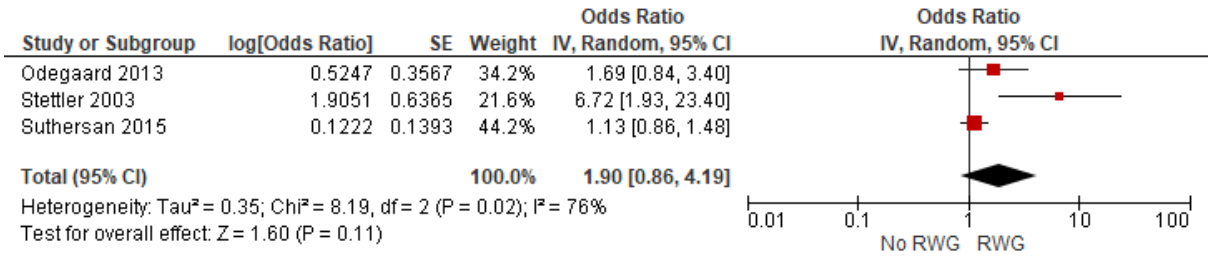


Figure 4: Forest plot for risk of overweight in adulthood after experiencing rapid weight gain at the interval from 0-6 months

Exposure – change in WAZ/SDS

One study[72] found that change in WAZ from birth to 112 days was associated with overweight in adulthood (OR 1.41, 95%FI 1.09, 1.82).

BMI

18 studies explored the relationship between infancy weight gain in the first two years of life and adult BMI,[69 74-90] with 12 finding a significant positive association between infancy weight gain and adult BMI[69 75-78 81-83 86 87 89 90] at one or more time point intervals between 0-2 years of life. Five studies[74 79 84 85 88] reported a positive but not significant association between infancy weight gain and adult BMI at one or more time point intervals between 0-2 years (table 7). One study did not report an effect.[80] 12 studies reported regression coefficients and three studies reported correlation coefficients.[78 82 84] One study performed logistic regression but not did not report any effects,[80] one study conducted an equality of means test and reported a *p* value[83] and one study conducted an ANOVA and reported a *p* value.[89] A meta-analysis of coefficients was not able to be conducted due to significant heterogeneity across the studies. Rapid weight gain was measured at several different time point intervals from 0-2 years, BMI was expressed as SDS, log transformed, or as kg/m^2, and the effect estimate was standardised or unstandardised, without sufficient consistency to combine any of the data to conduct a meta-analysis. Instead, data are presented in an albatross plot (figure 5) and grouped by age at exposure and discussed narratively.

Figure 5 is an albatross plot for the relationship between infancy weight gain and adult BMI, with contours for the approximate effect size, using data from 13 studies.[69 74-79 84-88 90] The effect size represents the number of standard deviation changes in the outcome (adult BMI)

for a standard deviation increase in the exposure (rapid weight gain or change in WAZ/SDS). The scatterplot shows a noticeable trend, with majority of data points showing a positive effect size, therefore suggesting a positive association between infancy weight gain and BMI in adulthood.

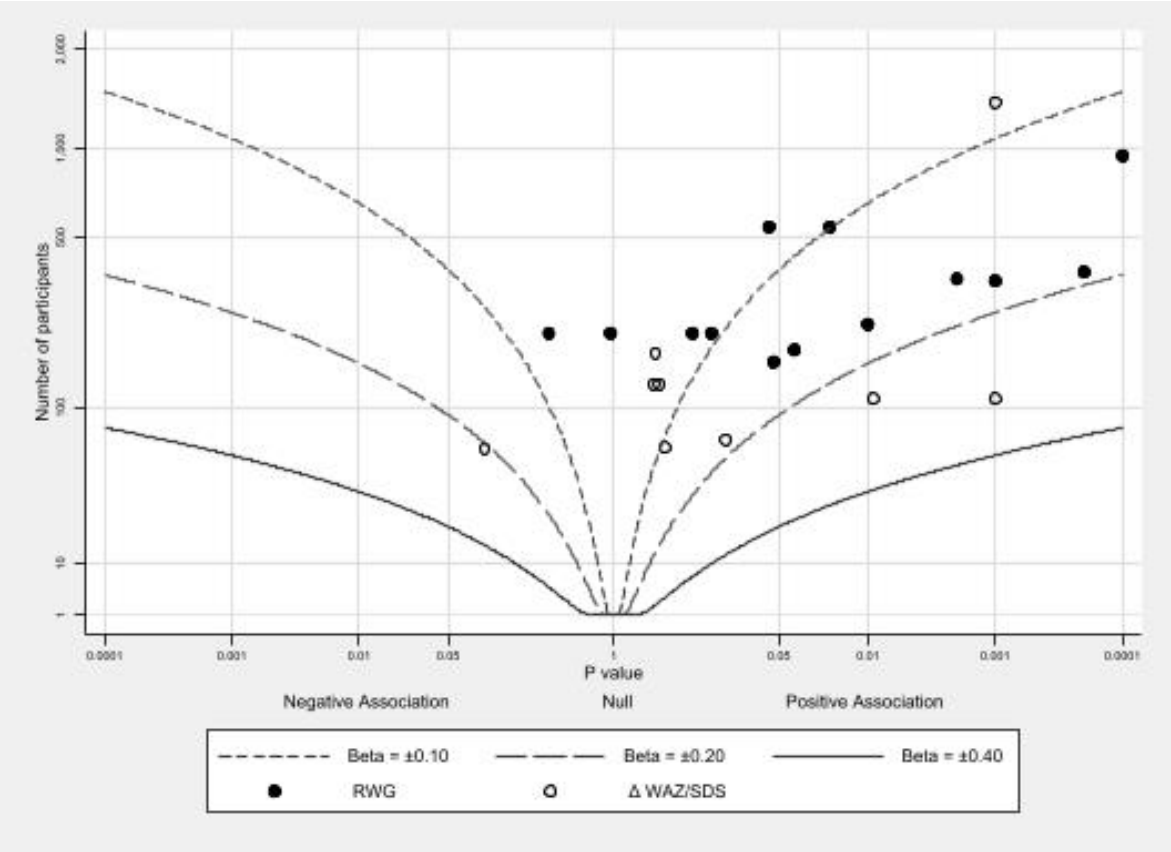


Figure 5: Albatross plot of relationship between rapid weight gain and change in WAZ/SDS and BMI in adulthood

Table 7 shows the data for exposure time points, effect size estimate and category of exposure for studies reporting on the relationship between infancy weight gain and BMI in adulthood. Four studies[80 82 83 89] are not included in table 7 as they did not report a standardized regression coefficient or Pearson's correlation coefficient as the effect estimate. The results and details of these studies can be found in the summary table of excluded studies (Appendix 5). The study by Salgin et al[89] investigated the difference in BMI SDS in adulthood between infants who experienced rapid weight gain (increase in weight-for-age SDS >0.67), catch down and no change, with an ANOVA finding that compared to catch down and no change, rapid weight gain was significantly associated with BMI SDS at

age 18 (BMI SDS 0.12, SD 1.24, p<0.001). In the study by Rzehak et al,[83] an equality of means test across BMI SDS trajectory classes found that infants who experienced rapid weight gain at the interval from 0-2 years were more likely to be overweight at 20 years of age than those with normal infant growth (BMI 25.92kg/m2 vs. 22.37kg/m2, p,0.0001). In the study by Ezzahir et al[82] a Spearman's correlation found rapid weight gain at the interval from 0-1 year as defined by a change in BMI SDS of >0.3 was not associated with adult BMI SDS (rho=-0.02, p=0.65). This relationship at the interval from 0-2 years, however, was significant (rho=0.34, p=0.04). In the study by Erriskon[80] data were only presented in visual format with no numerical estimates presented.

Table 7: Exposure time points, effect size estimate and exposure category for studies reporting on BMI

Study (author year)	Exposure time point	Exposure Category (Δ WAZ/SDS OR > expected)	Sample_size	*P*-value	Beta/correlation coefficient	Confidence interval/ standard error
Bjerregaard 2014*[74]	0-3m	Δ WAZ/SDS	1390	**0.001**	0.09	0.04 to 0.15
Breij 2014*[83]	0-3m	RWG	182	**0.038**	2.358	Not reported
Breij 2015*[82]	0-3m	RWG	162	0.055	3.54	Not reported
Buffarini 2018*[76]	0-1yr	RWG	946	**0.0001**	0.26	0.19 to 0.32
Demerath 2009*[66]	0-2yr	RWG	233	**0.01**	1.43	0.42 (SE)
Euser 2005*[84]	0-3m	Δ WAZ/SDS	373	**0.0002**	0.196	0.092 to 0.300
Euser 2005*[84]	>3m-1yr	Δ WAZ/SDS	351	**0.002**	0.215	0.078 to 0.356
Law 2002*[75]	0-1yr	RWG	346	**0.001**	0.22	Not reported
Leunissen 2009*[85]	0-3m	RWG	214	0.17	0.014	-0.006 to 0.035
Leunissen 2009*[85]	>3-6m	RWG	214	0.31	-0.021	-0.060 to 0.019
Leunissen 2009*[85]	>6-9m	RWG	214	0.24	0.033	-0.023 to 0.089
Leunissen 2009*[85]	>9-12m	RWG	214	0.95	-0.002	-0.062 to 0.058
McCarthy 2007*[87]	0-5m	RWG	542	**0.02**	0.42	0.07 to 0.77
McCarthy 2007*[87]	>5-20m	RWG	542	0.06	0.38	-0.01 to 0.77
Ni 2021*[76]	0-2.5yr	Δ WAZ/SDS	129	0.482	0.18	-0.33 to 0.69
Ni 2021*[76]	Birth – term age	Δ WAZ/SDS	129	0.438	0.3	-0.46 to 1.06
Oyama 2010*[81]	0-3m	Δ WAZ/SDS	69	0.132	0.18	Not reported
Oyama 2010*[81]	3-6m	Δ WAZ/SDS	62	0.097	-0.21	Not reported
Oyama 2010*[81]	6m-1.5yr	Δ WAZ/SDS	63	0.397	0.11	Not reported
Touwslwager 2013*[71]	1-6m	Δ WAZ/SDS	176	0.47	0.01	Not reported
Tzoulaki 2010[78]	0-2yr	RWG	3763	**0.0001**	0.68	0.39 to 0.97
Victora 2006*[75]	0-1yr	Δ WAZ/SDS	110	**0.001**	0.63	0.18 (SE)
Victora 2006*[75]	1-2yr	Δ WAZ/SDS	110	**0.009**	0.71	0.27 (SE)

*data included in albatross plot

Abbreviations: **Δ** WAZ, change in weight-for-age z-score; SDS, standard deviation score; RWG, rapid weight gain, SE; standard error

P-values <0.05 in bold

Exposure – rapid weight gain

11 studies[69 76 78 81-83 85 86 88-90] explored the relationship between weight gain in infancy and adult BMI. Of these, nine[69 76 78 81-83 86 89 90] found a significant positive association for at least one time point, while two studies found a positive but not significant association for at least one time point.[88 92] Results for eight[69 76 78 81 85 86 88 90] of these studies and associated time points are shown in table 7 and figure 5.

Exposure – change in WAZ/SDS

Seven studies[74 75 77 79 80 84 87] explored the relationship between change in WAZ/SDS and BMI. Of these, three showed a significant positive association[75 77 87], three showed a positive but not significant association for at least one time point measured[74 79 84] and one did not report an effect[80] (table 7).

Timing of exposure

The relationship between infancy weight gain and adult BMI was measured across 14 time points. The data is presented below for the time points that included multiple studies. For the time points only relevant to one study, the data is presented in table 7.

0-3 months

Five studies investigated infancy weight gain occurring at the interval from 0-3 months and the effect on adult BMI.[77 85-88] All five studies reported a positive association between infancy weight gain in the first 3 month of life and BMI in adulthood, with this being significant in three studies[77 86 87] (table 7).

Exposure – rapid weight gain

Three studies[85 86 88] investigated the relationship between rapid weight gain at the interval from 0-3 months and adult BMI with all three reporting a positive association. This was significant in one study[86] (table 7).

Exposure – change in WAZ/SDS

Two studies[77 87] investigated the relationship between change in WAZ/SDS at the interval from 0-3 months and adult BMI with both reporting a significant positive association (table 7).

3-6 months

Two studies[84 88] explored infancy weight gain occurring from 3-6 months and the effect on adult BMI. Both studies reported a negative association however this was not significant in either study (table 7).

Exposure – rapid weight gain

One study[88] explored rapid weight gain occurring from 3-6 months and the effect on adult BMI and found a negative association however this was not significant (table 7).

Exposure – change in WAZ/SDS

One study[84] explored the relationship between change in WAZ/SDS from 3-6 months rapid weight gain occurring from 3-6 months and the effect on adult BMI and found a negative association however this was not significant (table 7).

0-1 year

Six studies[75 76 78 80 82 89] explored infancy weight gain at the interval from 0-1 year and the effect on adult BMI. Four studies[75 76 78 89] reported a significant positive association between rapid weight gain occurring at the interval from 0-1 year and BMI in adulthood (table 7). One study reported BMI catch-up at the interval from 0-1 year was not associated with adult BMI (p=0.65).[82] One study did not report an effect.[80]

Exposure – rapid weight gain

Four studies[76 78 82 89] explored rapid weight gain at the interval from 0-1 year and the effect on adult BMI. Three studies[76 78 89] found a significant positive association (table 7).

Exposure – change in WAZ/SDS

Two studies[75 80] investigated change in WAZ/SDS at the interval from 0-12 months and the effect on adult BMI. One study[75] found a significant positive association (table 7). One study[80] did not report an effect.

0-2 years

Five studies[69 79 81-83] examined infancy weight gain at the interval from 0-2 years and the effect on adult BMI. This includes the study by Ni[79] where the exposure was measured at 2.5 years. Four studies[69 81-83] reported a significant positive association between rapid weight gain occurring at the interval from 0-2 years and BMI in adulthood (table 7).

Exposure – rapid weight gain

Four studies[69 81-83] examined rapid weight gain at the interval from 0-2 years and the effect on adult BMI. All four studies[69 81-83] reported a significant positive association between rapid weight gain at the interval from 0-2 years and BMI in adulthood (table 7).

Exposure – change in WAZ/SDS

One study[79] examined change in WAZ/SDS from 0-2.5 years and found a positive but not significant association with adult BMI (table 7).

1-2 years

Two studies[74 75] explored infancy weight gain from 1-2 years and the effect on adult BMI. Both studies reported a positive association however this was only significant in one study[75] (table 7).

Exposure – rapid weight gain

No studies

Exposure – change in WAZ/SDS

Two studies[74 75] explored change in WAZ/SDS from 1-2 years and the effect on adult BMI. Both studies reported a positive association however this was only significant in one study[75] (table 7).

PRETERM

Three studies[79 85 87] looked at infancy weight gain in preterm infants. These were unable to be combined for meta-analysis due to heterogeneity across studies in terms of timing of exposure, exposure and outcome. One study[79] assessed the effect of change in WAZ from birth to term age on adult BMI and found a positive but not significant association. The other two studies[85 87] found a positive association between rapid weight gain measured as an increase in WAZ of >0.5[85] and change in WAZ[87] experienced from birth to 3 months after term age on adult BMI however this was only significant in one study[87]. Data are presented in table 7.

SMALL FOR GESTATIONAL AGE

Three studies investigated rapid weight gain occurring in infants born small for gestational age[82 86 88] with two studies[82 86] reporting a significant positive association between rapid weight gain and BMI in adulthood (table 7).

0-3 months

Two studies[86 88] explored the effect of rapid weight gain occurring at the interval from 0-3 months on BMI in adulthood in infants born small for gestational age with both studies finding a positive association, however this was only significant in one study[86] (table 7).

3-6 months

One study investigated the effect of rapid weight gain occurring from 3-6 months of age on BMI in adulthood in subjects born small for gestational age[88] and found a negative association however this was not significant.

0-1 year

One study[82] investigated the effect of rapid weight gain occurring at the interval from 0-1 year in small for gestational age infants and did not find a significant association between change in BMI SDS >0.3 and adult BMI SDS (rho=-0.02, p=0.65).

0-2 years

One study[82] investigated the effect of rapid weight gain occurring at the interval from 0-2 years and found a significant positive association between change in BMI SDS >0.3 and adult BMI SDS (rho=0.34, p=0.04).

GENDER

Buffarini[76] explored the impact of rapid weight gain measured as conditional weight gain at the interval from 0-12 months on adult BMI stratified by gender. There was a significant positive association in both males (β = 0.26, 95% CI 0.18, 0.34) and females (β = 0.25, 95% CI 0.15, 0.35). One study included males only[75] and found no significant association with adult BMI and change in WAZ at the interval from 0-1 (p = 0.001) and 1-2 (p = 0.009) years of age. One study included females only[84] and found that change in WAZ at multiple time points in infancy was not significantly associated with adult BMI (table 7).

BOTTLE FED

One study[72] included formula fed infants only. This study found that change in WAZ in the first four months of life was associated with a significantly increased risk of being overweight in adulthood (OR 1.41, 95% CI 1.09, 1.82).

AGE AT OUTCOME

≥30 years of age

Four studies[69 77 80 81] measured the outcome of overweight or BMI at a mean age of ≥30 years. Three studies reported a significant positive association between infancy weight gain and adult BMI[77 81 69] (table 7 and figure 5). One study did not report an effect.[80]

18 to <30 years of age

19 studies[68 70-76 78 79 82-90] measured the outcome of overweight or BMI in adulthood at a mean age of 18 to < 30 years. All but six studies[73 74 79 84 85 88] reported a significant positive association between infancy weight gain and adult overweight or BMI. Of these six studies, all reported a positive but not significant association for at least one time point.

CHAPTER 4: DISCUSSION

The importance of weight gain and catch-up growth to optimise infant growth and development is well documented,[14] however in recent times there has been a question around the potential longer term adverse effects of this including the risk of overweight and obesity.[28] Overweight is a growing problem in the developing world, with WHO global data in 2016 estimating that 39% of adults aged 18 years and over were overweight, with the worldwide prevalence of obesity tripling since 1975.[93] Epidemiologic studies have demonstrated an association between high BMI and many chronic diseases such as non-alcoholic fatty liver disease, CVD, diabetes mellitus, several malignancies, musculoskeletal diseases, kidney disease and disorders of mental health.[94] Overweight and obesity is a complex and multifactorial condition, with genetic, behavioural, socioeconomic and environmental origins.[95] This systematic review and meta-analysis identified 23 studies exploring the impact of weight gain in infancy on risk of overweight or association with BMI in adulthood, and is the second quantitative analysis of systematically identified studies of rapid weight gain and subsequent obesity risk in adulthood. Overall, there was evidence to suggest a relationship between weight gain experienced in infancy and increased risk of overweight or association with BMI in adulthood, however, several studies were too heterogenous in nature to facilitate meta-analysis including all studies. Limitations of the review, implications of the results for practice and implications and scope for further research will be discussed.

SUMMARY OF MAIN RESULTS

Of the 23 studies included in this review, six did not report a significant association between infancy weight gain and adult overweight or BMI,[73 74 79 84 85 88] with one study not reporting an effect.[80] These six studies did not appear to differ significantly from the studies reporting a significant association, with four studies having a moderate risk of bias[84 79 85 88] and two studies having a high risk of bias,[73 74] similar proportions to the studies that did show an association. Two of these studies included infancy weights sought from existing medical records[74 84], with two other studies also using existing records[78 81] showing a significant positive association. One of these studies[84] also had the smallest sample size with only 86

participants. Two of the six studies that did not report a significant association were conducted in preterm infants.[79 85]

OVERWEIGHT

Six studies[68-73] explored infancy weight gain in the first 2 years of life and impact on adulthood overweight, with only one study finding no significant association.[73] This study had a high risk of bias, had outcome data available for only 56% of participants, and analysis was based on rapid weight gain occurring at the interval from 0-6 months.

In the four studies combined in a meta-analysis in this review, infants with rapid weight gain measured at any time point interval in the first two years of life had 2.59 times higher odds of being overweight in adulthood than those who did not experience rapid weight gain (pooled OR 2.59, 95% CI 1.16, 5.75, p = 0.02). When stratifying by age at exposure timing, infants who experienced rapid weight gain measured only at the interval from 0-2 years had higher odds of overweight (pooled OR 3.03, 95% CI 1.16, 7.89, p = 0.02), compared to when rapid weight gain was assessed only at the interval from 0-6 months of age, where it was not significantly associated with overweight in adulthood (pooled OR 1.90, 95% CI 0.86, 4.19, p = 0.11). There was substantial heterogeneity in the results at the intervals from both 0-2 years and 0-6 months.

In the pooled studies measuring rapid weight gain at the interval from 0-2 years only,[69 70] the study by Demerath et al[69] had the highest effect and widest confidence intervals. This study measured overweight at age 46.5 years, while the other two studies measured this between aged 18-31 years.

In the pooled studies measuring rapid weight gain at the interval from 0-6 months,[70 71 73] one of the studies[73] that did not find a significant positive association at 0-6 months found that rapid weight gain experienced from birth to 5 years of age was significantly associated with overweight in adulthood, which is in line with other studies included in this review exploring rapid weight gain at a later age range, at the interval from 0-2 years. Odegaard et al[70] measured rapid weight gain at a total of 23 time points from 0-2 years, finding a positive association at nine time points. Of the nine time points measured at time intervals from 3-

24 and 6-24 months, six of these associations were significant, while of the six time points measuring weight gain up to six months of age, only one time point at the interval from 3-6 months was significant (table 6), suggesting later infancy weight gain may be more likely to result in later overweight status, in line with the findings in this review for infancy weight gain experienced at the interval from 0-2 years. It may be that the early neonatal phase is the window of opportunity to optimize growth where weight gain is required to meet expected growth for age.

BMI

Of 18 studies exploring the relationship between infancy weight gain in the first two years of life and adult BMI,[69 74-90] 12 found a significant positive association between infancy weight gain and adult BMI[69 75-78 81-83 86 87 89 90] at one or more time point intervals from 0-2 years of age and one did not report an effect.[80] Of the five studies where there was no significant association, there were no obvious differences, with only one study having a high risk of bias[74] with a 50% participation rate and infancy weight measurements were taken from home records. Two of these studies were conducted in preterm infants and measured infancy weight gain up to three months only.[79 85] Overall, the data suggests a positive association between infancy weight gain and BMI in adulthood.

EXPOSURE

The data were categorised into two exposure categories, rapid weight gain and change in WAZ/SDS. Overall 15 studies assessed rapid weight gain[68-70 72 73 76 78 81-83 85 86 88-90] with all but three finding a significant positive association[73 85 88] with adult BMI and overweight. Of these, all measured rapid weight gain occurring at intervals from 0-6 months of age, while weight gain was assessed later into infancy in the studies reporting a significant association. Eight studies assessed change in WAZ/SDS[72 74 75 77 79 80 84 87] in infancy with three finding no significant association with adult BMI or overweight.[74 79 84] These studies measured infancy weight gain at multiple time point intervals between 0-2 years of age, however in two studies infancy weight measurements were taken from existing records which presents a source of bias.[74 84]

TIMING OF INFANCY WEIGHT GAIN

The relationship between infancy weight gain and later adulthood overweight or BMI was strongest in studies that explored rapid weight gain at the time point interval of 0-2 years, with six out of seven studies finding a significant positive association. The only study that did not find a significant association[79] was conducted in a small sample of 129 extremely preterm infants and found that change in WAZ was not associated BMI at age 19. The association between infancy weight gain experienced at time point intervals between 0-6 months and adult overweight or BMI was measured at 19 time point intervals across 11 studies[71-73 77 79 84-88 90], with a positive association found at eight time point intervals (42%) across eight studies,[70-72 74 77 86 87 90] which may suggest the relationship between weight gain experienced earlier in infancy and later overweight or BMI is not as strong as when rapid weight gain is experienced later in infancy.

The question of whether there is a more appropriate time for rapid weight gain to occur is important. Sammallahti et al 2017[96] sought to determine whether the benefits of faster growth in early preterm individuals extended to late preterm individuals and found that in late preterm infants born at 24-27 weeks, from birth to five months, every increase in 1SD for weight was significantly associated with increased IQ, executive functioning and grade point average in 25 year olds.[96] This benefit was not seen in 5-20 month olds who were exposed to rapid weight gain. Similarly, a study of more than 5,500 term infants in the UK demonstrated that infants who had slow growth and spent time below the 5th percentile for age between birth and eight weeks had a significantly lower IQ at eight years of age.[97] In contrast, slow growth from eight weeks to nine months of age was not associated with lower IQ at eight years of age. This, along with data from the present review suggests that focusing on nutrition interventions to promote weight gain in the early post term phase in infants born small or requiring catch-up growth may be most important for promoting positive neurodevelopmental outcomes while minimising later overweight and obesity risk.

PREMATURITY

Of the three studies investigating infancy weight gain in preterm infants only, one found a significant positive association between change in WAZ and adult BMI.[87] A recent systematic

review found accelerated weight gain in the first two years of life was significantly associated with later overweight in preterm infants, however in all studies overweight was measured in childhood.[98] Other studies have reported no association between early infancy weight gain in the first 3 months and later metabolic outcomes such as fat mass[99] and blood pressure.[98] It may be that rapid weight gain experienced in early infancy by preterm infants does not pose the same level of risk of overweight and association with BMI in adulthood as in term infants, however more research is required to test this. It is important to note that optimal brain development is of critical importance in premature infants and existing guidelines outlining rates of weight gain in this population[100] should be utilized to support this,[12] despite the potential risk of later obesity.

SMALL FOR GESTATIONAL AGE

Of the three studies investigating rapid weight gain occurring in infants born small for gestational age, two studies[82 86] reported a positive and significant association between rapid weight gain and BMI in adulthood. This is in line with the wider literature where there are reports of rapid weight gain leading to higher fat accumulation later in life in children born small for gestational age.[21] A recent study exploring five different types of weight gain including excessive catch-up growth, rapid catch-up growth, appropriate catch-up growth and no catch-up growth suggested that for term infants born small for gestational age, catch-up growth that crosses upwards over two percentile bands in the first several months, with growth then tracking at a median level by age two years may be the optimal catch-up growth trajectory, minimizing risk of later childhood adverse health outcomes.[101] This idea of slower weight gain over time is an important one, with studies of overfeeding demonstrating that 60-70% of increases in weight gain are fat mass.[102]

AGE

Of the six studies that did not report a significant association between infancy weight gain and later overweight, five studied the outcome of overweight or BMI between 18-30 years.[73 79 84 85 88] Three of the four studies measuring outcomes at a mean age of ≥30 years found a significant positive association[69 77 81] with infancy weight gain. It is known that rates

of overweight and obesity increase with age[91], however where relevant, adult age was adjusted for.[69]

LIMITATIONS AND QUALITY OF EVIDENCE INCLUDED IN THE REVIEW

The studies included in this review had several limitations. The participation rate of eligible subjects was unclear in six studies[68 72 79 83 85 89], and was under 70% in five studies,[71 73 74 84 86] while the response rate (outcome data available) was unclear in two studies[68 83] and under 70% in eight studies.[73 77-82 88] There was also a question around the exposure and outcome variable measurements in a number of studies. In four studies,[74 78 81 84] rapid weight gain was assessed using weight from existing records and in four studies[72 77 78 80] the method of measuring BMI was either self-reported or unclear, with the accuracy of these measurements therefore uncertain. Accounting for missing data was variable, with only seven of the 23 included studies reporting on how missing data on weight measurements in infancy was accounted for,[68 70 73 77 80 82 90] and five studies not commenting on how missing outcome data was managed.[75 81 83 88 89] There were also limitations in controlling for confounders known to affect risk of overweight such as type of feeding (breast vs. formula), social and maternal factors. Only eight out of 23 studies controlled for maternal BMI,[69-73 77 81 90] four studies controlled for maternal education[71 73 75 76] and six studies controlled for parental education.[69 71 73-76] Only three studies controlled for breastfeeding[69 73 76] and one study controlled for formula use.[89]

Risk of bias was assessed for each study using the QUIPS tool, with no studies returning an overall risk of bias score of “low”, 17 studies returning an overall risk of bias score of “moderate”, and six studies returning an overall risk of bias score of “high”. A key reason for moderate to high risk of bias scores was high study attrition rates, which are common in observational studies, particularly of birth cohorts.[103] The certainty of evidence for risk of overweight in adulthood from rapid weight gain in infancy ranged from very low to moderate. The meta-analysis for infancy weight gain and risk of overweight in adulthood for all studies combined showed an OR of 2.59, 95% CI 1.16, 5.75; low certainty. This certainty level was based on a risk of bias assessment for this finding of “serious” due to three studies scoring an overall risk of bias of moderate and one study scoring an overall risk of bias on high. The meta-analysis for infancy weight gain measured at the interval from 0-2 years of

age and adult overweight showed an OR of 3.03, 95% CI 1.16, 7.89; moderate certainty. This certainty level was based on a risk of bias of moderate in two studies, consistent data with confidence intervals that do not cross the line of no effect but are wide and likely cross important decision-making thresholds, and studies that include subjects from relevant populations. The meta-analysis for infancy weight gain at the time interval from 0-6 months of age showed an OR of 1.90, 95% CI 0.86, 4.19; very low certainty. This level of certainty was based on a risk of bias assessment of "serious" due to one study scoring an overall risk of bias of high and another of moderate. This was also an inconsistent and imprecise finding in that some confidence intervals did not overlap, and confidence intervals include the null effect.

STRENGTHS AND LIMITATIONS OF THE REVIEW PROCESS

Strengths of this review include the search strategy performed across multiple databases which allowed for a thorough examination of the literature, yielding over 15,000 articles, 78 of which were screened for inclusion at the full text level, resulting in 23 studies included for review. This search strategy and review were based on a clear and detailed systematic review protocol, which allow for both transparency and reproducibility should this review be conducted again in the future. Another strength was having two independent reviewers screen each article, conduct critical appraisal and complete data extraction for each article included in the review. This allowed for any discrepancies or disagreements to be discussed and agreed upon, increasing the quality of the data for analysis. Finally, the meta-analyses of results allowed for an estimate of effect with increased statistical power to be established, allowing for an objective summary of the evidence to be made and applied to clinical practice.

This review searched several databases and in any language. However, as in any review there is the possibility of missed data. In addition, all systematic reviews are limited by the quality of the studies included, and findings are only relevant until future research challenges conclusions and recommendations made. The nature of studies exploring the relationship between infant growth and later adverse outcomes is that studies are observational, with many of them being retrospective. While observational studies can be much larger than RCTs, the main limitation of observational studies is that a causal

inference is largely unable to be made.[104] Observational research also does not have the benefit of randomisation and is prone to confounding bias. Observational research can also be susceptible to other types of bias such as information bias; inaccurate assessment of the outcome, exposure or potential confounding variables, as well as selection bias with selection of subjects from a population not representative of the target population.[104] Another limitation of this review was that a review of all outcomes initially described was not able to be conducted, in part due to significant heterogeneity between studies, with different exposure definitions and effect estimates used.

AGREEMENTS AND DISAGREEMENTS WITH OTHER STUDIES OR REVIEWS

In the four studies that could be combined in a meta-analysis in this review, infants that experienced rapid weight gain in the first two years of life across a range of time points had 2.59 times higher odds of being overweight in adulthood than those who did not experience rapid weight gain (pooled OR 2.59, 95% CI 1.16, 5.75, p = 0.02). When a study that also included sum of skinfolds in the outcome assessment as well as overweight status was removed, this association was not as strong (pooled OR 2.02, 95% CI 0.93, 4.36). This is in line with the findings by Zheng which included the same studies in sub group analysis of adults[40] (pooled OR 2.02, 95% CI 0.93, 4.36), but not as high as when 15 studies exploring overweight experienced in childhood were pooled (pooled OR 3.66, 95% CI 2.59-5.17). In the current review, there was substantial heterogeneity in the result exploring rapid weight gain at any time interval from 0-2 years. Potential sources of heterogeneity include the measure and timing of exposure of rapid weight gain, age at outcome and adjustments.

The finding of infancy weight gain at the interval from 0-6 months being associated with adult overweight or BMI for only 42% of time points is in contrast with Zheng et al,[40] showing that rapid weight gain experienced to one year of age had a stronger association with overweight (pooled OR 4.12, 95% CI 1.83, 9.28) than rapid weight gain experienced to two years of age (pooled OR 3.66, 95% CI 2.59, 5.17). These studies did, however, all include overweight measured in childhood not adulthood.

APPLICABILITY OF RESULTS AND CONSIDERATIONS FOR PRACTICE

The mechanism by which rapid weight gain results in adult overweight is unclear, but is postulated to be influenced by maternal and early life factors such as in utero growth and birth size.[105] Addressing factors that contribute to rapid weight gain in infancy may be an important step in mitigating the risk of overweight and obesity later in life. A recent review exploring determinants of rapid weight gain in infancy found that a higher birthweight and higher gestational age in weeks was associated with lower rapid weight gain risk.[106] Rapid weight gain is most likely to occur in infants born small and those who have had a period of growth restriction or faltering.[107] Reducing the incidence of low birthweight through maternal pre-natal education could be an approach to mitigate later obesity risk. It is worth noting however, that when adjusting for birthweight in studies included in this review, the association between rapid weight gain and adulthood overweight remained significant, indicating this relationship extends to those born at a normal weight.

Type of feeding

It is well understood that infants who are breastfed have different weight gain patterns to infants who are formula fed, with formula fed infants growing more rapidly than breastfed infants from around three months of age to one year of age.[108] In the present review into the relationship between weight gain in infancy and overweight that persists into adulthood, only one study reported on infants who had been formula fed and found that weight gain in the first four months of life was associated with overweight in adulthood.[72] All infants in this study were formula fed however, so the relationship cannot be simply attributed to feeding modality. Only one study adjusted for formula use and found that after adjustment, at age 18 years, those who experienced rapid weight gain in infancy had a higher BMI SDS.[89] A 2015 systematic review demonstrated that breastfeeding is protective against later obesity[109] while being breastfed has also been shown to be protective against rapid weight gain in infancy.[106] This data supports the idea that strategies to promote and support breastfeeding over formula feeding may be important in preventing rapid weight gain in infancy and longer term overweight and obesity. With respect to formula feeding, recent attention has been given to the role of protein in contributing to rapid weight gain in infancy, with a large European multicentre randomized controlled trial finding that infants

fed formula with a higher protein content experienced more rapid weight gain up to age two years than those fed a formula with a lower protein content.[110] A follow up study demonstrated infants fed a higher protein formula were more likely to be overweight at age six years.[111] It has been postulated that the higher protein content of infant formula compared to breastmilk could increase the secretion of insulin and insulin like growth factor 1 (IGF-1) (a hormone that works with growth hormone to promote normal growth), leading to an increased amount of glucose stored as fat and in turn, overweight and obesity.[111] This gives further merit to the importance of promotion of breastfeeding as preferred feeding modality.

Education of care providers

While the relationship between rapid infancy weight gain and later overweight and obesity risk is known and this systematic review provides further quantitative evidence to support this, the literature shows that paediatricians are uncertain about the concept, definition and implications of rapid infancy weight gain, are more comfortable with the management of inadequate vs. excessive or rapid weight gain, and perceive the primary cause of excessive or rapid infancy weight gain to be overfeeding.[26] Primary care paediatricians, general practitioners, community health nurses and other health care workers are crucial to weight gain prevention efforts in early life as they are better able to partner with families to promote and facilitate positive health behaviours, such as reading feeding cues, promoting and supporting breastfeeding and developmentally appropriate active play and movement.[26] Guidelines for the management of faltering growth provide strategies to achieve catch-up growth such as the use of high calorie formula,[112] often achieved through the addition of carbohydrate polymers. These guidelines discuss the later risks of poor growth however do not address the concerns associated with rapid or excessive growth and the need to monitor for this.[112] Moreover, existing guidelines do not give specific advice around rates of weight gain to aim for after a period of growth faltering once strategies to address this have been implemented, except in the case of severe malnutrition. Unfortunately, no studies included in this review explored the impact of rapid weight gain on later overweight and obesity after a period of malnutrition or faltering growth in infancy. One study that was excluded from this review due to failure to meet the inclusion criteria for age at exposure found that a rehabilitation weight gain in survivors of severe

malnutrition of >12.9g/kg/day was associated with higher adult BMI,[113] a rate of weight gain which is in line with the WHO recommendation of achieving ≥10g/kg/day in this population.[114] Further research is needed to determine optimal rates of weight gain in infants who have experienced faltering growth.

Existing guidelines would benefit from the inclusion of information on the risks of excessive weight gain, while caregivers would benefit from education on balancing the benefits of strategies such as high calorie infant formula with the potential risks for later overweight and obesity. Moreover, it is well known that breastfed infants grow faster in the first three months of life compared to their formula fed counterparts, followed by a reduction in velocity of weight gain.[108] The Centres for Disease Control and Prevention (CDC) 2000 growth reference charts for children <24 months provide a reference based on cross sectional data for how children who were predominately formula fed grew.[115] In contrast, the World Health Organisation (WHO) growth standard charts, developed in 2006, are based on longitudinal data of children who were exclusively breastfeed until four months of age and still breastfeeding at 12 months of age.[116] Given the WHO charts provide a standard for how children *should* grow based on recommended feeding practices, the CDC recommends the WHO charts be used for children <24 months and should be used in practice rather than the CDC charts.[117] When the WHO charts are used for this age group, fewer children will be identified as underweight between 3-18 months compared to use of the CDC charts, given breastfed infants growth more slowly from three months of age. [117] Healthcare providers need to be educated on use of the correct growth charts to ensure the assessment of faltering growth is not incorrectly made and strategies to promote weight gain such as high calorie formula are not provided unnecessarily.

Education of families

No studies in this review adjusted for feeding practices or mode of milk delivery. A recent meta-systematic review found that there is some evidence to suggest that adding cereal to infant formula, putting a baby to bed with a bottle, and overfeeding formula by using larger vs. smaller bottles can lead to rapid or excess weight gain.[118] A separate meta-analysis found that starting solids at ≥ six months of age is protective against rapid weight gain in the first year of life.[106] Moreover, responsive parenting programs that educate on responding

appropriately to hunger and sleep cues have shown to be effective in reducing rates of weight gain at one year of age.[119 120] It is clear health care workers have an important role to play in providing parents with education on appropriate feeding practices in infancy to prevent against rapid weight gain, and in turn later overweight, with calls being made recently to screen for rapid weight gain in infancy and provide advice on six key topics; breastfeeding, formula feeding, complementary feeding practices, sleep, responsive parenting practices and education on growth charts, when rapid weight gain is identified.[121]

IMPLICATIONS FOR FUTURE RESEARCH

While used more consistently since recommended by Ong in 2000,[122] the use of ≥0.67SD change in WAZ to define rapid weight gain between two timepoints more frequently and the use of standardized effect estimates would allow for a more meaningful comparison of data. Reporting of overweight status in addition to BMI would also facilitate more meaningful comparison of the impact of rapid weight gain in infancy on overweight status rather than only the relationship with BMI. While more difficult due to loss to follow up, harmonisation of prospective research protocols that follow subjects into adulthood would allow for a stronger conclusion on the impact of rapid weight gain in infancy on overweight status into adulthood, as is the case with overweight status in childhood due to infant rapid weight gain. The inclusion of more standardised time points, for example three monthly, to assess rapid weight gain in infancy would allow for more meaningful combination of these results and would allow stronger conclusions around the impact of timing of rapid weight gain on later overweight risk to be made. More consistent reporting on and controlling for important factors known to affect infancy weight gain such as birth status (preterm vs. small for gestational age vs. term), formula use vs. breastfeeding, formula and solids intake, maternal BMI, parental education and other factors would allow for more meaningful analysis and interpretation of the data. Measurements of weight and linear growth (length or height) in both infancy and adulthood should always be conducted by trained professionals on calibrated equipment rather than being sought from existing records or through self-reporting. Across studies screened for but ultimately not included in this review, use of more standardized unit measures for outcome data would allow for more meaningful and potentially pooled analysis of other potential long term cardiometabolic risk factors such as increased blood pressure, dyslipidemia, dysglycemia, and abnormal body

composition. Focusing efforts onto research that ultimately prevents the need for rapid weight gain in infants, such as mitigating the risk of infants born small for gestational age or preterm, is warranted. Finally, more rigorous guidelines to inform management of faltering growth should be developed to guide healthcare workers.

SUMMARY OF RECOMMENDATIONS

Considering the findings of this review, while a formal recommendations process into the prevention of rapid weight gain using the GRADE approach has not been conducted, preliminary recommendations are provided below. It is prudent to suggest that healthcare workers are mindful of modifiable determinants of rapid weight gain, and undertake the following:

- Promote and support breastfeeding
- Promote weight gain early in preterm infants according to current guidelines[100]
- Promote early and slow catch-up growth across a period of months in small for gestational age infants where required, and infants who have experienced a period of faltering growth
- Educate clinicians on the longer term risks of rapid weight gain, the appropriate use of hyper-caloric formula and the need to closely monitor growth on the appropriate WHO growth chart
- Educate families on topics associated with infancy weight gain: breastfeeding, formula feeding, complementary feeding, sleep, responsive parenting and growth chart monitoring when rapid weight gain in infancy is identified.

CHAPTER 5: CONCLUSION

This systematic review and meta-analysis provides updated evidence to support the risk of overweight from rapid weight gain in infancy, as well as providing an updated and more nuanced perspective into the positive association between weight gain in infancy and BMI in adulthood. Based on this review, healthcare workers should be mindful of unnecessary weight gain in infancy, particularly after the neonatal stage, and should educate families on the risks of rapid weight gain in infancy. Future research focused on strategies to manage infants who have experienced a period of faltering growth, that ultimately inform practice guidelines, is required.

REFERENCE LIST

1. Balasundaram P, Avulakunta ID. Human Growth and Development. *StatPearls Publishing* 2022;01:01.
2. Nutzenadel W. Failure to thrive in childhood. *Dtsch Arztebl Int* 2011;108(38):642-9. doi: 10.3238/arztebl.2011.0642
3. Cole SZ, Lanham JS. Failure to thrive: an update. *Am Fam Physician* 2011;83(7):829-34.
4. Black MM, Krishnakumar A. Predicting longitudinal growth curves of height and weight using ecological factors for children with and without early growth deficiency. *Journal of Nutrition* 1999;129(2S Suppl):539S-43S. doi: https://dx.doi.org/10.1093/jn/129.2.539S
5. Corbett SS, Drewett RF. To what extent is failure to thrive in infancy associated with poorer cognitive development? A review and meta-analysis. *J Child Psychol Psychiatry* 2004;45(3):641-54. doi: 10.1111/j.1469-7610.2004.00253.x [published Online First: 2004/04/02]
6. Osuchukwu OO, Reed DJ. Small for Gestational Age. StatPearls. Treasure Island (FL) ineligible companies. Disclosure: Danielle Reed declares no relevant financial relationships with ineligible companies.2023.
7. Lodygensky GA, Seghier ML, Warfield SK, et al. Intrauterine growth restriction affects the preterm infant's hippocampus. *Pediatr Res* 2008;63(4):438-43. doi: 10.1203/PDR.0b013e318165c005 [published Online First: 2008/03/22]
8. Young A, Beattie RM, Johnson MJ. Optimising growth in very preterm infants: reviewing the evidence. *Arch Dis Child Fetal Neonatal Ed* 2023;108(1):2-9. doi: 10.1136/archdischild-2021-322892 [published Online First: 2022/03/02]
9. Karlberg J, Albertsson-Wikland K. Growth in full-term small-for-gestational-age infants: from birth to final height. *Pediatr Res* 1995;38(5):733-9. doi: 10.1203/00006450-199511000-00017
10. Bocca-Tjeertes IF, Kerstjens JM, Reijneveld SA, et al. Growth and predictors of growth restraint in moderately preterm children aged 0 to 4 years. *Pediatrics* 2011;128(5):e1187-94. doi: 10.1542/peds.2010-3781
11. Lundgren EM, Tuvemo T. Effects of being born small for gestational age on long-term intellectual performance. *Best Pract Res Clin Endocrinol Metab* 2008;22(3):477-88. doi: 10.1016/j.beem.2008.01.014
12. Ehrenkranz RA, Dusick AM, Vohr BR, et al. Growth in the neonatal intensive care unit influences neurodevelopmental and growth outcomes of extremely low birth weight infants. *Pediatrics* 2006;117(4):1253-61. doi: 10.1542/peds.2005-1368 [published Online First: 2006/04/06]
13. Kay's SK, Hindmarsh PC. Catch-up growth: an overview. *Pediatr Endocrinol Rev* 2006;3(4):365-78.
14. Shields B, Wacogne I, Wright CM. Weight faltering and failure to thrive in infancy and early childhood. *BMJ* 2012;345:e5931. doi: 10.1136/bmj.e5931
15. Lundgren EM, Cnattingius S, Jonsson B, et al. Intellectual and psychological performance in males born small for gestational age with and without catch-up growth. *Pediatr Res* 2001;50(1):91-6. doi: 10.1203/00006450-200107000-00017
16. Glass HC, Costarino AT, Stayer SA, et al. Outcomes for extremely premature infants. *Anesth Analg* 2015;120(6):1337-51. doi: 10.1213/ANE.0000000000000705 [published Online First: 2015/05/20]
17. Olsen EM, Petersen J, Skovgaard AM, et al. Failure to thrive: the prevalence and concurrence of anthropometric criteria in a general infant population. *Arch Dis Child* 2007;92(2):109-14. doi: 10.1136/adc.2005.080333
18. Perrin EC, Cole CH, Frank DA, et al. Criteria for determining disability in infants and children: failure to thrive. *Evid Rep Technol Assess (Summ)* 2003(72):1-5.
19. Daniel M, Kleis L, Cemeroglu AP. Etiology of failure to thrive in infants and toddlers referred to a pediatric endocrinology outpatient clinic. *Clin Pediatr (Phila)* 2008;47(8):762-5. doi: 10.1177/0009922808316989

20. Schwartz ID. Failure to thrive: an old nemesis in the new millennium. *Pediatr Rev* 2000;21(8):257-64; quiz 64. doi: 10.1542/pir.21-8-257 [published Online First: 2000/08/02]
21. Cho WK, Suh BK. Catch-up growth and catch-up fat in children born small for gestational age. *Korean J* 2016;59(1):1-7. doi: http://dx.doi.org/10.3345/kjp.2016.59.1.1
22. Black RE. Global Prevalence of Small for Gestational Age Births. *Nestle Nutr Inst Workshop Ser* 2015;81:1-7. doi: 10.1159/000365790
23. Beck S, Wojdyla D, Say L, et al. The worldwide incidence of preterm birth: a systematic review of maternal mortality and morbidity. *Bull World Health Organ* 2010;88(1):31-8. doi: 10.2471/BLT.08.062554
24. Eid EE. Follow-up study of physical growth of children who had excessive weight gain in first six months of life. *British medical journal* 1970;2(5701):74-6. doi: 10.1136/bmj.2.5701.74 [published Online First: 1970/04/11]
25. Monteiro PO, Victora CG. Rapid growth in infancy and childhood and obesity in later life--a systematic review. *Obes Rev* 2005;6(2):143-54. doi: 10.1111/j.1467-789X.2005.00183.x [published Online First: 2005/04/20]
26. Pesch MH, Levitt KJ, Danziger P, et al. Pediatrician's Beliefs and Practices Around Rapid Infant Weight Gain: A Qualitative Study. *Glob* 2021;8:2333794X21992164. doi: https://dx.doi.org/10.1177/2333794X21992164
27. Weaver LT. Rapid growth in infancy: balancing the interests of the child. *J Pediatr Gastroenterol Nutr* 2006;43(4):428-32. doi: 10.1097/01.mpg.0000235977.59873.e0 [published Online First: 2006/10/13]
28. ud Din Z, Emmett P, Steer C, et al. Growth outcomes of weight faltering in infancy in ALSPAC. *Pediatrics* 2013;131(3):e843-9. doi: 10.1542/peds.2012-0764
29. National Heart Blood and Lung Institute. What is Metabolic Syndrome? : NIH; 2022 [Available from: https://www.nhlbi.nih.gov/health/metabolic-syndrome#:~:text=Metabolic%20syndrome%20is%20a%20group,also%20called%20insulin%20resistance%20syndrome. accessed 7th September 2023.
30. Roseboom T, de Rooij S, Painter R. The Dutch famine and its long-term consequences for adult health. *Early human development* 2006;82(8):485-91. doi: 10.1016/j.earlhumdev.2006.07.001 [published Online First: 2006/08/01]
31. Barker DJ, Osmond C, Golding J, et al. Growth in utero, blood pressure in childhood and adult life, and mortality from cardiovascular disease. *BMJ* 1989;298(6673):564-7. doi: 10.1136/bmj.298.6673.564 [published Online First: 1989/03/04]
32. Hales CN, Barker DJ. Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. *Diabetologia* 1992;35(7):595-601. doi: 10.1007/BF00400248 [published Online First: 1992/07/01]
33. Eriksson JG, Forsen T, Tuomilehto J, et al. Catch-up growth in childhood and death from coronary heart disease: longitudinal study. *BMJ* 1999;318(7181):427-31. doi: 10.1136/bmj.318.7181.427 [published Online First: 1999/02/12]
34. de Boo HA, Harding JE. The developmental origins of adult disease (Barker) hypothesis. *Aust N Z J Obstet Gynaecol* 2006;46(1):4-14. doi: 10.1111/j.1479-828X.2006.00506.x [published Online First: 2006/01/31]
35. Weng SF, Redsell SA, Swift JA, et al. Systematic review and meta-analyses of risk factors for childhood overweight identifiable during infancy. *Arch Dis Child* 2012;97(12):1019-26. doi: 10.1136/archdischild-2012-302263
36. Leunissen RW, Kerkhof GF, Stijnen T, et al. Effect of birth size and catch-up growth on adult blood pressure and carotid intima-media thickness. *Horm Res Paediatr* 2012;77(6):394-401. doi: 10.1159/000338791
37. Ong KK, Dunger DB. Birth weight, infant growth and insulin resistance. *Eur J Endocrinol* 2004;151 Suppl 3:U131-9. doi: 10.1530/eje.0.151u131 [published Online First: 2004/11/24]

38. Monteiro PO, Victora CG, Barros FC, et al. Birth size, early childhood growth, and adolescent obesity in a Brazilian birth cohort. *Int J Obes Relat Metab Disord* 2003;27(10):1274-82. doi: 10.1038/sj.ijo.0802409
39. Belfort MB, Gillman MW, Buka SL, et al. Preterm infant linear growth and adiposity gain: trade-offs for later weight status and intelligence quotient. *J Pediatr* 2013;163(6):1564-69 e2. doi: 10.1016/j.jpeds.2013.06.032 [published Online First: 2013/08/06]
40. Zheng M, Lamb KE, Grimes C, et al. Rapid weight gain during infancy and subsequent adiposity: a systematic review and meta-analysis of evidence. *Obesity Reviews* 2018;19(3):321-32. doi: https://dx.doi.org/10.1111/obr.12632
41. Ong KK, Loos RJ. Rapid infancy weight gain and subsequent obesity: systematic reviews and hopeful suggestions. *Acta Paediatr* 2006;95(8):904-8. doi: 10.1080/08035250600719754 [published Online First: 2006/08/03]
42. Baird J, Fisher D, Lucas P, et al. Being big or growing fast: systematic review of size and growth in infancy and later obesity. *BMJ* 2005;331(7522):929. doi: 10.1136/bmj.38586.411273.E0
43. World Health Organization. BMI-for-age (5-19 years): WHO; 2007 [cited 2023 7th September]. Available from: https://www.who.int/tools/growth-reference-data-for-5to19-years/indicators/bmi-for-age.
44. Cole TJ, Bellizzi MC, Flegal KM, et al. Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ* 2000;320(7244):1240-3. doi: 10.1136/bmj.320.7244.1240 [published Online First: 2000/05/08]
45. Centers for Disease Control & Prevention. BMI and BMI Categories for Children and Teens: CDC; 2000 [Available from: https://www.cdc.gov/obesity/basics/childhood-defining.html accessed 7th September 2023.
46. Simmonds M, Llewellyn A, Owen CG, et al. Predicting adult obesity from childhood obesity: a systematic review and meta-analysis. *Obes Rev* 2016;17(2):95-107. doi: 10.1111/obr.12334 [published Online First: 2015/12/24]
47. Jordan Z, Lockwood C, Munn Z, et al. The updated Joanna Briggs Institute Model of Evidence-Based Healthcare. *Int J Evid Based Healthc* 2019;17(1):58-71. doi: 10.1097/XEB.0000000000000155 [published Online First: 2018/09/27]
48. Thoma A, Eaves FF, 3rd. A brief history of evidence-based medicine (EBM) and the contributions of Dr David Sackett. *Aesthet Surg J* 2015;35(8):NP261-3. doi: 10.1093/asj/sjv130 [published Online First: 2015/07/15]
49. Sackett DL, Rosenberg WM, Gray JA, et al. Evidence based medicine: what it is and what it isn't. *BMJ* 1996;312(7023):71-2. doi: 10.1136/bmj.312.7023.71 [published Online First: 1996/01/13]
50. Aromataris E, Munn Z. JBI Manual for Evidence Synthesis 2020 [Available from: https://synthesismanual.jbi.global. https://doi.org/10.46658/JBIMES-20-01 accessed 2nd October 2023.
51. Aromataris E, Pearson A. The systematic review: an overview. *Am J Nurs* 2014;114(3):53-8. doi: 10.1097/01.NAJ.0000444496.24228.2c [published Online First: 2014/02/28]
52. Munn Z, Stern C, Aromataris E, et al. What kind of systematic review should I conduct? A proposed typology and guidance for systematic reviewers in the medical and health sciences. *BMC Med Res Methodol* 2018;18(1):5. doi: 10.1186/s12874-017-0468-4 [published Online First: 2018/01/11]
53. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71 [published Online First: 2021/03/31]
54. Cumpston M, Li T, Page MJ, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. *Cochrane Database Syst Rev* 2019;10(10):ED000142. doi: 10.1002/14651858.ED000142 [published Online First: 2019/10/24]

55. Pearson A, Wiechula R, Court A, et al. The JBI model of evidence-based healthcare. *Int J Evid Based Healthc* 2005;3(8):207-15. doi: 10.1111/j.1479-6988.2005.00026.x [published Online First: 2005/09/01]
56. van der Haak N, Wood K, Sweeney A, et al. Risk of metabolic consequences of rapid weight gain and catch-up growth in the first two years of life: a systematic review protocol. *JBI Database Of Systematic Reviews And Implementation Reports* 2019;17(1):10-15. doi: https://dx.doi.org/10.11124/JBISRIR-2017-003451
57. Aromataris E, Riitano D. Constructing a search strategy and searching for evidence. A guide to the literature search for a systematic review. *Am J Nurs* 2014;114(5):49-56. doi: 10.1097/01.NAJ.0000446779.99522.f6 [published Online First: 2014/04/25]
58. Lefebvre C GJ, Briscoe S, Featherstone R, Littlewood A, Metzendorf M-I, Noel-Storr A, Paynter R, Rader T, Thomas J, Wieland LS. Chapter 4: Searching for and selecting studies. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated October 2023). Cochrane; 2023 [Available from: www.training.cochrane.org/handbook accessed January 28 2024].
59. Riley RD, Moons KGM, Snell KIE, et al. A guide to systematic review and meta-analysis of prognostic factor studies. *BMJ* 2019;364:k4597. doi: 10.1136/bmj.k4597 [published Online First: 2019/02/01]
60. Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia [accessed August 2021].
61. Hayden JA, van der Windt DA, Cartwright JL, et al. Assessing bias in studies of prognostic factors. *Ann Intern Med* 2013;158(4):280-6. doi: 10.7326/0003-4819-158-4-201302190-00009 [published Online First: 2013/02/20]
62. Dettori JR, Norvell DC, Chapman JR. Seeing the Forest by Looking at the Trees: How to Interpret a Meta-Analysis Forest Plot. *Global Spine J* 2021;11(4):614-16. doi: 10.1177/21925682211003889 [published Online First: 2021/05/04]
63. Tufanaru C, Munn Z, Stephenson M, et al. Fixed or random effects meta-analysis? Common methodological issues in systematic reviews of effectiveness. *Int J Evid Based Healthc* 2015;13(3):196-207. doi: 10.1097/XEB.0000000000000065
64. Altman DG, Bland JM. How to obtain the confidence interval from a P value. *BMJ* 2011;343:d2090. doi: 10.1136/bmj.d2090 [published Online First: 2011/08/10]
65. Nieminen P. Application of Standardized Regression Coefficient in Meta-Analysis. *BioMedInformatics* 2022;2(3)
66. Foroutan F, Guyatt G, Zuk V, et al. GRADE Guidelines 28: Use of GRADE for the assessment of evidence about prognostic factors: rating certainty in identification of groups of patients with different absolute risks. *J Clin Epidemiol* 2020;121:62-70. doi: 10.1016/j.jclinepi.2019.12.023 [published Online First: 2020/01/27]
67. Moola S, Munn Z, Sears K, et al. Conducting systematic reviews of association (etiology): The Joanna Briggs Institute's approach. *Int J Evid Based Healthc* 2015;13(3):163-9. doi: 10.1097/XEB.0000000000000064 [published Online First: 2015/08/12]
68. Adair LS, Fall CH, Osmond C, et al. Associations of linear growth and relative weight gain during early life with adult health and human capital in countries of low and middle income: findings from five birth cohort studies. *Lancet* 2013;382(9891):525-34. doi: 10.1016/S0140-6736(13)60103-8
69. Demerath EW, Reed D, Choh AC, et al. Rapid postnatal weight gain and visceral adiposity in adulthood: the Fels Longitudinal Study. *Obesity (Silver Spring)* 2009;17(11):2060-6. doi: 10.1038/oby.2009.105 [published Online First: 2009/04/18]
70. Odegaard AO, Choh AC, Nahhas RW, et al. Systematic examination of infant size and growth metrics as risk factors for overweight in young adulthood. *PLoS One* 2013;8(6):e66994. doi: 10.1371/journal.pone.0066994 [published Online First: 2013/07/03]

71. Stettler N, Kumanyika SK, Katz SH, et al. Rapid weight gain during infancy and obesity in young adulthood in a cohort of African Americans. *Am J Clin Nutr* 2003;77(6):1374-8. doi: 10.1093/ajcn/77.6.1374 [published Online First: 2003/06/07]
72. Stettler N, Stallings VA, Troxel AB, et al. Weight gain in the first week of life and overweight in adulthood: a cohort study of European American subjects fed infant formula. *Circulation* 2005;111(15):1897-903. doi: 10.1161/01.CIR.0000161797.67671.A7 [published Online First: 2005/04/20]
73. Sutharsan R, O'Callaghan MJ, Williams G, et al. Rapid growth in early childhood associated with young adult overweight and obesity--evidence from a community based cohort study. *J Health Popul Nutr* 2015;33:13. doi: 10.1186/s41043-015-0012-2 [published Online First: 2016/01/31]
74. Touwslager RN, Gielen M, Mulder AL, et al. Genetic and environmental factors in associations between infant growth and adult cardiometabolic risk profile in twins. *Am J Clin Nutr* 2013;98(4):994-1001. doi: 10.3945/ajcn.112.039131 [published Online First: 2013/08/30]
75. Victora CG, Sibbritt D, Horta BL, et al. Weight gain in childhood and body composition at 18 years of age in Brazilian males. *Acta Paediatr* 2007;96(2):296-300. doi: 10.1111/j.1651-2227.2007.00110.x [published Online First: 2007/04/13]
76. Buffarini R, Restrepo-Mendez MC, Silveira VM, et al. Growth across life course and cardiovascular risk markers in 18-year-old adolescents: the 1993 Pelotas birth cohort. *BMJ Open* 2018;8(1):e019164. doi: https://dx.doi.org/10.1136/bmjopen-2017-019164
77. Bjerregaard LG, Rasmussen KM, Michaelsen KF, et al. Effects of body size and change in body size from infancy through childhood on body mass index in adulthood. *Int J Obes (Lond)* 2014;38(10):1305-11. doi: 10.1038/ijo.2014.108 [published Online First: 2014/06/20]
78. Law CM, Shiell AW, Newsome CA, et al. Fetal, infant, and childhood growth and adult blood pressure: a longitudinal study from birth to 22 years of age. *Circulation* 2002;105(9):1088-92. doi: 10.1161/hc0902.104677 [published Online First: 2002/03/06]
79. Ni Y, Beckmann J, Hurst JR, et al. Size at birth, growth trajectory in early life, and cardiovascular and metabolic risks in early adulthood: EPICure study. *Archives of Disease in Childhood Fetal & Neonatal Edition* 2021;106(2):149-55. doi: https://dx.doi.org/10.1136/archdischild-2020-319328
80. Eriksson J, Forsen T, Osmond C, et al. Obesity from cradle to grave. *Int J Obes Relat Metab Disord* 2003;27(6):722-7. doi: 10.1038/sj.ijo.0802278 [published Online First: 2003/07/02]
81. Tzoulaki I, Sovio U, Pillas D, et al. Relation of immediate postnatal growth with obesity and related metabolic risk factors in adulthood: the northern Finland birth cohort 1966 study. *Am J Epidemiol* 2010;171(9):989-98. doi: 10.1093/aje/kwq027 [published Online First: 2010/04/03]
82. Ezzahir N, Alberti C, Deghmoun S, et al. Time course of catch-up in adiposity influences adult anthropometry in individuals who were born small for gestational age. *Pediatr Res* 2005;58(2):243-7. doi: 10.1203/01.PDR.0000169980.35179.89 [published Online First: 2005/08/02]
83. Rzehak P, Oddy WH, Mearin ML, et al. Infant feeding and growth trajectory patterns in childhood and body composition in young adulthood. *American Journal of Clinical Nutrition* 2017;106(2):568-80. doi: http://dx.doi.org/10.3945/ajcn.116.140962
84. Oyama M, Saito T, Nakamura K. Rapid weight gain in early infancy is associated with adult body fat percentage in young women. *Environ Health Prev Med* 2010;15(6):381-5. doi: 10.1007/s12199-010-0152-3 [published Online First: 2011/03/25]
85. Breij LM, Kerkhof GF, Hokken-Koelega AC. Risk for Nonalcoholic Fatty Liver Disease in Young Adults Born Preterm. *Horm Res Paediatr* 2015;84(3):199-205. doi: 10.1159/000437054 [published Online First: 2015/08/19]
86. Breij LM, Kerkhof GF, Hokken-Koelega AC. Accelerated infant weight gain and risk for nonalcoholic fatty liver disease in early adulthood. *J Clin Endocrinol Metab* 2014;99(4):1189-95. doi: 10.1210/jc.2013-3199 [published Online First: 2014/01/16]

87. Euser AM, Finken MJ, Keijzer-Veen MG, et al. Associations between prenatal and infancy weight gain and BMI, fat mass, and fat distribution in young adulthood: a prospective cohort study in males and females born very preterm. *Am J Clin Nutr* 2005;81(2):480-7. doi: 10.1093/ajcn.81.2.480 [published Online First: 2005/02/09]
88. Leunissen RW, Kerkhof GF, Stijnen T, et al. Timing and tempo of first-year rapid growth in relation to cardiovascular and metabolic risk profile in early adulthood. *Jama* 2009;301(21):2234-42. doi: http://dx.doi.org/10.1001/jama.2009.761
89. Salgin B, Norris SA, Prentice P, et al. Even transient rapid infancy weight gain is associated with higher BMI in young adults and earlier menarche. *Int J Obes (Lond)* 2015;39(6):939-44. doi: 10.1038/ijo.2015.25 [published Online First: 2015/03/17]
90. McCarthy A, Hughes R, Tilling K, et al. Birth weight; postnatal, infant, and childhood growth; and obesity in young adulthood: evidence from the Barry Caerphilly Growth Study. *Am J Clin Nutr* 2007;86(4):907-13. doi: 10.1093/ajcn/86.4.907 [published Online First: 2007/10/09]
91. Australian Institute of Health and Welfare. Overweight and obesity: AIHW; 2023 [Available from: https://www.aihw.gov.au/reports/overweight-obesity/overweight-and-obesity/contents/overweight-and-obesity accessed 2nd October 2023.
92. Breij LM, Steegers-Theunissen RP, Briceno D, et al. Maternal and Fetal Determinants of Neonatal Body Composition. *Hormone research in paediatrics* 2015;84(6):388-95. doi: https://dx.doi.org/10.1159/000441298
93. World Health Organization. Obesity and overweight: WHO; 2021 [accessed 30th September 2023.
94. Boutari C, Mantzoros CS. A 2022 update on the epidemiology of obesity and a call to action: as its twin COVID-19 pandemic appears to be receding, the obesity and dysmetabolism pandemic continues to rage on. *Metabolism* 2022;133:155217. doi: 10.1016/j.metabol.2022.155217 [published Online First: 2022/05/19]
95. Hruby A, Hu FB. The Epidemiology of Obesity: A Big Picture. *Pharmacoeconomics* 2015;33(7):673-89. doi: 10.1007/s40273-014-0243-x [published Online First: 2014/12/05]
96. Sammallahti S, Heinonen K, Andersson S, et al. Growth after late-preterm birth and adult cognitive, academic, and mental health outcomes. *Pediatr Res* 2017;81(5):767-74. doi: 10.1038/pr.2016.276 [published Online First: 2017/01/06]
97. Emond AM, Blair PS, Emmett PM, et al. Weight faltering in infancy and IQ levels at 8 years in the Avon Longitudinal Study of Parents and Children. *Pediatrics* 2007;120(4):e1051-8. doi: 10.1542/peds.2006-2295 [published Online First: 2007/10/03]
98. Ou-Yang MC, Sun Y, Liebowitz M, et al. Accelerated weight gain, prematurity, and the risk of childhood obesity: A meta-analysis and systematic review. *PLoS One* 2020;15(5):e0232238. doi: 10.1371/journal.pone.0232238 [published Online First: 2020/05/06]
99. Embleton ND, Korada M, Wood CL, et al. Catch-up growth and metabolic outcomes in adolescents born preterm. *Archives of Disease in Childhood* 2016;101(11):1026-31. doi: https://dx.doi.org/10.1136/archdischild-2015-310190
100. Embleton ND, Jennifer Moltu S, Lapillonne A, et al. Enteral Nutrition in Preterm Infants (2022): A Position Paper From the ESPGHAN Committee on Nutrition and Invited Experts. *J Pediatr Gastroenterol Nutr* 2023;76(2):248-68. doi: 10.1097/MPG.0000000000003642 [published Online First: 2023/01/28]
101. Shi H, Yang X, Wu D, et al. Insights into infancy weight gain patterns for term small-for-gestational-age babies. *Nutr J* 2018;17(1):97. doi: 10.1186/s12937-018-0397-z [published Online First: 2018/10/31]
102. Leaf A, Antonio J. The Effects of Overfeeding on Body Composition: The Role of Macronutrient Composition - A Narrative Review. *Int J Exerc Sci* 2017;10(8):1275-96. [published Online First: 2018/02/06]
103. MacBean V, Drysdale SB, Zivanovic S, et al. Participant retention in follow-up studies of prematurely born children. *BMC Public Health* 2019;19(1):1233. doi: 10.1186/s12889-019-7575-6 [published Online First: 2019/09/08]

104. Boyko EJ. Observational research--opportunities and limitations. *J Diabetes Complications* 2013;27(6):642-8. doi: 10.1016/j.jdiacomp.2013.07.007 [published Online First: 2013/09/24]
105. Eriksson J, Forsen T, Tuomilehto J, et al. Size at birth, childhood growth and obesity in adult life. *Int J Obes Relat Metab Disord* 2001;25(5):735-40. doi: 10.1038/sj.ijo.0801602 [published Online First: 2001/05/22]
106. Zheng M, Hesketh KD, Vuillermin P, et al. Determinants of rapid infant weight gain: A pooled analysis of seven cohorts. *Pediatric Obesity* 2022;17(10):e12928. doi: https://dx.doi.org/10.1111/ijpo.12928
107. Singhal A, Cole TJ, Fewtrell M, et al. Promotion of faster weight gain in infants born small for gestational age: is there an adverse effect on later blood pressure? *Circulation* 2007;115(2):213-20. doi: 10.1161/CIRCULATIONAHA.106.617811 [published Online First: 2006/12/21]
108. Ziegler EE. Growth of breast-fed and formula-fed infants. *Nestle Nutr Workshop Ser Pediatr Program* 2006;58:51-9; discussion 59-63. doi: 10.1159/000095010 [published Online First: 2006/08/12]
109. Horta BL, Loret de Mola C, Victora CG. Long-term consequences of breastfeeding on cholesterol, obesity, systolic blood pressure and type 2 diabetes: a systematic review and meta-analysis. *Acta Paediatr* 2015;104(467):30-7. doi: 10.1111/apa.13133 [published Online First: 2015/07/21]
110. Koletzko B, von Kries R, Closa R, et al. Lower protein in infant formula is associated with lower weight up to age 2 y: a randomized clinical trial. *American Journal of Clinical Nutrition* 2009;89(6):1836-45. doi: https://dx.doi.org/10.3945/ajcn.2008.27091
111. Weber M, Grote V, Closa-Monasterolo R, et al. Lower protein content in infant formula reduces BMI and obesity risk at school age: follow-up of a randomized trial. *American Journal of Clinical Nutrition* 2014;99(5):1041-51. doi: http://dx.doi.org/10.3945/ajcn.113.064071
112. Dubowitz H, Black M. BMJ Best Practice: Faltering Growth 2021 [Available from: https://bestpractice.bmj.com/topics/en-us/747 accessed 7th September 2023.
113. Thompson DS, McKenzie K, Opondo C, et al. Faster post-malnutrition weight gain during childhood is associated with risk of noncommunicable disease in adult survivors of severe malnutrition. *medRxiv* 2022;04 doi: https://dx.doi.org/10.1101/2022.03.02.22271635
114. World Health Organization. Pocket Book of Hospital Care for Children: Guidelines for the Management of Common Childhood Illnesses. 2nd ed. Geneva2013.
115. Kuczmarski RJ, Ogden CL, Guo SS, et al. 2000 CDC Growth Charts for the United States: methods and development. *Vital Health Stat 11* 2002(246):1-190.
116. de Onis M, Garza C, Onyango AW, et al. [WHO growth standards for infants and young children]. *Arch Pediatr* 2009;16(1):47-53. doi: 10.1016/j.arcped.2008.10.010
117. Grummer-Strawn LM, Reinold C, Krebs NF, et al. Use of World Health Organization and CDC growth charts for children aged 0-59 months in the United States. *MMWR Recomm Rep* 2010;59(RR-9):1-15.
118. Appleton J, Russell CG, Laws R, et al. Infant formula feeding practices associated with rapid weight gain: A systematic review. *Matern Child Nutr* 2018;14(3):e12602. doi: https://dx.doi.org/10.1111/mcn.12602
119. Paul IM, Savage JS, Anzman SL, et al. Preventing obesity during infancy: a pilot study. *Obesity (Silver Spring)* 2011;19(2):353-61. doi: 10.1038/oby.2010.182 [published Online First: 2010/08/21]
120. Savage JS, Birch LL, Marini M, et al. Effect of the INSIGHT Responsive Parenting Intervention on Rapid Infant Weight Gain and Overweight Status at Age 1 Year: A Randomized Clinical Trial. *JAMA Pediatr* 2016;170(8):742-9. doi: 10.1001/jamapediatrics.2016.0445 [published Online First: 2016/06/09]
121. Fangupo L, Daniels L, Taylor R, et al. The care of infants with rapid weight gain: Should we be doing more? *Journal of Paediatrics & Child Health* 2022;58(12):2143-49. doi: https://dx.doi.org/10.1111/jpc.16247

122. Ong KK, Ahmed ML, Emmett PM, et al. Association between postnatal catch-up growth and obesity in childhood: prospective cohort study. *BMJ* 2000;320(7240):967-71. doi: 10.1136/bmj.320.7240.967 [published Online First: 2001/02/07]

APPENDICIES

APPENDIX 1: UPDATED PROTOCOL

The risk of metabolic consequences in adulthood from rapid weight gain and catch-up growth in the first two years of life: a systematic review protocol

Natalie van der Haak*[1]

Zachary Munn[2]

1 Nutrition Department, Women's and Children's Hospital, North Adelaide, Australia
2 Joanna Briggs Institute, Faculty of Health Science, The University of Adelaide, Australia

*Corresponding author: natalie.vanderhaak@sa.gov.au

Introduction

Failure to Thrive (FTT) or Faltering Growth (FG) results from an imbalance in energy intake versus energy expenditure. This can arise from an insufficient intake of Calories due to a child not being offered enough or not taking enough, or a child's current intake of Calories being insufficient to meet the increased requirements associated with a medical condition. FG can also occur due to a loss of Calories through malabsorption associated with a number of medical conditions such as celiac disease or cystic fibrosis.[1]

FG is a symptom of under nutrition rather than a diagnosis.[1] There is a lack of consensus in the current literature as to the definition of FG with a number of definitions described.[2] Common anthropometric criteria used for diagnosing FG include body mass index (BMI), weight velocity, weight-for-age or length for age less than the 5th percentile, weight less than the 75th percentile of median weight-for-age, or weight-for-length less than the 10th percentile,[3] with the most accepted definition being weight falling through two or more percentile bands.[4]

FG is not uncommon in the developed world, and is seen in 5 to 10 percent of infants and toddlers in primary care settings[5] and 3 to 5 percent of infants and toddlers in the hospital setting[6] Children who experience FG in infancy are lighter and shorter[7] and have a lower IQ[8] than their age matched counterparts, therefore prevention and treatment of FG are imperative.
Small for gestational age (small for gestational age) refers to infants born at less than 2 standard deviations from the mean, or weight below the 10th percentile.[9] The prevalence of small for gestational age is difficult to determine as birth weights and gestational age are not often recorded in most national databases. One study estimated that in 2010, 32.4 million babies were born small for gestational age in low and middle income countries, constituting 27% of all live births.[10] Similarly to

those who experience FG, children who are born small for gestational age are also more likely to be shorter[11] with reduced intellectual capacity compared to their age matched counterparts.[12]
Preterm birth refers to birth occurring before 37 weeks of gestation and has a global incidence of 9.6%.[13] Children born very premature are also shorter and thinner later in life[14] and lower rates of weight gain in the neonatal period are associated with poorer neurodevelopmental outcomes[15]
Catch-up growth refers to growth at a rate that is faster and beyond normal expectations for age which occurs after a period of impaired growth.[16] Catch-up growth and rapid weight gain in infants identified with FG can prevent the detrimental effects of FG, such as muscle wasting, infection, gastrointestinal dysfunction, developmental delay, and deficits in cognition and social and emotional competence.[17] In infants born small for gestational age, catch-up growth in infancy can prevent deficits in final adult height[11] as well as suboptimal intellectual and psychological performance.[18]
Interventions employed to facilitate catch-up growth and achieve rapid weight gain depend on the age of the child, method of feeding and severity of growth impairment. Common interventions can include more frequent breastfeeding and lactation support, formula to supplement breastmilk intake, concentrated formula, and food fortification with energy dense foods.[2]
While catch-up growth and achieving adequate growth rates is recognized as an important determinant of health, recent attention has focussed on the longer term consequences of catch-up growth and rapid weight gain in infancy.[19] The association between rapid weight gain in the first year of life and the development of overweight and obesity later in life is now well established,[20] with those born small for small for gestational age at an increased risk for both obesity and increased fat mass later in life.[9] Other reported metabolic consequences of rapid weight gain or catch-up growth experienced in infancy include cardiovascular disease,[21] hypertension[22] and insulin resistance.[23] This creates a dilemma in that for infants with FG and born premature or small for gestational age, catch-up weight gain may result in both short-term benefits and long-term risks.[24] Currently, the diverse range of populations studied in the literature (including term infants, small for gestational age and premature infants) and range of outcomes measured make it difficult to determine appropriate growth targets for infants and toddlers, particularly for those who experience FG. A search of Medline, Embase and the Joanna Briggs Institute and Cochrane databases in July 2021 did not identify any systematic reviews currently on this topic. This review aims to provide clarity to this discussion, and evaluate the metabolic outcomes of rapid weight gain and catch-up growth in infancy across those born term, prematurely or small for gestational age. It is hoped that the results of this review provide clear information to direct dietetic practice in infants requiring catch-up growth.

Review question

The specific review question to be addressed is: what is the risk of metabolic outcomes in adulthood for individuals who experienced rapid weight gain or catch-up growth during the first two years of life?

Keywords

Rapid weight gain; catch-up growth; infant; toddler; metabolic outcomes

Inclusion and exclusion criteria

Participants

This review will consider studies that include participants 18 years and older who experienced any type of rapid weight gain or catch-up growth in the first two years of life. Studies that include infants with a specific medical condition known to impair growth including but not limited to kidney disease, cardiac disease and coeliac disease will be excluded.

Exposure

This review will consider studies that evaluate the impact, risk or association between rapid weight gain or catch-up growth in the first two years of life and future metabolic outcomes. For the purposes of this review, catch-up growth and rapid weight gain are defined as any weight above what is normally expected for age, including but not limited to an increase in weight standard deviation score of >0.67.

Outcomes

This review will consider studies that assess metabolic outcomes experienced after 18 years, including but not limited to:

- Overweight and obesity - measured by a body mass index (BMI) score
- Hypertension – measured by blood pressure
- Hyperlipidemia – measured by serum cholesterol and triglycerides
- Cardiovascular disease (CVD) – measured by presence of Coronary Heart Disease
- Type 2 diabetes and Insulin Resistance – measured by blood glucose levels
- Body composition – as measured by waist circumference, percentage fat mass, abdominal fat distribution and/or visceral adiposity

This review will not include studies that investigate non-metabolic outcomes including but not limited to cancer, type-1 diabetes mellitus, asthma and cognitive ability.

Study types

This review will consider both experimental and quasi-experimental study designs including randomized controlled trials, non-randomized controlled trials, before and after studies and interrupted time-series studies. In addition, analytical observational studies including prospective and retrospective cohort studies, case-control studies and analytical cross-sectional studies will be considered for inclusion.

No language limits will be applied. No date limits will be stipulated in this review.

Methods

The proposed systematic review will be conducted in accordance with JBI methodology and the

methodology for reviews of prognostic factors. [25] The final review will be reported in line with the Preferred Reporting Items for Systematic reviews and MetaAnalyses (PRISMA) guidelines. [26]

Search strategy

The search strategy was initially developed using the key terms or concepts of the review question in a logic grid. [27] An initial limited search of Medline and Embase was undertaken to identify articles on this topic, followed by analysis of the text words contained in the titles and abstracts, and of the index terms used to describe these articles. This informed the development of a search strategy including identified keywords and index terms which will be tailored for each information source. The reference list of all studies considered for this review will be screened for additional studies. The full search strategy is detailed in Appendix 1. The search strategy will aim to find both published and unpublished studies.

Initial search terms to be used include:

- Infant* or toddler* or child* or babies or small for gestational age or neonat* or premature or newborn*
- faltering growth or failure to thrive or malnourish* or intrauterine growth restriction or IUGR
- ((rapid* or catchup or catch-up or accelerat* or velocit* or fast or faster) adj6 (weight or growth or adipos*))
- (metaboli* or obesity or overweight or adiposity or blood pressure or hypertensi* or hyperlipidemia or type 2 diabetes or cvd or coronary heart disease or body composition or body mass index or percentage mass fat or abdominal fat distribution

Information Sources

The Ovid platform will be used to conduct the literature search. The databases to be searched include:

- Medline and Embase

The trial registers to be searched include:

- Cochrane register of controlled trials

Study selection

Following the search, all identified citations will be collated and uploaded into Endnote and duplicates removed. Titles and abstracts will then be screened by the main author and an independent reviewer for assessment against the inclusion criteria for the review. Studies that may meet the inclusion criteria will be retrieved in full and their details imported into the Joanna Briggs Institute's System for the Unified Management, Assessment and Review of Information (JBI-SUMARI). The full text of selected citations will be retrieved and assessed in detail against the inclusion criteria by the main author and an independent reviewer. Full text studies that do not meet the inclusion criteria will be excluded and reasons for exclusion will be provided in an appendix in the final systematic review report. Included studies will undergo a process of critical appraisal. The results of the search will be reported in full in the final report and presented in a PRISMA flow diagram.

Critical appraisal

Selected studies will be critically appraised by the main author and an independent reviewer at the study level for methodological quality using the Quality in Prognosis Studies (QUIPS) tool. [28] The results of critical appraisal will be reported in narrative form and in a table.

All studies, regardless of the results of their methodological quality, will undergo data extraction and synthesis (where possible).

Data extraction

Data will be extracted from papers included in the review using bespoke excel sheets. The data extracted will include specific details about the interventions, populations, study methods and outcomes of significance to the review question and specific objectives. Any uncertainty with data extraction will be discussed with a second reviewer. Authors of papers will be contacted to request missing or additional data where required.

Data synthesis

Where possible, studies will be pooled in statistical meta-analysis using Cochrane's Review Manager. Effect sizes will be expressed as relative risks (for dichotomous data) and weighted (or standardized) mean differences (for continuous data) and their 95% confidence intervals will be calculated for analysis. Where possible, adjusted estimates will be preferred for use but unadjusted estimates will be used if no adjusted estimates are available. For effect sizes reported as correlation or regression coefficients, these will be combined in meta-analysis using statsdirect. Heterogeneity will be assessed statistically using the standard chi-squared and I^2 tests. The choice of model (random or fixed effects) and method for meta-analysis will be based on the guidance by Tufanaru et al. 2015.[29] A funnel plot will be generated in RevMan to assess publication bias if there are 10 or more studies included in a meta-analysis. Statistical tests for funnel plot asymmetry (Egger test, Begg test, Harbord test) will be performed where appropriate. Subgroup analyses will be conducted where there is sufficient data to investigate. Participants may be stratified by population, exposure or metabolic outcome, including but not limited to; term, small for gestational age or preterm infants; rapid weight gain experienced at 3,6,9,12,18 and/or 24 months; and obesity, CVD, high blood pressure or insulin resistance experienced after 18 years respectively. Participants may also be stratified by age at outcome, for example 18-30 years and >30 years. Where statistical pooling is not possible the findings will be presented in narrative form including tables and figures to aid in data presentation where appropriate. Sensitivity analyses will be conducted to determine the impact of decisions made by the authors, including the combination of different correlation coefficients, the decision of combining multiple study designs in one analysis, and decisions regarding combination of adjusted estimates that have adjusted for different variables.

Assessing certainty in the findings

A 'Summary of Findings' table using GRADE for prognostic factors Pro GDT software will be developed. The GRADE approach for grading the quality of evidence will be followed.[30] The 'Summary of Findings' table will present the following information where appropriate: absolute risks for the treatment and control, estimates of relative risk, and a ranking of the quality of the evidence-based on the risk of bias, directness, heterogeneity, precision and risk of publication bias of the review results. All outcomes will be included in the 'Summary of Findings' table.

Conflicts of interest

The authors declare there are no conflicts of interest.

Acknowledgements

This review will contribute towards a Master of Clinical Science from the University of Adelaide for the main author NV.

References

1. Nutzenadel W. Failure to thrive in childhood. *Dtsch Arztebl Int.* 2011;108(38):642-649.
2. Cole SZ, Lanham JS. Failure to thrive: an update. *Am Fam Physician.* 2011;83(7):829-834.
3. Perrin EC, Cole CH, Frank DA, Glicken SR, Guerina N, Petit K, et al. Criteria for determining disability in infants and children: failure to thrive. *Evid Rep Technol Assess (Summ).* 2003(72):1-5.
4. Olsen EM, Petersen J, Skovgaard AM, Weile B, Jorgensen T, Wright CM. Failure to thrive: the prevalence and concurrence of anthropometric criteria in a general infant population. *Arch Dis Child.* 2007;92(2):109-114.
5. Daniel M, Kleis L, Cemeroglu AP. Etiology of failure to thrive in infants and toddlers referred to a pediatric endocrinology outpatient clinic. *Clin Pediatr (Phila).* 2008;47(8):762-765.
6. Schwartz ID. Failure to thrive: an old nemesis in the new millennium. *Pediatr Rev.* 2000;21(8):257-264; quiz 264.
7. Black MM, Krishnakumar A. Predicting longitudinal growth curves of height and weight using ecological factors for children with and without early growth deficiency. *J Nutr.* 1999;129(2S Suppl):539S-543S.
8. Corbett SS, Drewett RF. To what extent is failure to thrive in infancy associated with poorer cognitive development? A review and meta-analysis. *J Child Psychol Psychiatry.* 2004;45(3):641-654.
9. Cho WK, Suh BK. Catch-up growth and catch-up fat in children born small for gestational age. *Korean J.* 2016;59(1):1-7.
10. Black RE. Global Prevalence of Small for Gestational Age Births. *Nestle Nutr Inst Workshop Ser.* 2015;81:1-7.
11. Karlberg J, Albertsson-Wikland K. Growth in full-term small-for-gestational-age infants: from birth to final height. *Pediatr Res.* 1995;38(5):733-739.
12. Lundgren EM, Tuvemo T. Effects of being born small for gestational age on long-term intellectual performance. *Best Pract Res Clin Endocrinol Metab.* 2008;22(3):477-488.

13. Beck S, Wojdyla D, Say L, Betran AP, Merialdi M, Requejo JH, et al. The worldwide incidence of preterm birth: a systematic review of maternal mortality and morbidity. *Bull World Health Organ.* 2010;88(1):31-38.
14. Bocca-Tjeertes IF, Kerstjens JM, Reijneveld SA, de Winter AF, Bos AF. Growth and predictors of growth restraint in moderately preterm children aged 0 to 4 years. *Pediatrics.* 2011;128(5):e1187-1194.
15. Ehrenkranz RA, Dusick AM, Vohr BR, Wright LL, Wrage LA, Poole WK. Growth in the neonatal intensive care unit influences neurodevelopmental and growth outcomes of extremely low birth weight infants. *Pediatrics.* 2006;117(4):1253-1261.
16. Kay's SK, Hindmarsh PC. Catch-up growth: an overview. *Pediatr Endocrinol Rev.* 2006;3(4):365-378.
17. Shields B, Wacogne I, Wright CM. Weight faltering and failure to thrive in infancy and early childhood. *BMJ.* 2012;345:e5931.
18. Lundgren EM, Cnattingius S, Jonsson B, Tuvemo T. Intellectual and psychological performance in males born small for gestational age with and without catch-up growth. *Pediatr Res.* 2001;50(1):91-96.
19. ud Din Z, Emmett P, Steer C, Emond A. Growth outcomes of weight faltering in infancy in ALSPAC. *Pediatrics.* 2013;131(3):e843-849.
20. Weng SF, Redsell SA, Swift JA, Yang M, Glazebrook CP. Systematic review and meta-analyses of risk factors for childhood overweight identifiable during infancy. *Arch Dis Child.* 2012;97(12):1019-1026.
21. Eriksson JG, Forsen T, Tuomilehto J, Winter PD, Osmond C, Barker DJ. Catch-up growth in childhood and death from coronary heart disease: longitudinal study. *BMJ.* 1999;318(7181):427-431.
22. Leunissen RW, Kerkhof GF, Stijnen T, Hokken-Koelega AC. Effect of birth size and catch-up growth on adult blood pressure and carotid intima-media thickness. *Horm Res Paediatr.* 2012;77(6):394-401.
23. Ong KK, Dunger DB. Birth weight, infant growth and insulin resistance. *Eur J Endocrinol.* 2004;151 Suppl 3:U131-139.
24. Monteiro PO, Victora CG, Barros FC, Monteiro LM. Birth size, early childhood growth, and adolescent obesity in a Brazilian birth cohort. *Int J Obes Relat Metab Disord.* 2003;27(10):1274-1282.
25. Riley RD, Moons KGM, Snell KIE, Ensor J, Hooft L, Altman DG, et al. A guide to systematic review and meta-analysis of prognostic factor studies. *BMJ.* 2019;364:k4597.
26. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ.* 2021;372:n71.
27. Aromataris E, Riitano D. Constructing a search strategy and searching for evidence. A guide to the literature search for a systematic review. *Am J Nurs.* 2014;114(5):49-56.
28. Hayden JA, van der Windt DA, Cartwright JL, Cote P, Bombardier C. Assessing bias in studies of prognostic factors. *Ann Intern Med.* 2013;158(4):280-286.
29. Tufanaru C, Munn Z, Stephenson M, Aromataris E. Fixed or random effects meta-analysis? Common methodological issues in systematic reviews of effectiveness. *Int J Evid Based Healthc.* 2015;13(3):196-207.
30. Foroutan F, Guyatt G, Zuk V, Vandvik PO, Alba AC, Mustafa R, et al. GRADE Guidelines 28: Use of GRADE for the assessment of evidence about prognostic factors: rating certainty in identification of groups of patients with different absolute risks. *J Clin Epidemiol.* 2020;121:62-70.

APPENDIX 2: PROTOCOL DEVIATONS

Protocol Deviation 1:

After initial full text screen 40 studies met inclusion criteria. 46 outcomes measured in adulthood after rapid weight gain was experienced in infancy were identified. After consideration by the student and primary supervisor it was determined data extraction and analysis for all 46 outcomes exceeded what is achievable within the scope of this research program. While a number of studies explored areas where the relationship between rapid weight gain in infancy and later adverse outcomes is yet to be well established, such as coronary heart disease, insulin resistance and metabolic syndrome, the heterogeneity between different outcome measures was so significant that a meta-analysis would have been unable to be performed. For example, 9 studies explored the relationship between infant weight gain and insulin resistance in adulthood, with insulin resistance determined using 8 different outcome measures (appendix 8) After careful consideration it was decided that only studies that identified overweight and BMI as the outcome measure would be included in this review, to facilitate a systematic review of studies more similar in nature with outcomes measured in the same way. Therefore 23 studies were included in the final review.

APPENDIX 3: SEARCH STRATEGY

The final search strategy is as follows:

1. ((rapid* or catchup or catch up or accelerat* or velocit* or fast or faster) adj6 (weight or growth or adipos*)).ti,ab,kw.
2. exp infant/ or (infan* or child* or toddler* or babies or neonat* or newborn*).ti,ab,kw.
3. 1 and 2
4. exp Metabolism/
5. exp Obesity/
6. exp Body Mass Index/
7. exp Weight Gain/
8. exp Anthropometry/
9. exp Hypertension/
10. exp Hyperlipidemias/
11. exp Diabetes Mellitus, Type 2/
12. exp Cardiovascular Disease/
13. exp Coronary Disease/
14. (metaboli* or obesity or overweight or adiposity or blood pressure or hypertensi* or hyperlipidemia or type 2 diabetes or cvd or coronary heart disease or body composition or body mass index or pecentage mass fat or abdominal fat distribution).ti,ab,kw.
15. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. 3 and 15
17. 16 not (animals/ not humans.sh.)

APPENDIX 4: DESCRIPTION OF INCLUDED STUDIES

Adair et al[68] assessed the impact of rapid weight gain experienced between 0-2 years in 8362 infants on overweight status in adults between 18-31 years. The data were pooled from birth cohorts in Brazil, Guatemala, India, the Philippines and South Africa. Rapid weight was assessed by conditional weight gain, a change in weight-for-age z-score larger than expected, and overweight was assessed using BMI ≥ 25kg/m^2. Results were adjusted for adult age.

Demerath et al[69] followed 233 appropriate weight for gestational age infants in the Fels Longitudinal Study to a mean age of 46.5. They were assessed for an association between rapid weight gain in infancy and risk of overweight/obesity in adulthood. Rapid weight gain was defined as an increase in weight-for-age SDS of ≥0.67 between time points of interest. Overweight was defined as BMI ≥ 25kg/m^2. Adjustments were made for gestational age at birth, sex, current age, birthweight SDS, stature, birth year, mother's age at birth, maternal BMI, birth order, breastfeeding, education, activity and smoking status.

Odegaard et al[70] retrospectively assessed 422 appropriate weight for gestational age singletons for the risk of overweight/obesity resulting from rapid weight gain between multiple time points from 0-2 years. Rapid weight gain was defined as an increase in weight-for-age z-score of ≥0.67. Results were adjusted for many variables including parental BMI, sex, gestational age at birth, age at adulthood obesity assessment, birth year, birth WHO WAZ or weight-for-length z-score.

In 2003 Stettler et al[71] followed 300 African American infants born at full term to 20 years of age where overweight/obesity resulting from rapid weight gain from 0-4 months was assessed. Rapid weight gain was defined as an increase in weight-for-age z-score ≥ 1 SD. Overweight-overfat was defined as BMI ≥ 25kg/m^2 and sum of skinfolds ≥85th percentile. Results were adjusted for age, gender, gestational age, maternal BMI, maternal age, smoking and maternal education.

Stettler et al[72] in 2005 evaluated 653 European American formula fed infants for the risk of overweight/obesity from rapid weight gain experienced between 0-4 months. Rapid weight

gain was assessed as change in weight z-score. Overweight was assessed as BMI ≥ 25kg/m^2 at 26 years of age. Results were adjusted for age, gender and formula type.

The study by Sutharsan et al[73] was a prospective cohort study examining overweight/obesity status in 1,768 adults aged 21 years who experienced rapid weight gain from 0-6 months. Rapid weight gain was defined as an increase in weight SDS of ≥0.67 and overweight was defined as a BMI ≥25 kg/m^2. Results were adjusted for gender, gestation, breastfeeding and other potential confounders gender, gestation, breast-feeding, parity, fast food consumption at 14 years, television viewing at 14 years, physical activity at 14 years, maternal education, maternal age at birth, maternal pre-pregnancy BMI, maternal smoking and race.

Bjerregaard et al[77] investigated change in body weight in healthy singletons between multiple time points in the first year of life and association with adult BMI at 42 years of age. Change in weight was measured using weight SDS and BMI was expressed in SDS units. Associations were adjusted for age at infant measure, sex, parental social class, pre-pregnancy BMI, gestational weight gain and preterm birth.

Breij et al[86] retrospectively assessed 182 adults at a mean age of 21 years who were born small for gestational age and/or had short stature in adulthood for the association between catch-up growth in the first year of life and adult BMI. Rapid catch-up growth was defined as a SDS of ≥0.67 SDS in first year of life plus the increase of ≥0.5 SDS after term age in first three months of life. BMI data in adulthood was log transformed. Associations were adjusted for age, gender, socio-economic status, gestational age, birth length SDS and gain in length 0-3 months.

Breij et al[85] explored the increase in weight SDS in the first year of life plus the increase of ≥0.5 SDS after term age in first three months of life in 162 preterm infants compared with full term infants and the association with BMI in adulthood. BMI data was log transformed. Adjustments were made for age, gender, socio-economic status, gestational age, birth length SDS and gain in length from 0-3 months.

Buffarini et al[76] assessed impact of the increase in conditional weight gain (expressed as z-scores) in the first year of life on BMI SDS at 19 years of age in a prospective cohort study. Results were adjusted for smoking during pregnancy, breastfeeding, mother's education, household wealth, skin colour BMI, CH, CRP, CWh, DBP, HDL-C, LDL-C, LDL chol, SBP, TC, TGL and WC.

Euser et al[87] investigated the relationship between change in weight-for-age SDS in the first year of life in 403 infants born < 32 weeks and BMI SDS at 19 years of age. Results were adjusted for birthweight and age.

Ezzahir et al[82] explored the impact of change in BMI SDS in 127 term singletons from 0-2 years of age on BMI SDS at 20 years of age. Results were adjusted for age and gender.
Eriksson et al[80] assessed the impact of change in BMI z-score from birth to one year in 4,515 infants on BMI at age 55-65 years. Data was adjusted for year of birth and gender.
Law et al[78] explored the impact of change in conditional weight SDS in the first year of life in 1,867 term singletons on BMI at age 22 years in a retrospective study. It is unclear if results were adjusted for any variables.

Leunissen et al[88] investigated the impact of an increase in weight-for-age SDS of ≥0.67 SDS in first year of life + >increase of ≥0.5 SDS after term age in first 3 months of life in 323 infants on BMI at age 21 years. Results were adjusted for gestational age, sex, age, socio-economic status socio-economic status and height growth.

McCarthy et al[90] assessed the impact of weight gain greater than expected in 542 infants at multiple time points in the first 21 months of life on BMI at 25 years. Results were adjusted for adult age, sex, gestational age, maternal and paternal weight, parental socio-economic status in childhood, maternal smoking in pregnancy and current adult smoking status.

Ni et al[79] retrospectively explored the relationship between change in weight-for-age z-score in 129 extremely premature infants and BMI at age 19 years. Results were adjusted for sex, maternal age and smoking during pregnancy.

Oyama et al[84] assessed the impact of weight-for-age z-score in 86 female university students with school weight records and impact on BMI at age 19 years. Weight change was measured at multiple time points in the first 1.5 years of life. Results were adjusted for physical activity.

Rzehak et al[83] presented data from 4 different birth cohorts. The West Australian Pregnancy (Raine) cohort included data for 2,440 participants and explored the impact of an increase in BMI SDS of >1 from 0-2 years on BMI SDS at age 18. It is unclear if adjustments were made.

Salgin et al[89] investigated the impact of rapid weight gain in the first year of life in 2,352 black South African singletons on BMI SDS at age 18. Rapid weight gain was defined as an increase in weight-for-age z-score of ≥0.67. Results were adjusted for smoking during pregnancy, birth order, gestational age, formula milk feeding and socio-economic status.

In 2013 Touwslager et al[74] prospectively assessed the impact of change in weight-for-age z-score in healthy infant twins on BMI at age 18-34 years. There were data for 522 infants and rapid weight gain was assessed at multiple time points in the first 2 years. Results were adjusted for birthweight, gestational age, sex, zygosity-chronicity, age, parental educational level, family history of CVD, smoking, alcohol use, physical activity, abdominal circumference, systolic blood pressure, glucose, HDL, and triglycerides.

Tzoulaki et al[81] prospectively investigated the impact of peak weight velocity experienced in the first two years of life in 4,026 infants in the Northern Finland Birth Cohort on BMI at age 31 years. Results were adjusted for sex, socio-economic status at birth, maternal age, maternal height and weight before pregnancy, maternal smoking after the second month of pregnancy, gestational age at birth and birthweight.

Victora et al[75] measured the impact of change in weight-for-age z-score at ages 0-1 and 0-2 years in 132 infant males on BMI at age 18. For 0-1 years, results were adjusted for income, maternal education, maternal height, maternal smoking status. For 0-2 years, results were adjusted as per 0-1 year plus small for gestational age.

APPENDIX 5: SUMMARY TABLE OF INCLUDED STUDIES

Author, year	Study Design	Subjects (n)	Cohort	Characteristics of participants	Country	Exposure and how exposure measured	Exposure Category (RWG or Δ WAZ/SDS)	Exposure time points	Outcomes (measurement)	Age at outcome - years, range or mean ± SD	Statistical method	Associations	Significant association between RWG or Δ WAZ/SDS and adult overweight or BMI (Y/N)
Adair, 2013	Prospective cohort	2710	Cohorts from Brazil, Guatemala, India, the Philippines and South Africa in the COHORTS study	Health infants, average gestation 39 weeks	America	Conditional weight gain (one SD of conditional relative weight at 2 years corresponds to change in WAZ from birth to 2 years that is slightly less than 0.67SD)	RWG	0-2 years	Overweight (BMI ≥25 kg/m2)	18-31	Logistic regression	Conditional relative weight at 2 yrs. was associated with likelihood of BMI ≥25kg/m2 in adulthood (OR 1.51, 95% CI 1.43,1.60)	Y
Bjerregaard, 2014	Retrospective analysis of prospective birth cohort	1633	Copenhagen perinatal cohort	Healthy singletons	Denmark	Change in weight-for-age SDS	Δ WAZ/SDS	0-3 months	BMI SDS	42	Linear regression	Per 1 unit increase in infant weight SDS 0-3 months, BMI SDS at 42 years was 0.09 SDS higher (95% CI 0.04,0.15)	Y
Breij, 2014	Retrospective cohort	182	PROGRAM (Programming factors for growth and metabolism) study cohort	Term Caucasian healthy singletons - small for gestational age and/or short stature as adults	Netherlands	Increase in weight-for-length SDS of ≥0.67 SDS in first year of life and increase of >0.5 SDS in first 3 months of life	RWG	0-3 months	BMI (log transformed)	21 (18-24)	Linear regression	Gain in weight SDS for length SDS in the first 3 months of life was significantly associated with BMI in adulthood (β=2.358, p=0.038)	Y
Breij, 2015	Retrospective cohort	162	PREMS study	Healthy adults, born preterm <36 weeks vs full term, Caucasian singletons	Netherlands	Increase in weight-for-age SDS of >0.67 SDS in first year of life + increase of >0.5 SDS after term age in first 3 months of life	RWG	0-3months corrected age	BMI (log transformed)	21	Linear regression	Gain in weight SDS for length SDS in the first 3 months of life after term age was not significantly associated with BMI in adulthood (β=3.54, p=0.055)	N
Buffarini, 2018	Prospective cohort	946	Pelotas birth cohort	Infants	Brazil	Conditional weight gain	RWG	0-1 year	BMI SDS	18.5	Linear regression	Conditional weight gain 0-1 year was positively associated with BMI in adulthood (β=0.26, p=0.0001)	Y
Demerath, 2009	Prospective cohort	233	Fels longitudinal Study	AGA singleton white children	America	Increase in weight-for-age SDS >0.67	RWG	0-2 years	Overweight (BMI ≥25 kg/m2)/ BMI (kg/m2)	46.5	Multivariate linear model	Infants with RWG 0- 2 years had an increased risk of overweight in adulthood (OR 5.54, 95%CI 1.88, 16.31)	Y

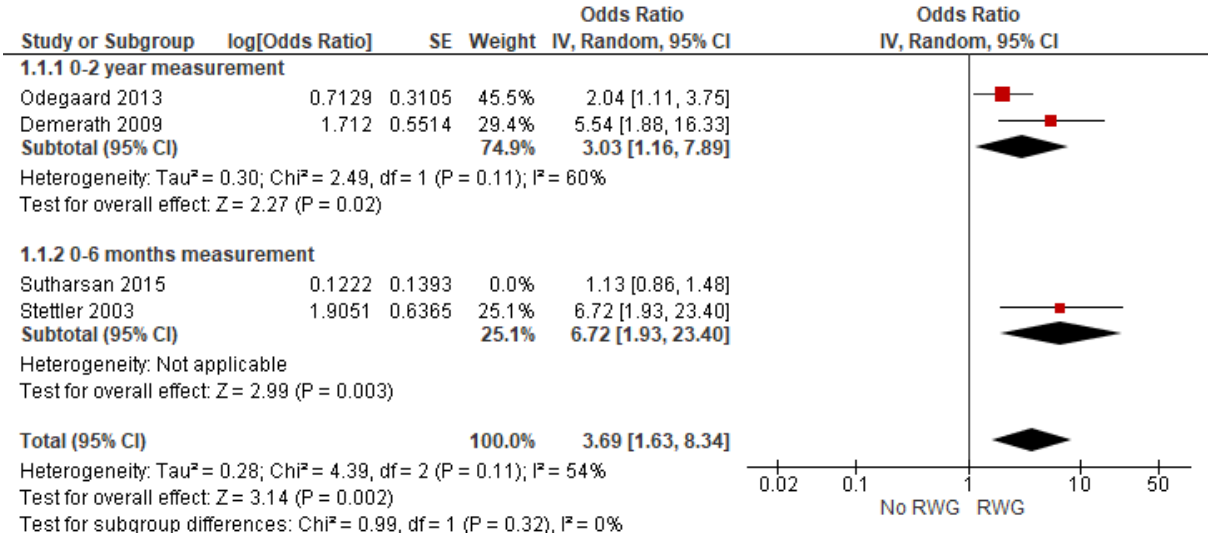
Eriksson, 2003	Retrospective analysis of prospective birth cohort	4515		Infants	Finland	Change in BMI z-score	Δ WAZ/SDS	0-1 year	Obese (BMI ≥30kg/m2	55-65	Logistic regression	N/A	N/A
Euser, 2005	Retrospective analysis of prospective birth cohort	403	POPS (Project on Preterm and Small for gestational age) study cohort	Infants born <32 weeks, without congenital malformations alive at age 19	Netherlands	Change in weight-for-age SDS	Δ WAZ/SDS	0-3 months	BMI SDS	19	Linear regression	Early postnatal weight gain (0-3 months) was positively associated with adult BMI (β=0.196, p=0.0002). Late postnatal weight gain (3-12 months) was positively associated with adult BMI (β=0.215, p=0.002)	Y
Ezzahir, 2005	Prospective cohort	127		Singletons born ≥37 weeks gestation with small for gestational age	France	Change in BMI SDS >0.3	RWG	0-1 year and 0-2 years	BMI SDS	20	Spearman's Correlation	BMI catch-up from 0-2 years was associated with adult BMI (rho=0.34, p=0.04). BMI catch-up from 0-1 year was not associated with adult BMI (rho=-0.02, p=0.65)	Y
Law, 2002	Retrospective analysis of prospective birth cohort	346	Brompton study cohort	Term singletons	England	Conditional weight gain	RWG	0-1 year	BMI (kg/m2)	22	Pearson's Correlation	Infant conditional weight gain was weakly correlated with adult BMI (0.22, p=0.001)	Y
Leunissen, 2009	Retrospective cohort	217	PROGRAM (Programming factors for growth and metabolism) study cohort	Term Caucasian healthy singletons - small for gestational age and/or short stature as adults	Netherlands	Increase in weight-for-age SDS of ≥0.67 SDS in first year of life + increase of ≥0.5 SDS after term age in first 3 months of life	RWG	0-3 months, >3-6months, >6-9 months and >9-12 months	BMI (log transformed)	21 (18-24)	Linear regression	Rapid weight gain in the first 12 months was not significantly associated with adult BMI	N
McCarthy, 2007	Retrospective analysis of prospective birth cohort	679	Barry Caerphilly growth study	Singleton infants	Wales	spline model (increase above normal expectations) converted to z-score	RWG	0-5 months and >5-20 months	BMI (kg/m2)	25	Linear regression	Increase in WAZ from 0-5 months was associated with adult BMI (β=0.42, p=0.02). Increase in WAZ from 5mo - 1yr 9mo was not significantly associated with adult BMI (0.38, p=0.06).	Y
Ni, 2021	Prospective cohort	129	EPICure	Extremely Premature infants (<26 weeks gestation)	England	Change in weight-for-age z-score	Δ WAZ/SDS	0-2.5 years	BMI (kg/m2)	19	Linear regression	Change in WAZ from birth to term age was not significantly associated with adult BMI (β=0.3, p=0.438). Change in WAZ from term age to 2.5 years was not significantly associated with adult BMI (β=0.18, p=0.482)	N
Odegaard, 2013	Prospective cohort	422	Fels longitudinal Study	AGA white singletons	America	Increase in weight-for-age z-score of ≥0.67	RWG	0 - 1, 3, 6, 9, 12, 18 and 24 months	Overweight (BMI ≥25 kg/m2)	20-29	Logistic regression	Rapid growth from 6-9 months showed the strongest association with adult overweight (OR 4.71, 95% CI 1.86,11.94). 0-24 months OR 2.04 (1.11, 3.74). 0-6 months OR 1.69 (0.84, 3.41)	Y
Oyama, 2010	Retrospective cohort	86		Female university students who had maternity and	Japan	Change in weight-for-age z-score	Δ WAZ/SDS	0-3months, 3-6months and 6months-1.5 years	BMI (kg/m2)	19 (19-21)	Pearson's Correlation	Change in WAZ in infancy from 0-3 months, 3-6 months and 6m-1.5 years was not significantly associated with BMI at age 19 years	N

				school weight records									
Rzehak, 2017	Prospective cohort	2440	West Australia Pregnancy (Raine) Cohort	Infants	Germany	Increase in BMI SDS > ~1	RWG	0-2 years	BMI SDS	20	Equality of means test	Infants with an increase in BMI SDS >1 from 0-2 years were more likely to be overweight at age 20 than those with normal infant growth (BMI 25.92kg/m^2 vs. 22.37kg/m^2, p,0.0001)	Y
Salgin, 2015	Prospective cohort	1613	Birth to Twenty prospective birth cohort study	Black South African singletons	South Africa	Increase in weight-for-age z-score of ≥0.67	RWG	0-1 year	BMI SDS	18	ANOVA	catch-up weight gain from birth to 1 year was associated with BMI at age 18 (p<0.001)	Y
Stettler, 2003	Prospective cohort	300	National collaborative perinatal project	African American term infants	America	Increase in weight-for-age z-score ≥1SDS	RWG	0-4 months	Overweight (BMI ≥25 kg/m2)	18-23	Logistic regression	Rapid weight gain during early infancy was associated with an increased risk of overweight at age 20 (OR 6.72, 95% CI 1.93, 23.4)	Y
Stettler, 2005	Retrospective analysis of prospective birth cohort	653		Formula fed infants >2500g of European descent	America	Change in weight-for-age z-score	Δ WAZ/SDS	0-4 months	Overweight (BMI ≥25 kg/m2)	26 (20-32)	Logistic regression	Change in WAZ in the first 4 months of life was associated with adult overweight stats (OR 1.41, 95% CI 1.09, 1.82)	Y
Sutharsan, 2015	Prospective cohort	2077	Mater university of Queensland study of pregnancy (MUSP)	Term singletons	Australia	Increase in weight-for-age SDS >0.67	RWG	0-6m	Overweight (BMI ≥25 kg/m2)	21	Logistic regression	Rapid weight gain in the first 6 months of life did not significantly increase the risk of overweight in adulthood (OR = 1.13, 95 % CI 0.86, 1.49)	N
Touwslager, 2013	Retrospective analysis of prospective birth cohort	522	East Flanders prospective twin survey	Healthy infant twins	Belgium	Change in weight-for-age z-score	Δ WAZ/SDS	0-1month, 1-6months, 6-12months, 12-24months	BMI (log transformed)	18-34	Multivariate multilevel regression	No association between infant weight gain and adult BMI	N
Tzoulaki, 2010	Prospective cohort	4026	Northern Finland birth cohort	Singleton infants	Finland	Peak weight velocity	RWG	0-2 years	BMI (kg/m2)	31	Multivariable linear regression analysis	Peak weight velocity in infancy was significantly associated with adult BMI (p<0.0001)	Y
Victora, 2007	Retrospective analysis of prospective birth cohort	110	Pelotas birth cohort	Males	Brazil	Change in weight-for-age z-score	Δ WAZ/SDS	0-1 year and 1-2 years	BMI (kg/m2)	18	Regression analysis	Change in WAZ from 0-1 year and 1-2 years was associated with adult BMI (β=0.63, p=0.001 and β=0.71, p=0.009 respectively)	Y

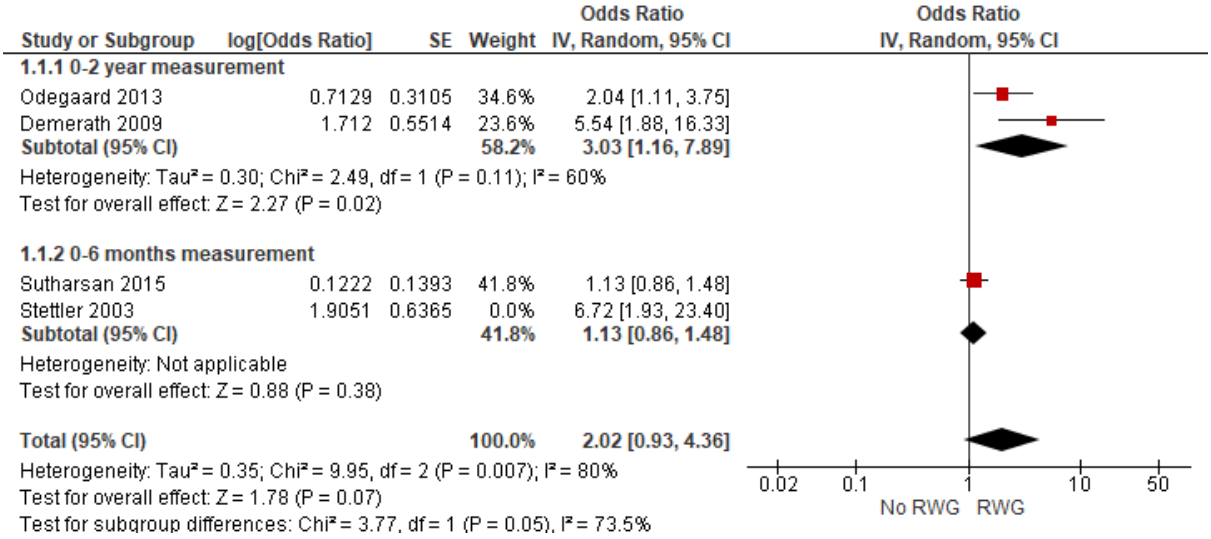
Abbreviations: ΔWAZ , change in weight-for-age z-score; BMI, body mass index; SDS, standard deviation score; RWG, rapid weight gain; OR, odds ratio; β, beta

APPENDIX 6: SENSITIVITY ANALYSES

Forest Plot for risk of being overweight based on adjustment for birthweight



Forest Plot for risk of being overweight not including outcome of overweight-overfat



APPENDIX 7: ADJUSTMENTS BY STUDY

Study	Adult age	Gender	Year of birth	Gestational age	Birth weight	Birth length	Birth order	Gain in length 0-3 months	Preterm birth	small for gestational age	Maternal age	Maternal BMI	Maternal education	Maternal height	Parental social class	Parental BMI	Breastfeeding	Education	Activity
Adair 2013	✓	✓																	
Bjerregaard 2014		✓		✓					✓			✓			✓				
Breij 2014	✓	✓		✓		✓		✓							✓				
Breij 2015	✓	✓		✓		✓		✓							✓				
Buffarini 2018													✓				✓		
Demerath 2009	✓	✓		✓	✓						✓	✓					✓	✓	✓
Eriksson 2003		✓	✓																
Euser 2005	✓				✓														
Ezzahir 2005	✓	✓																	
Law 2002																			
Leunissen 2009	✓	✓		✓				✓											
McCarthy 2007	✓	✓		✓								✓			✓				
Ni 2021		✓									✓								
Odegaard 2013	✓	✓		✓	✓						✓	✓				✓			
Oyama 2010																			✓
Rzehak 2017																			
Salgin 2015				✓			✓								✓				
Stettler 2003	✓	✓		✓	✓						✓	✓	✓						
Stettler 2005	✓	✓			✓							✓				✓			
Sutharsan 2015	✓	✓		✓							✓	✓	✓				✓		
Touwslager 2013	✓	✓																✓	
Tzoulaki 2010		✓		✓	✓							✓			✓				
Victora 2007										✓*			✓	✓					

Study	Smoking status	Maternal smoking	Parity	Formula use	Income	Zygosity-chorionicity	Alcohol use	Skin colour	Family history of CVD	Waist Circumference	Systolic blood pressure	Glucose	HDL-C	Triglycerides	Conditional height	CRP	Diastolic blood pressure	LDL Cholesterol	Total Cholesterol
Adair 2013																			
Bjerregaard 2014																			
Briej 2014																			
Briej 2015																			
Buffarini 2018		✓			✓			✓		✓	✓		✓		✓	✓	✓	✓	✓
Demerath 2009	✓																		
Eriksson 2003																			
Euser 2005																			
Ezzahir 2005																			
Law 2002																			
Leunissen 2009																			
McCarthy 2007	✓	✓																	
Ni 2021		✓																	
Odegaard 2013																			
Oyama 2010																			
Rzehak 2017																			
Salgin 2015		✓		✓															
Stettler 2003	✓																		
Stettler 2005					✓														
Sutharsan 2015		✓	✓																
Touwslager 2013	✓					✓	✓		✓	✓	✓	✓	✓	✓					
Tzoulaki 2010		✓																	
Victora 2007		✓			✓														

Abbreviations: CVD; cardiovascular disease; HDL-C, high density lipoprotein cholesterol; CRP, c reactive protein; LDL, low density lipoprotein; TC, total cholesterol
* 0-2 years only

APPENDIX 8: OUTCOMES MEASURED IN ADULTHOOD BY STUDY

	Blood Pressure							Coronary Heart Disease							Hyperlipidemia	
Study	Central DBP	Central SPB	Hypertension (prescribed medication for)	Seated brachial DBP	Seated brachial SBP	Supine brachial DBP	Supine brachial SBP	Coronary Heart Disease (admitted to hospital for)	ApoA-I (mg/dl)	ApoB (mg/dl)	HDL-c (mg/dl)	LDL-c (mg/dl)	Ration of TC to HDL-c	Ratio of ApoB to ApoA	Total cholesterol (mg/dl)	Triglycerides (mg/dl)
Adair 2009				✔	✔											
Adair 2013				✔	✔											
Araujo de Franca 2016																
Barker 2002			✔													
Ben-Shlomo 2008				✔	✔											
Bjerregaard 2014																
Breij 2014																✔
Breij 2015																✔
Buffarini 2018				✔	✔						✔	✔			✔	✔
Cheng 2015																
Demerath 2009																
East 2020				✔	✔						✔				✔	✔
Ekelund 2006																
Euser 2005																
Ezzahir 2005																
Errikson 2001								✔								
Eriksson 2003																
Fall 2008					✔						✔				✔	✔
Finken 2006																
Howe 2014		✔		✔	✔											
Jarvelin 2004				✔	✔											

Kerkhof 2012					✓					✓	✓	✓	✓			✓		✓	✓
Law 2002																			
Leunissen 2009					✓					✓	✓	✓	✓	✓		✓		✓	
McCarthy 2007																			
Ni 2021	✓	✓				✓		✓											
Norris 2012																			
Oyama 2010																			
Odegaard 2013																			
Rzehak, 2017																			
Salgin 2015																			
Sutharsan 2015																			
Stettler 2003																			
Stettler 2005																			
Touwslager 2013				✓	✓							✓	✓	✓				✓	✓
Tu 2010					✓														
Tu 2013				✓	✓														
Tzoulaki 2010	✓	✓										✓							✓
Victora 2007																			
Workman 2015																			

	Body Composition																	
Study	% abdominal fat	%VAT/ASAT	%VAT/TBF	%Visceral adipose tissue	Abdominal subcutaneous adipose tissue (ASAT, kg)	BMI kg/m2	Body fat (%)	Fat free mass (kg)	Fat mass (kg)	Fat mass index (kg/m2)	Fat free mass index (kg/m2)	Overweight/ Obesity (BMI ≥25kg/m2)	Ratio of trunk fat to total fat	Skeletal muscle mass (kg)	Subcutaneous abdominal fat thickness (cm)	Visceral fat thickness (cm)	Visceral adipose tissue (VAT, kg)	Waist circumference (cm)	Waist to hip ratio
Adair 2009																			
Adair 2013												✓							
Araujo de Franca 2016															✓	✓			
Barker 2002																			
Ben-Shlomo 2008																			
Bjerregaard 2014						✓													
Breij 2014						✓													
Breij 2015						✓													
Buffarini 2018						✓												✓	
Cheng 2015										✓	✓								
Demerath 2009	✓	✓	✓	✓	✓	✓	✓	✓	✓			✓					✓	✓	
East 2020																			
Ekelund 2006																			
Euser 2005						✓	✓	✓	✓									✓	
Ezzahir 2005						✓													
Errikson 2001																			
Eriksson 2003						✓													
Fall 2008																		✓	
Finken 2006																			
Howe 2014																			
Jarvelin 2004																			
Kerkhof 2012							✓						✓					✓	
Law 2002						✓													
Leunissen 2009						✓	✓						✓					✓	✓
McCarthy 2007						✓													✓

Ni 2021	✓						
Norris 2012							
Oyama 2010	✓	✓					
Odegaard 2013				✓			
Rzehak, 2017	✓						
Salgin 2015	✓						
Sutharsan 2015				✓		✓	✓
Stettler 2003				✓			
Stettler 2005				✓			
Touwslager 2013	✓	✓				✓	✓
Tu 2010							
Tu 2013							
Tzoulaki 2010	✓					✓	
Victora 2007	✓		✓				
Workman 2015					✓		

	Insulin Resistance								Metabolic Syndrome		Non Alcoholic Fatty Liver Disease
Study	**Acute insulin response (mU/liter)**	**C-peptide**	**Disposition index**	**Insulin resistance index (HOMA-IR)**	**Insulin sensitivity (μU/ml)**	**Impaired fasting glucose/ Diabetes Mellitus (IFG/DM) (≥6.1 - >7mmol/l / ≥7mmol/l)**	**Plasma glucose concentration (mmol/L)**	**Plasma insulin concentration (mU/l)**	**Metabolic syndrome - ≥ 3 risk factors (↑WC, ↑BP, ↑TG, ↓HDL-C, fasting hyperglycemia)**	**Clustered Metabolic risk score (average of standardised values of WC, BP, TG, HDL-c, glucose + insulin)**	**Fatty Liver Index (FLI)**
Adair 2009											
Adair 2013							✓				
Araujo de Franca 2016											
Barker 2002											
Ben-Shlomo 2008											
Bjerregaard 2014											
Breij 2014											✓
Breij 2015											✓
Buffarini 2018											
Cheng 2015											
Demerath 2009											
East 2020							✓		✓		
Ekelund 2006										✓	
Euser 2005											
Ezzahir 2005											
Errikson 2001											
Eriksson 2003											
Fall 2008				✓			✓		✓		
Finken 2006		✓		✓				✓			
Howe 2014											

Jarvelin 2004							
Kerkhof 2012	✓	✓		✓			
Law 2002							
Leunissen 2009	✓	✓		✓			
McCarthy 2007							
Ni 2021							
Norris 2012			✓		✓	✓	
Oyama 2010							
Odegaard 2013							
Rzehak, 2017							
Salgin 2015							
Sutharsan 2015							
Stettler 2003							
Stettler 2005							
Touwslager 2013						✓	✓
Tu 2010							
Tu 2013							
Tzoulaki 2010						✓	
Victora 2007							
Workman 2015							

Abbreviations: VAT, visceral adipose tissue; ASAT, abdominal visceral adipose tissue; BMI, body mass index; IGF, insulin-like growth factor; WC, waist circumference; BP, blood pressure; TG, triglyceride