Sex Differences in Risk and Outcomes from Severe Malnutrition:

Implications For Management

Susan Anne Thurstans

Thesis submitted in accordance with the requirements for the degree of Doctor of Philosophy of the University of London

January 2024

Department of Population health
Faculty of Epidemiology & Population Health

LONDON SCHOOL OF HYGIENE & TROPICAL MEDICINE

Partially funded by: Emergency Nutrition Network (ENN)

Declaration of own work

I Susan Thurstans declare that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signed

Date 2nd July 2023

Abstract

Background

Excess male morbidity and mortality is well recognised in fields like neonatal medicine and evolutionary biology. In contrast, within the global nutrition community, it is less understood and often stated that girls are most at risk of nutritional deficits. With a focus on a clinical, biological, evolutionary, and social perspective, this PhD sets out to explore the evidence for sex differences in the epidemiology of undernutrition, the reasons for these differences and whether and how these might need to be addressed in policy and practice.

Methods

A systematic review and meta-analysis examined undernutrition-specific estimates for wasting, stunting and underweight by age and sex using a random-effects model. A qualitative synthesis reviewed how sex differences were reported and explained within studies. A narrative review explored which early life mechanisms might underlie these differences. A further random effects meta-analyses described mortality risk associated with anthropometric deficits (wasting, underweight and stunting) in children 6–59 months by age and sex in multi-country cohort data. A pooled secondary analysis assessed treatment outcomes by age and sex.

Results

Boys are more likely to be wasted (pooled OR 1.26, 95% CI 1.13 to 1.40), stunted (pooled OR 1.29 95% CI 1.22 to 1.37) and underweight (pooled OR 1.14, 95% CI 1.02 to 1.26) than girls with variations in differences by regions and age groups. A complex interaction of social, environmental, physiological, and genetic factors likely underlies these differences throughout the life cycle. Sex differences appear to be more pronounced in early infancy, in more severe presentations of malnutrition and in more fragile contexts. For wasted children, there is no difference in mortality risk between children 6–23 months and children 24–59 months (pooled RR 1.08, 95% CI 0.52-2.22, p=0.826 for MUAC <125 mm; RR 1.35, 95% CI 0.79-2.33, p=0.272 for WHZ <−2). For underweight and stunting, younger children had a significantly higher risk of mortality than older children (underweight - pooled RR 2.57, 95% CI 1.65–4.00, p<0.001; stunting - pooled RR 2.83 95% CI 2.09–3.82, p<0.001). Despite a higher risk of wasting, stunting and underweight in boys, in pooled analysis for each anthropometric deficit, we found no differences in mortality risk between girls and boys. In wasting treatment programmes, we observed very few differences between girls and boys in treatment outcomes but have highlighted the need for future research that considers the effect of health and social care indicators.

Conclusions

The risk of undernutrition differs according to sex and the extent and direction of differences is greatly influenced by age and context. This highlights the need to improve data collection in programmes, surveys and research through the full disaggregation and analysis of sex and age to identify which children are most vulnerable in specific contexts, and to allow comparison of programme data with population-level burdens. Ultimately this research aims to contribute to a better understanding of risk so that nutrition interventions, and resources can be targeted according to need.

Acknowledgements

There are many people to whom I am grateful for their time and support in conducting this research. Firstly, thank you to my two supervisors Dr Marko Kerac and Professor Rebecca Sear for their support, guidance, and mentorship over the last 5 years. I am beyond grateful for your belief in my work, especially when I lacked it, and for the continued encouragement to overcome obstacles faced along the way. I am especially grateful for their confidence in me and their guidance through the submission process for my first research paper which wasn't as straightforward as we might have hoped for.

I also owe a great debt of gratitude to Dr Charles Opondo. From my early experience in research and throughout my masters I have strived to improve my understanding of statistics and analysis skills. Your aptitude for statistics and your ability to teach and instil confidence is unsurpassed. I am so grateful for the hours we have spent discussing many of the methods used in this research and how available you have made yourself. I will be forever amazed by your ability to turn 30 lines of my coding into 1 line of yours!

I am also incredibly grateful to the Emergency Nutrition Network, in particular to Tanya Khara who has provided no end of guidance, encouragement and support throughout this research, not to mention work and funding opportunities and a platform for some of my research dissemination. I am so grateful for the opportunities you have provided for me as a consultant, technical associate and member of the wasting and stunting technical interest group. The work of this group is inspirational and an important source of evidence generation for the improvement of the management of undernutrition worldwide.

I have been fortunate to have collaborated with a large number of experienced and committed professionals both within my advisory committee and as an extension of this. I am so thankful to each of them for dedicating their time and expertise to support this research.

Finally, to my husband and two children, thank you for your love and eternally welcome distraction throughout the course of this research.

Supervisors and advisory committee members

Supervisors

- Dr Marko Kerac - Associate professor public health nutrition, Faculty of Epidemiology and population health, Department of population health, LSHTM
- Professor Rebecca Sear – Faculty of Epidemiology and population health, Department of Population Health, LSHTM

Scientific advisory committee members

During the early stages of this research, a group was formed of people with an interest in this subject and its relevance to policy and practice in the management of undernutrition. Throughout, the group has provided feedback on my work as well as support to dissemination efforts. This group consisted of the following people:

- Andre Briend - School of Medicine, Centre for Child Health Research, University of Tampere, Tampere, Finland, Department of Nutrition, Exercise and Sports, University of Copenhagen, Copenhagen, Denmark
- Tanya Khara – Emergency Nutrition Network, Oxford, UK
- Michel Garenne - Institut de Recherche pour le Développement (IRD), Unité Mixte Internationale (UMI) Résiliences, Paris, France, Institut Pasteur, Epidémiologie des Maladies Emergentes, Paris, France, Senior Fellow, FERDI, Université d'Auvergne, Clermont-Ferrand, France, MRC/Wits Rural Public Health and Health Transitions Research Unit, School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
- Mark Myatt – Brixton Health, Llwyngwril, Gwynedd, Wales. United Kingdom
- Charles Opondo - Department of Medical Statistics, London School of Hygiene and Tropical Medicine, National Perinatal Epidemiology Unit, Nuffield Department of Population Health, University of Oxford.
- Andrew Seal – Institute for Global Health, University College London,
- Jonathan Wells – Childhood nutrition research centre, University College London, Institute for Global Health. London

Contributors and co-authors of research in this PhD:

The following people have contributed data to this research, and/or co-authored papers from this research:

- Paluku Bahwere - Université libre de Bruxelles
- Jeanette Bailey – International Rescue Committee
- Robert E Black - Johns Hopkins Bloomberg School of Public Health
- Erin Boyd - Johns Hopkins Bloomberg School of Public Health; USAID/Bureau of Humanitarian Assistance
- James A Berkley - University of Oxford; Kenya Medical Research Institute (KEMRI)
- Carmel Dolan – N4D
- Bridget Fenn - Emergency Nutrition Network
- Saul Guerrero - United Nations Children's Fund
- Sheila Isanaka - Harvard T.H. Chan School of Public Health; Epicentre, Paris, France
- Natasha Lelijveld - Emergency Nutrition Network
- Fabrizio Loddo - Médecins Sans Frontières
- Christine M. McDonald - University of California
- Andrew Mertens - University of California, Berkeley School of Public Health
- Martha Mwangome - Kenya Medical Research Institute (KEMRI)
- Kieran S. O'Brien - University of California
- Natalie Sessions - Emergency Nutrition Network
- Heather Stobaugh - Action Against Hunger, USA
- Sunita Taneja - Center for Health Research and Development, Society for Applied Studies, New Delhi, India
- Keith P West, Jr. - Johns Hopkins Bloomberg School of Public Health
- Stephanie Wrottesley - Emergency Nutrition Network

Funding

Specific work pieces within this PhD have received financial support from the Emergency Nutrition Network via various grants.

Paper 1 was supported by funding from Irish Aid (grant number HQPU/2020/ENN) and the generous support of the American people through the United States Agency for International Development (USAID).

Paper 2 was supported with funding from Irish Aid (grant number HQPU/2021/ENN).

Paper 3 was funded by Irish Aid (grant number (HQPU/2021/ENN) and the generous support of the American people through the United States Agency for International Development (USAID).

The ideas, opinions and comments throughout are entirely the responsibility of its authors and do not necessarily represent or reflect the views of USAID or the United States Government or represent or reflect Irish Aid policy.

Research group affiliations

ENN Wasting and Stunting Technical interest group

Contents

List of figures

List of tables

List of abbreviations

BMI	Body Mass Index
CF	Complementary Feeding
CMAM	Community based management of acute malnutrition
CHNRI	Child Health and Nutrition Research Initiative
DHS	Demographic Health Survey
ENN	Emergency Nutrition Network
FSH	Follicle Stimulating Hormone
GNR	Global nutrition report
HAZ	Height-for-age Z-score
IYCF	Infant and young child feeding
IRC	International Rescue Committee
LAZ	Length-for-age z-score
LBW	Low birth weight
LH	Luteinising Hormone
LMIC	Low- and Middle- Income Countries
LNS	Lipid nutrient supplement
LSHTM	London School of Hygiene and Tropical Medicine
MAM	Moderate Acute Malnutrition
MMN	Multiple micronutrient
MUAC	Mid upper arm circumference
MSF	Médecins Sans Frontières
NCHS	National Centre for Health Statistics
PAF	Population Attributable Fraction
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
SAM	Severe acute malnutrition
SQ-LNS	Small Quantity lipid nutrient supplement
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology
SUN	Scaling Up Nutrition

UN	United Nations
UNICEF	United Nations Children's fund
WaSt	Concurrent wasting and stunting
WHO	World Health Organisation
WHZ	Weight-for-height Z-score
WAZ	Weight-for-age Z-score
WASH	Water, Sanitation and Hygiene

Definition of key terms

Gender:	Socially constructed roles, behaviours and identities of girls, women, men and boys and gender diverse people[2].
Severe malnutrition:	Any form of malnutrition (undernutrition) associated with high risk of severe adverse outcomes[1].
Sex:	A set of biological attributes associated with physiological features such as chromosomes, hormones and reproductive anatomy that define males and females[2].
Stunting:	Defined by low height-for-age. Stunting results from chronic or recurrent undernutrition, usually associated with poverty, poor maternal health and nutrition, recurring ill health, and/or inappropriate feeding and care during infancy and early childhood. Stunting has consequences for a child's ability to achieve their physical and cognitive potential.
Undernutrition:	Insufficient intake of adequate energy and nutrients to meet individual needs for good health and growth. This definition may comprise wasting, stunting, underweight or micronutrient deficiencies, or a combination of any of these.
Underweight:	Defined by low weight-for-age. A child who is underweight may be stunted, wasted or both.
Wasting:	Defined by low weight-for-height, or low mid-upper-arm-circumference. Wasting results from recent and severe weight loss which usually occurs when a child does not have adequate quality and quantity of energy and nutrients and/or they have frequent or prolonged illnesses.

[1] Kerac M, McGrath M, Connell N, et al. 'Severe malnutrition': thinking deeply, communicating simply. BMJ Global Health 2020;5:e003023. doi:10.1136/ bmjgh-2020-003023

[2] Heidari, Shirin, Thomas F. Babor, Paola De Castro, Sera Tort, and Mirjam Curno. 2016. 'Sex and Gender Equity in Research: rationale for the SAGER guidelines and recommended use', *Research Integrity and Peer Review*, 1:2

1 Background and rationale

1.1 Global undernutrition - epidemiology

Good health and nutrition both support a child's growth and development and are a pre-requisite to a child's ability to both survive and thrive. Undernutrition, however, is a devasting obstacle to physiological and cognitive development, affecting millions of children around the world, therefore representing a major public health concern.

Estimates on the global burden show that despite successes in the reduction of prevalence estimates, undernutrition persists. Wasting, is a life-threatening condition characterised by loss of muscle and fat mass, resulting from poor nutrient intake and/or disease. Wasting affects an estimated 45 million (6.8%) children around the world, 13.6 million (2.1%) of whom are severely wasted. Stunting results from poor nutrition in-utero and in early childhood and affects an estimated 148.1 million (22.3%) children globally, down from the year 2000 when an estimated 203 million children (33%) were stunted [1]. The estimates presented here are based on prevalence. If considered in terms of incidence, the true numbers may be considerably higher [2]. Figure 1 and Figure 2 show the global distribution of wasting and stunting. Wasting is most prevalent in Southern Asia (25.1% of global share) and Africa (22% of global share). Stunting is most prevalent in Asia (52% of global share), and Africa (43% of global share) [1].

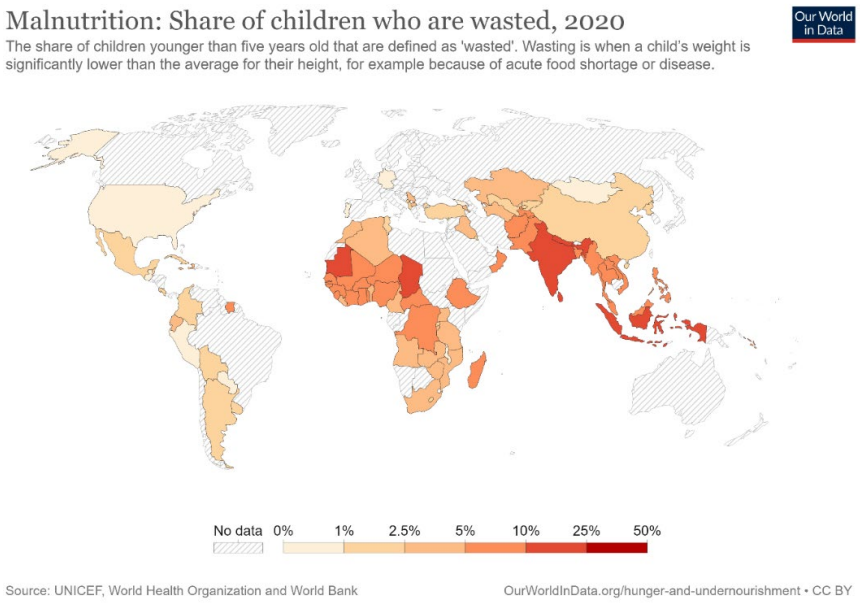


Figure 1 Global distribution of wasting (<-2 WHZ score)

Source: Our World in Data https://ourworldindata.org/ CC-BY

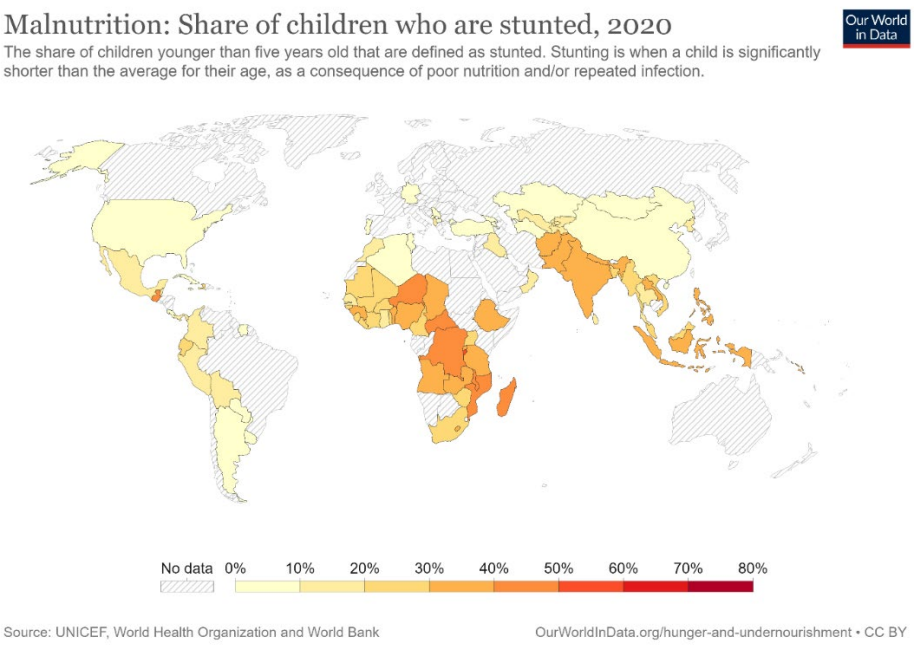


Figure 2 Global distribution of stunting (<-2 HAZ score)

Source: Our World in Data https://ourworldindata.org/ CC-BY

Initiatives such as community based management of acute malnutrition (CMAM), and the up-scaling of prevention activities following the Scaling Up Nutrition (SUN) movement[3] have resulted in progress in the management of undernutrition, however, according to the Global nutrition report (GNR) 2021 [3], nutrition targets set for 2025 (Figure 3) will not be achieved globally, nor in most countries around the world. As an example, the coverage of wasting treatment is a key challenge. According to the UN Global action plan on child wasting [4], in 2019, only 11 million of the estimated 45 million wasted children in the world were reached with treatment, highlighting the urgent need for the acceleration of progress towards fully addressing undernutrition, alongside focussing treatment on the most at risk children and ensuring that prevention efforts are effective.

Challenges to achieving this persist. Whilst coverage estimates for some nutrition interventions remain very low, resources for nutrition services are increasingly limited alongside increasing needs linked to climate change, an increase in displaced persons due to new and ongoing conflicts, food systems breakdown and Covid-19. Although funding for international humanitarian assistance has nearly doubled in a decade, it largely plateaued over the period from 2018-2021 [5] resulting in high levels of unmet needs.

[3] https://scalingupnutrition.org/

The Global nutrition targets (WHO 2014) set for 2025 include:

- A 40% reduction in the number of children under-5 who are stunted
- A 50% reduction of anaemia in women of reproductive age
- A 30% reduction in low birth weight
- Ensure that there is no increase in childhood over-weight
- Increase the rate of exclusive breastfeeding in the first 6 months up to at least 50%
- Reduce and maintain childhood wasting to less than 5%

Figure 3 The 2025 global Nutrition Targets

Source: WHO https://www.who.int/publications/i/item/WHO-NMH-NHD-14.2

1.2 Defining undernutrition

Malnutrition comprises both under and over nutrition. Major forms of undernutrition include wasting, stunting, underweight and micronutrient deficiencies. Overnutrition includes overweight and obesity which are also associated with nutrition related non-communicable diseases [6]. Many countries now face the challenge of a double burden of malnutrition, with high prevalence of both under- and over-nutrition [7].

This PhD focuses on undernutrition in the form of wasting, stunting, concurrent wasting and stunting and underweight, also defined as severe malnutrition [8]. Undernutrition is traditionally measured through clinical assessment and anthropometric measures and indices. Table 1 shows the various references and cut-off points which will serve to define undernutrition throughout this research. In addition to the below Undernutrition can also be defined by the presence of bilateral pitting oedema (nutritional oedema, also commonly known as “kwashiorkor”). The terms severe malnutrition and undernutrition will both be used throughout this research.

Table 1 WHO criteria for major forms of undernutrition.

	Measured by	Definition of undernutrition
Wasting	Mid-Upper-Arm-Circumference (MUAC)	<115mm severe acute malnutrition (SAM) 115mm to <125mm moderate acute malnutrition
	Weight for height	Weight for height z-score (WHZ) • <-3 = severe acute malnutrition • <-2 = moderate acute malnutrition
Stunting	Height for age	Height for age z-score (HAZ) • <-3 = severe stunting • <-2 = moderate stunting
Underweight	Weight for age	Weight for age z-score (WAZ) • <-3= severe underweight • <-2= moderate underweight

1.3 Causes of undernutrition

To effectively address undernutrition, it is important to understand the aetiology. The conceptual framework for undernutrition provides an outline for understanding the determinants of both maternal and child undernutrition (Figure 4). Many of the driving forces for the different types of undernutrition are similar. For example, analyses of the individual determinants of wasting and stunting have demonstrated common pathways which include poor maternal nutrition, high parity, low levels of education, low birthweight, and poor infant feeding practices [9-15].

This suggests that preventative interventions such as achieving adequate maternal nutrition, both before and during pregnancy and breastfeeding, ensuring optimal infant and young child feeding practices and ensuring a healthy environment which includes access to basic health, water, hygiene and sanitation services and opportunities for safe physical activity, have a role in addressing multiple forms of undernutrition [16].

A large proportion of undernutrition is understood to originate in-utero. In 2006, the introduction of revised WHO growth standards demonstrated that growth faltering in early infancy was more pronounced than previous analysis using NCHS standards had suggested [17]. Recent longitudinal research provides further evidence that both wasting and stunting are prevalent at birth, peaking between 0-3 months [13, 18]. Wasting and stunting present at birth can contribute to further growth failure during infancy and childhood highlighting the critical need to improve maternal health and nutrition as a means of prevention [19].

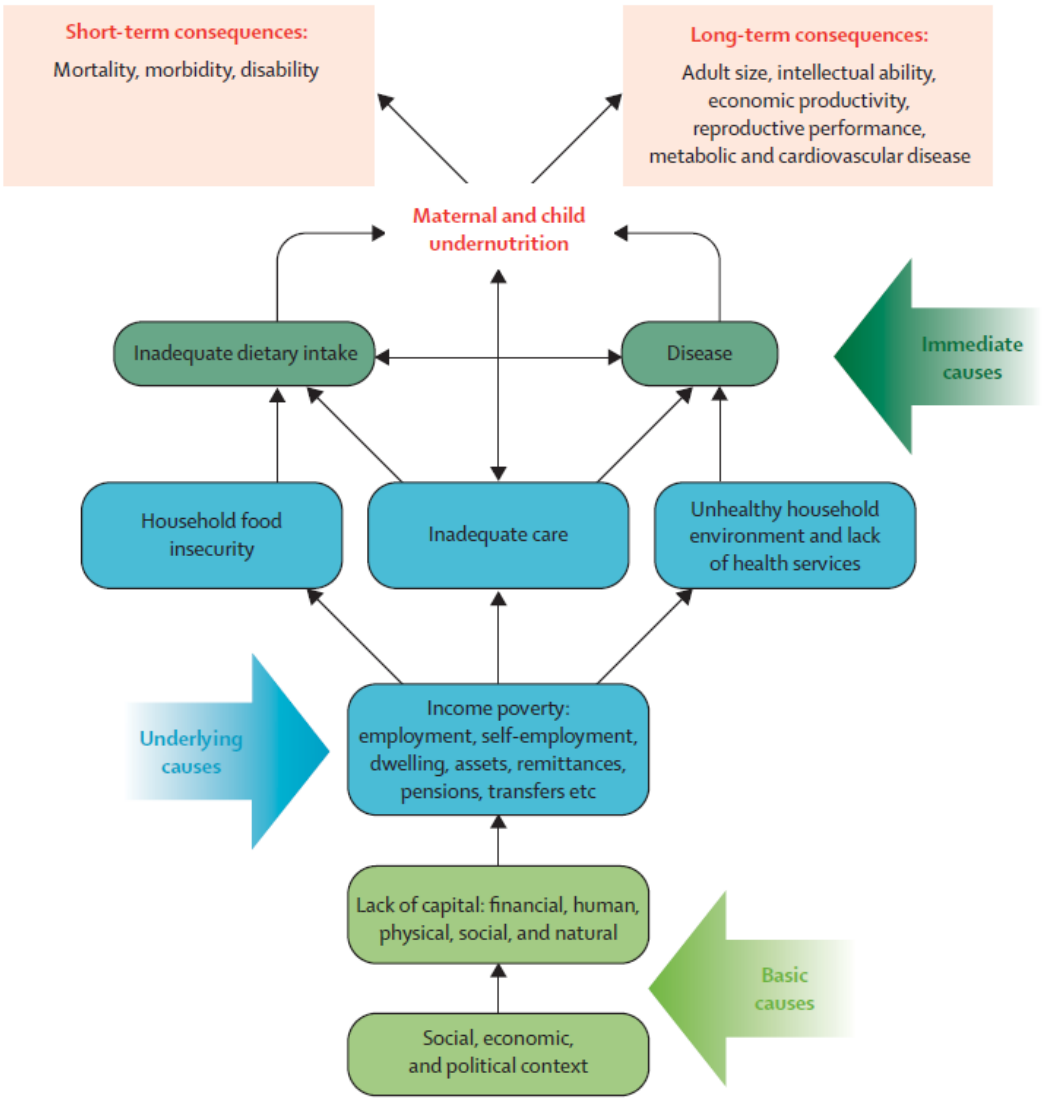


Figure 4 Framework of the relations between poverty, food insecurity, and other underlying and immediate causes to maternal and child undernutrition and its short-term and long-term consequences

Source: Black, R. et al, (2008), Maternal and child undernutrition: global and regional exposures and health consequences. CC BY-NC-ND [20]

1.4 Consequences of undernutrition

1.4.1 Short term

In addition to undernutrition being a leading cause of poor health [21], globally, around 45% of deaths that occur in children under 5 years of age are linked to undernutrition [22]. In the case of wasting, a child who is severely wasted has a mortality risk up to 12 times higher than a child who is not wasted [23]. Stunting also carries an increased risk of mortality. Severe stunting is associated with a risk of death up to five times higher than a non-stunted child [24]. Figure 5 and Figure 6 demonstrate the association between higher levels of wasting and stunting and mortality. With the exception of a few outliers, the majority of countries follow a similar trend, whereby as the prevalence of wasting or stunting increases in different countries and regions, so too does child mortality. There are many other non-nutrition related determinants of child mortality. Anthropometric measures despite being a helpful measure of nutrition status are not always representative of long term and repeated deficits. The strength of association between mortality and nutritional status is therefore likely to vary between settings and may explain some of the observed outliers. The trend that is observed in rising mortality as levels of wasting and stunting increase highlights the association between the two and provides justification as to why addressing it effectively should be a global public health priority.

1.4.2 Long-term

In addition to mortality risks, there are further consequences associated with undernutrition, though these are often more understood for stunting and less studied for wasting. Children who experience stunting, especially in the first “1000 days” of life have particularly marked risks of long-term consequences for adult height, educational attainment, reduced adult income, and decreased offspring birthweight [25-27]. Questions remain as to whether it is possible to prevent further linear growth failure and support catch up growth after the first 1000 days [28]. Associations between early stunting and increased risk of chronic diseases have also been demonstrated, but are not as clearly understood [26].

Until recently most understanding of the long-term consequences of wasting originated from studies exploring populations with famine exposure. However, a growing body of evidence is emerging on cohorts exposed to episodes of childhood wasting in other contexts. One systematic review of 30 studies demonstrated strong evidence that childhood malnutrition has a negative impact on neurodevelopment and impairs academic achievement and cognition

[29]. Another study following a cohort of children previously treated for severe acute malnutrition at 7 years post discharge, found that long term survivors were more stunted, had less catch-up growth, smaller head circumference, weaker hand grip strength and poorer school achievement compared with controls [30].

There is also evidence of an association between exposure to severe malnutrition or famine in childhood and an increased risk of cardiovascular disease, hypertension, impaired glucose metabolism and metabolic syndrome in later life; and some evidence of an association with obesity and effects on lipid metabolism, although less consistently so [31].

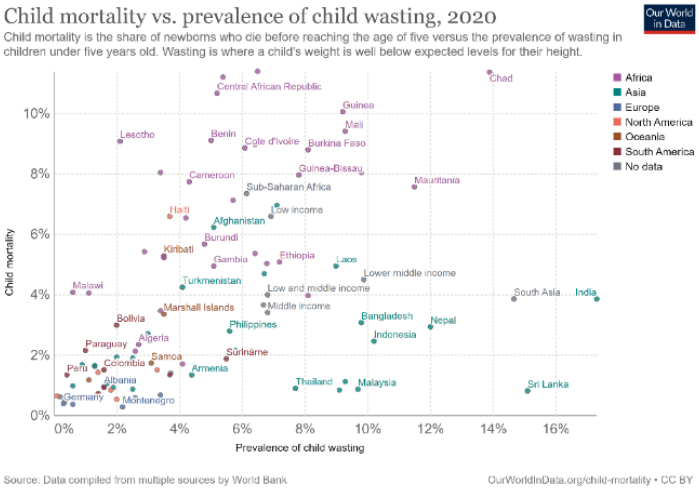


Figure 5 Child mortality versus the prevalence of child wasting.

Source: Our World in Data https://ourworldindata.org/ CC-BY

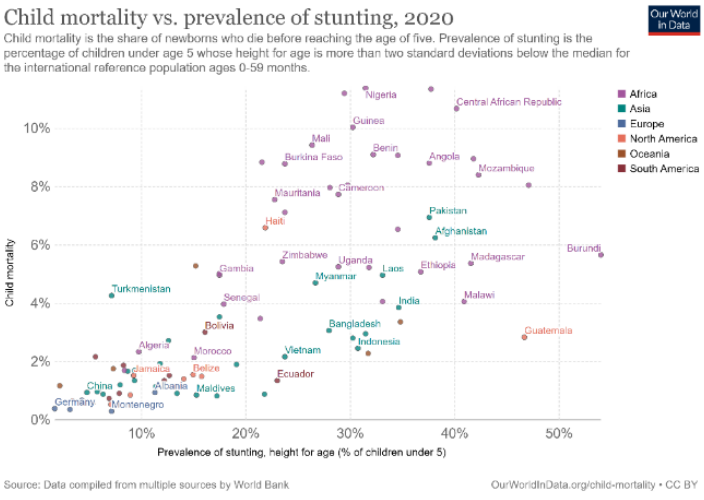


Figure 6 Child mortality versus the prevalence of child stunting.

Source: Our World in Data https://ourworldindata.org/ CC-BY

1.5 Multiple nutritional deficits

Wasting and stunting have in the past been viewed as separate conditions resulting in a division in policy, programming, and financing [7, 32]. Typically stunting has been addressed in stable contexts with a focus on prevention and the mitigation of longer-term developmental deficits. Wasting on the other hand has been viewed as a humanitarian problem which is addressed when reaching certain levels [33], with a focus on treatment [19].

Recent work has challenged this categorisation, highlighting that often wasting and stunting co-exist in many individual children and that the distinction between the two is arbitrary. Since 2014, a technical interest group led by the Emergency Nutrition Network (ENN) has been researching the relationship between wasting and stunting, and have generated evidence supportive of a direct relationship between the two conditions whereby wasting can lead to stunting and stunting can lead to wasting [19] (See appendix 6). For many children, common risk factors drive an accumulation of vulnerabilities and anthropometric deficits, exacerbated by factors such as seasonality.

Wasting and stunting can also occur at the same time, often referred to as concurrence. An estimated 15.9 million children are affected by concurrence, and consequently face a mortality risk equal to that of the most severe form of wasting [32]. A meta-analysis exploring the prevalence of concurrence in 84 countries [34] showed that the pooled prevalence of concurrent wasting and stunting in fragile and conflict affected states (FCAS) was significantly higher than in stable contexts (3.6%, 95% CI 3.5, 3.6, versus 2.24%, 95% CI 2.18, 2.30%, test of proportion p value <.0001), suggesting that the more fragile a context, the more vulnerable a child to concurrent and cumulative anthropometric insults.

A recent viewpoint published in the lancet has called for a shift in thinking regarding how actors assess undernutrition highlighting that approaching wasting and stunting separately neglects to recognise the risk of a child being exposed to both conditions and the cumulative effects of these. They call for further research into the pathways and process involved throughout the maternal and child lifecycle, as well as evaluation of and operational research into preventative and therapeutic interventions that can address the diverse causes and biological processes underlying childhood undernutrition [32].

Some of the early work in this project noted sex differences in prevalence estimates whereby boys (younger boys in particular) were more likely to be concurrently wasted and stunted than girls, particularly before the age of 30 months, after which the difference becomes smaller [34, 35], (see Figure 7).

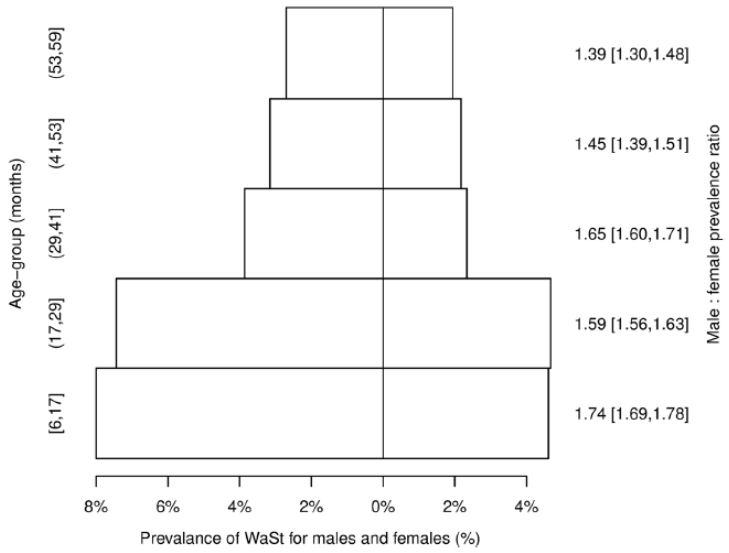


Figure 7 Male and Female prevalence of concurrent wasting and stunting by age in 51 countries.

Males are plotted on the left and females on the right.

Source: Myatt, M. (2018) Children who are both wasted and stunted are also underweight and have a high risk of death: a descriptive epidemiology of multiple anthropometric deficits using data from 51 countries. [35] CC-BY

1.6 Childhood sex differences

Neonatal and infant health fields have long recognised sex differences in neonatal, infant, and child health outcomes, with boys recognised as the more vulnerable of the two sexes from as early as the point of conception, and through to early infancy [36-41]. Overall, morbidity and mortality rates are higher in males than in females throughout life [42].

Perinatal outcomes are worse when mothers have a male neonate compared to a female, with increased risk of complications such as placental insufficiency, pre-term delivery, higher incidence of infections and increased risk of pre-eclampsia [43, 44]. This disadvantage continues into early infancy and childhood, with increased susceptibility to and severity of infectious diseases in males [40]. For example, conditions common in childhood such as lower respiratory infections, diarrhoeal diseases, and malaria, are all more common in boys than in girls [45]. There are however exceptions to this. Mortality associated with conditions such as measles, pertussis, and tuberculosis, is higher among girls than among boys. A defining feature of this difference is age, whereby the higher vulnerability to disease occurs in late childhood and early adulthood [37].

Early male vulnerability has also been noted in the context of famine whereby women have been shown to live longer than men, due in part to differences in infant mortality. Male infants are less likely to survive in harsh famine conditions compared with female infants, reportedly due to a combination of biological, environmental and social factors [46].

1.7 Sex and gender

Sex and gender are related but often confused concepts. Historically, sex and gender differences have been overlooked in research design and science communication, limiting the generalisability of findings for both females and males. In response to this, in 2016, the European Association of Science Editors developed the Sex and Gender Equity in Research Guidelines (SAGER) to provide guidance on a systematic approach to the reporting of sex and gender across disciplines [47]. SAGER define gender as referring to the socially constructed roles, behaviours, and identities of female, male and gender-diverse people. By this definition, gender can influence people's own perceptions of themselves and others, and their understanding and opinion of behaviours, interactions and distributions of power and resources in societies. Sex on the other hand refers to biological attributes associated with physiological features such as chromosomes, genetics, hormone functions and reproductive anatomy, and is usually categorised as male or female [47].

Gender is recognised as an important cross cutting issue to be addressed within humanitarian, health, and development programmes. Across the globe, girls are often identified as the more vulnerable of the two sexes and face barriers to equal access to education, health care, work and representation in both political and economic decision making [48]. Sex differences however are not typically considered when developing programmes and policy inclusive of a gender lens.

The language used to discuss sex and gender can also be emotive. A recent study highlighted the importance of sexed language in effective communication in certain fields such as pregnancy, breastfeeding, newborn care and where sex is central to the discussion [49]. For this research, I will therefore adopt the SAGER recommendations on defining sex and gender.

1.8 Origins of research

The idea for this research was born from a practical question relating to the use of joint sex charts to determine WHZ-scores and classify children as “severely wasted”; “moderately wasted” or “normal” for malnutrition programme admission. Previous NCHS growth reference tools included joint sex charts for ease of use, however WHO [50] tools only provided single sex tables, meaning that two charts were needed in each health/assessment centre. In 2009, the MOYO chart was developed by a group in Malawi [51] both in response to field demand for a more user-friendly version of the 2006 WHO growth standards tables to measure children and to define discharge targets, and to ensure high quality data collection for a research project [52]. The team had identified that look up reference charts were often hard to use and entailed multiple errors, resulting in misdiagnosis of children, and so designed a novel weight for height slide chart to aid health workers in the correct assessment and interpretation of a child’s weight for height Z score.

Since their development, the MOYO charts have been field tested and shown to improve the speed and accuracy of assessment of nutritional status [52]. Following the previous example of NCHS tables, the MOYO chart was formatted in both single sex and joint sex slide charts (see figure 8). To date over 16, 000 copies of the chart have been distributed or bought around the world[4], to be used in settings such as CMAM programmes and growth monitoring sites. In developing the joint sex version of the chart, the midpoint value between boys and girls was chosen. However, this was a rapid, pragmatic choice and the question arose as to whether a different, more evidence-informed method should have been chosen, and if so, what were the practical, programme and outcome implications of the joint sex chart?

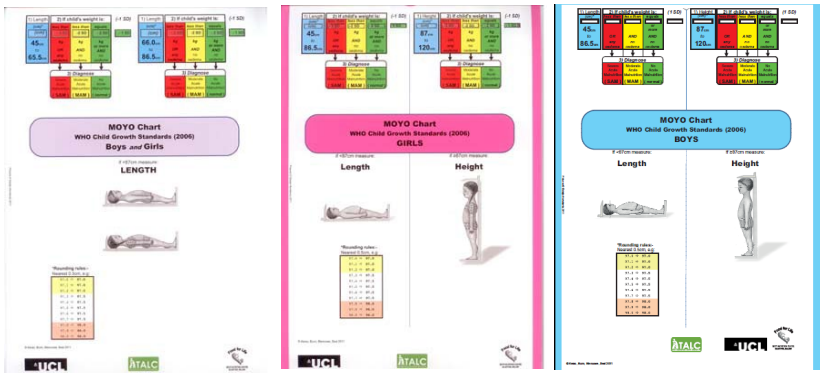


Figure 8 MOYO WH/LZ Look up charts for boys and girls, girls, and boys (Image reproduced with permission)

[4] Personal communication with Marko Kerac

At the same time as this question arose, during an international nutrition sector meeting, there were discussions as to whether the observed higher numbers of boys within malnutrition treatment programmes should be a cause for concern. The example of Yemen was given:

"In Yemen, higher numbers of male admissions have been noted and this is thought to be due to discrimination against female children".

Similarly, during a discussion on the Emergency Nutrition Networks (ENN) EN-Net forum[5] one user suggested that the use of single sex charts are likely to discriminate against girls and result in higher numbers of boys being admitted to therapeutic feeding programmes, as a girl would need to lose more weight than a boy to become eligible for admission:

"Using separate tables for boys and girls may lead to many more boys being admitted to therapeutic programs than girls…...the use of the boys table for both sexes is recommended to avoid discrimination against female children".

It became evident that to determine whether revision of the joint sex MOYO chart was needed to account for sex differences, firstly, a better understanding of sex differences in the field of undernutrition and what the implications of these differences might be was needed.

1.9 Rationale for research

Despite the recognition of sex differences in neonatal and infant health disciplines, there is a limited understanding related to sex differences in the field of undernutrition. For many years now, the concept of gender has been a consideration within nutrition programming and policy , where women and girls are often viewed as being more vulnerable to nutrition deficits. Globally women and adolescent girls are disproportionately affected by undernutrition compared with men, with gender disparity often cited as the cause [54]. However, little attention has been given to biological or other sex differences in child undernutrition and the programme and policy implications of these.

Some evidence [34, 55] suggests that boys are more at risk when it comes to anthropometric deficits, however, prior to this research there was no systematic overview looking specifically at understanding the patterns and causes of these differences. How underlying biological mechanisms and other differences in sex and gender translate to risk of anthropometric

[5] https://www.en-net.org/question/1826.aspx

deficits and related morbidity and mortality in undernutrition remains understudied. Likewise, the practical implications of these differences for programming remain to be determined.

This research therefore aims to explore the evidence for sex differences to understand whether and how these might need to be addressed in prevention and treatment policy and practice. Focusing on a clinical, biological, evolutionary, and social perspective, this research sets out to explore the evidence for sex differences in the epidemiology of undernutrition and the reasons for these differences. I have tried to understand the prevalence, and patterns in sex differences (specifically related to age and geography) and explore potential reasons for differences observed.

The research also aims to determine the implications of age and sex differences for mortality patterns associated with anthropometric deficits. Finally, this research looks at whether outcomes from wasting treatment programme differ between boys and girls and age groups. The findings will inform recommendations for both policy and programming within the field of undernutrition.

2 Research aims, objectives and structure

2.1 Overall aim

The aim of this PhD is to improve the assessment and treatment of undernutrition in *both* female and male children aged 0-5 years.

This will be achieved by a deeper understanding of differences between the two and exploring whether and how these might need to be addressed in prevention and treatment policy and practice.

2.2 Overall objectives

Focusing on a biological/clinical, evolutionary, and social perspective, the overall objectives of this PhD are to:

1. Review the evidence for female/male differences in the risk of developing undernutrition:
    a. Are girls or boys at greater risk?
    b. What is the epidemiology of risk differences - are there age-specific and/or geographical differences?
    c. If differences are found, what are the possible underlying reasons and mechanisms– for example, social reasons might be likely if strong geographical patterns emerge; biological reasons might explain consistent global patterns?
2. Review the evidence for female/male differences in mortality associated with anthropometric deficits (wasting, stunting and underweight):
    a. Are girls or boys at greater risk of mortality associated with anthropometric deficits?
    b. What is the epidemiology of risk differences - are there age-specific and/or geographical differences?
3. Review the evidence for female/male differences in outcomes in current wasting treatment programmes.
    a. Do differences occur in outcomes following wasting treatment?
    b. What is the epidemiology of differences - are there age-specific and/or geographical differences?

2.3 Thesis structure

This thesis follows the research paper structure.

Chapter 1 provides a background on the global burden of undernutrition, the different forms that it takes and how these affect child health and survival outcomes. It also provides background on sex differences in related public health fields and provides a rationale for why it is important to understand sex differences in the context of undernutrition.

Chapter 2 outlines the aims and objectives of the work and describes how the thesis is presented.

Chapter 3 outlines methods involved in the research to complement the methods sections in the publications.

Chapter 4 presents the findings of a systematic review and meta-analysis of sex differences in undernutrition which has been published in BMJ Global Health. It describes how sex differences present in wasting, stunting and underweight, and how these differences are reported in published work.

Chapter 5 presents the findings from a narrative review which formed an extension of the systematic review, exploring the early life mechanisms which might underlie sex differences in undernutrition. The paper has been published in Nutrients.

Chapter 6 presents the findings from a meta-analysis of mortality risk associated with anthropometric deficits (wasting, stunting and underweight) in children 6–59 months by age and sex, to explore whether differences in age and sex affect mortality risk. The paper has been published in Maternal and Child Nutrition Journal.

Chapter 7 presents the findings from a multi-country secondary analysis exploring whether age and sex affect treatment outcomes for severe malnutrition. The paper has been published in Maternal and Child Nutrition Journal.

Chapter 8 summarises the main findings from the research in relation to the objectives set. It draws on research findings from this PhD and other work that has taken place during the course of this research. The strengths and limitations of the research are outlined.

Chapter 9 considers the implications of the findings for current policy and practices and outlines future research recommendations and final conclusions.

Table 2 Overview of chapters aims, objectives, methods and outputs

Chapter number and title		**Objective**	**Specific objectives**	**Methods**	**Related Outputs**
1	Background and rationale	NA	Describe undernutrition and the rationale for this research	Literature review	NA
2	Research, objectives and structure	NA	NA	NA	NA
3	Methods	NA	To provide additional detail on methods adopted for each of the study chapters	NA	NA
4	Systematic review and meta-analysis	Overall PhD Objective 1	Review the evidence for sex differences in undernutrition Review the recognition and understanding of these differences if they occur Review the explanations offered for these differences	Systematic review and meta-analysis, using both qualitative and quantitative synthesis:	**Published**: peer-reviewed paper 1 **Podcast:** Sex differences in undernutrition **Blog**
5	Understanding Sex differences in childhood undernutrition	Overall PhD objective 1	Review the underlying causes or reasons for sex differences in undernutrition	Narrative review expanding on the above systematic review	**Published:** peer-reviewed paper 2 **Podcast:** Sex differences in undernutrition **Blog**
6	Mortality review	Overall PhD objective 2	Describe variation in mortality risk associated with anthropometric deficits in children 6-59 months by age, sex and geographical region	Meta-analysis of multi-country pooled data from 12 cohort studies.	**Published**: peer-reviewed paper 3 **Blog/opinion piece**
7	Treatment analysis	Overall PhD objective 3	To describe demographic variations in treatment outcomes in children 6-59 months according to age, sex, admission anthropometry and geographical region, using secondary data.	Multi-country secondary analysis using logistic and linear regression methods	**Submitted:** paper 4, in peer review, June 2023
8	Discussion	Overall PhD objectives 1-3	To bring together the main findings of this thesis, and consider the strengths and limitations of the research	NA	NA

9	Implications and conclusions	Overall PhD objectives 1-3	To consider the implications for future research based on evidence presented	NA	NA
10	Appendices	NA	NA	NA	**Peer reviewed papers**

2.4 List of publications

List of papers included in this PhD

Paper 1: Boys are more likely to be undernourished than girls: a systematic review and meta-analysis of sex differences in undernutrition

Thurstans S, Opondo C, Seal A, et al. Boys are more likely to be undernourished than girls: a systematic review and meta-analysis of sex differences in undernutrition BMJ Global Health 2020. http://dx.doi.org/10.1136/bmjgh-2020-004030

Paper 2: Understanding Sex Differences in Childhood Undernutrition: A Narrative Review

Thurstans, S.; Opondo, C.; Seal, A.; Wells, J.C.; Khara, T.; Dolan, C.; Briend, A.; Myatt, M.; Garenne, M.; Mertens, A.; Sear, R.; Kerac, M. Understanding Sex Differences in Childhood Undernutrition: A Narrative Review. Nutrients 2022, 14, 948. https://doi.org/10.3390/nu14050948

Paper 3: Anthropometric deficits and the associated risk of death by age and sex in children aged 6–59 months: A meta-analysis

Thurstans, S., Wrottesley, S. V., Fenn, B., Khara, T., Bahwere, P., Berkley, J. A., Black, R. E., Boyd, E., Garenne, M., Isanaka, S., Lelijveld, N., McDonald, C. M., Mertens, A., Mwangome, M., O'Brien, K. S., Stobaugh, H., Taneja, S., West, K. P., Guerrero, S., … Myatt, M. (2023). Anthropometric deficits and the associated risk of death by age and sex in children aged 6–59 months: A meta-analysis. *Maternal & Child Nutrition*, 19, e13431. https://doi.org/10.1111/mcn.13431

Paper 4: How age and sex affect treatment outcomes for severe malnutrition: a multi-country secondary data analysis

Thurstans, S., Opondo, C., Bailey, J., Stobaugh, H., Loddo, F., Wrottesley, S. V., Seal, A., Myatt, M., Briend, A., Garenne, M., Mertens, A., Wells, J., Sear, R., & Kerac, M. (2023). How age and sex affect treatment outcomes for children with severe malnutrition: A multi‐country secondary data analysis. Maternal & Child Nutrition, e13596. https://doi.org/10.1111/mcn.13596

Supporting research papers (see appendices)

Paper 5: Changing sex differences in undernutrition of African children: findings from Demographic and Health Surveys

Garenne M, Thurstans S, Briend A, Dolan C, Khara T, Myatt M, Seal A, and Wells JC. Changing sex differences in undernutrition of African children: findings from Demographic and Health Surveys. Journal of Biosocial Science. https://doi.org/10.1017/S0021932021000468

Paper 6: The relationship between wasting and stunting in young children: A systematic review

Thurstans, S., Sessions, N., Dolan, C., Sadler, K., Cichon, B., Isanaka, S., Roberfroid, D., Stobaugh, H., Webb, P., & Khara, T. (2021). The relationship between wasting and stunting in young children: A systematic review. Maternal & Child Nutrition, e13246. https://doi.org/10.1111/mcn.13246

2.5 Ethics

All of the data used in this PhD is secondary. Much of the previous research in which this data was collected has received previous ethical approval. Further approval has been granted by the London School of Hygiene and Tropical Medicine ethics committee for the following papers:

Paper 3: Thurstans, S. et al. (2022). Anthropometric deficits and the associated risk of death by age and sex in children aged 6–59 months: A meta-analysis. Maternal & Child Nutrition, e13431. https://doi.org/10.1111/mcn.13431
LSHTM Ethics Reference 22958.

Paper 4: Thurstans, S. et al. (2023). How age and sex affect treatment outcomes for severe malnutrition: a multi-country secondary data analysis. Maternal & Child Nutrition, e13246. https://doi.org/10.1111/mcn.13246
LSHTM Ethics Reference 26401

3 Methods

3.1 Scope of chapter

This chapter aims to describe the processes and methods involved in the research to complement the methods sections in each of the publication chapters.

3.2 Overview of the PhD research process

After registering for my PhD in April 2018, I shared my initial concept paper with a number of experts in the field of undernutrition with an interest in the area of sex differences, inviting them to join the advisory committee and to review and comment on the concept paper. This group aligned with a sub-working group of the overall wasting and stunting project led by ENN (as described in section 1.5). I have continued to communicate with this group throughout the process of my PhD, mostly through emails and sharing of research concepts and various iterations of the publications, to discuss direction of the research and key themes. All members of the group have contributed to the papers produced through this research. The roles for each of the individual studies are outlined in Appendix 4.

3.3 Summary of methods for objective 1

The first stage of the research was a systematic review and meta-analysis to determine if sex differences do occur in undernutrition. I designed the review and shared the research concept paper with the advisory committee. I also shared the search strategy with the advisory committee and invited them to share any papers they considered relevant to the review. All other papers, including grey literature were identified through the search of databases, described in detail in paper 1. Though we did include grey literature, we excluded standard nutrition survey reports to manage the amount of data. Grey literature that considered the effects of sex or gender on nutrition outcomes were included. The search, selection, data extraction, analysis and write up were all managed by myself (see appendix 4 for a full list of responsibilities). Funding restrictions meant that screening for the studies was conducted by only one author, this has been acknowledged in the limitations section in the paper, and in Chapter 8 of this thesis.

Where papers identified in the search results were not available online attempts were made to source these through the LSHTM, UCL and Senate House libraries. If after these additional attempts to locate the papers they could still not be found, they were excluded.

The systematic review and meta-analysis aimed to assess if and how studies recognised and explained sex differences identified. In the data extraction table, I included a section to determine if differences were acknowledged, and if they were, what explanations were given. All explanations given were extracted and coded into one of the following categories:

1. No explanation/discussion
2. No new explanation/discussion but similar results cited
3. Social explanation for the differences (for example, gender preferences or the roles in which girls and boys play in society)
4. Biological differences (for example, physiological/hormonal differences between girls and boys)
5. A combination of social or biological reasons

The broad nature of the search strategy meant that there was a large amount of literature identified that did not necessarily fit into the scope of the systematic review and meta-analysis but which were helpful to explain the possible reasons for why sex differences occur. This promoted discussions with my supervisors as to how to manage the scope of the review. I made the decision to perform a less formal narrative review (paper 2), utilising studies identified in the initial search as a starting point, which offered more detailed explanation as to why sex differences might occur. Around twenty-six papers from the systematic review and meta-analysis search which explored the causes of sex differences and how they might relate to undernutrition were taken forward to the narrative review. I extracted explanations for sex differences given in the papers used for paper 1 (where they were given – 43 papers), alongside explanations from the additional 26 papers and used Nvivo software to generate a word graph to try and identify themes for the narrative review (see Figure 9). As in-utero origins and age seemed to emerge as a theme from my reading, I chose a lifecycle approach around which to theme the presentation of the paper. I also felt this was fitting for the way in which nutrition programming is considered and would be able to capture the distinction between the effects of sex and gender for boys and girls at different stages of the lifecycle, capturing the general principles as described in the SAGER guidance. Following this, additional papers were sourced in two ways, the first was through reference lists in these papers and the second was by searching around themes identified within these papers.

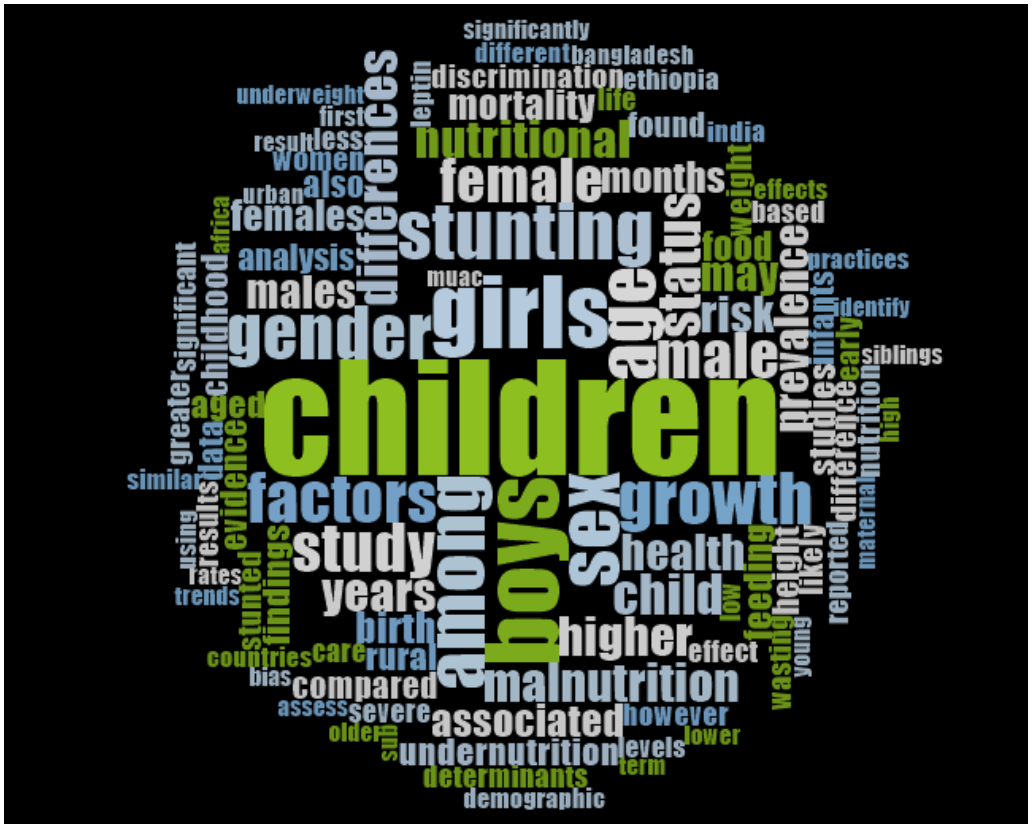


Figure 9: Word graph for sex differences in undernutrition

3.4 Summary of methods for objective 2

After the systematic review and meta-analysis and narrative review, I looked more closely at the implications of the differences identified. The idea of male biological vulnerability was a surprising finding for many. My own programming experience, alongside presentation of these findings in different meetings highlighted the need to understand what if anything do sex differences mean for programming. For example, what are the practical implications, do outcomes differ for boys and girls in terms of overall mortality risk or wasting treatment outcomes?

At the same time, the ENN technical working group for wasting and stunting, with which this work aligned, were looking at the best anthropometric criteria for identifying children at high risk of mortality to determine if a combined case definition of WAZ and MUAC would identify children at highest risk of mortality, including children with concurrent and cumulative deficits [56]. Understanding sex and age differences was not a direct objective in the first analysis and so we used the same dataset to perform a meta-analysis to explore if age and sex affect

the risk of mortality associated with anthropometric deficits. Full details of methods followed can be found in paper 3.

3.5 Summary of methods for objective 3

Following the mortality analysis, whether sex affects outcomes specific to wasting treatment outcomes remained as a practical outstanding question. To answer this question, I developed a research concept and following a discussion with a fellow researcher, I applied for access to a dataset they had stored on the LSHTM data repository which comprised data from community based therapeutic feeding programmes from four different countries. This data originated from phase 1 of the ComPAS trial [57] which comprised analysis of routine NGO data from CMAM programmes to assess theoretical performance of a simplified dose of ready to use therapeutic foods. This preceded a randomised control trial comparing simplified and standardised treatment protocols, which found that simplified protocols were non-inferior to standard care [58]. The stage one data was not collected under research conditions but represents real life programme implementation of standard CMAM programmes. I was granted access and signed a data sharing agreement with owners of the datasets.

Following an exploration of the data obtained, I performed a multi-country secondary data analysis using logistic and linear regression to determine if age and sex affect treatment outcomes for children with severe malnutrition. Full details of methods followed can be found in paper 4.

3.6 Addressing sex and gender throughout the research

As highlighted in chapter 1, I felt it was important to ensure that the distinction between sex and gender was captured throughout the research as both are likely to contribute towards sex differences in undernutrition. For example, physiological sex differences in early infancy are more likely to affect male vulnerability towards undernutrition, whilst gender discrimination is more likely to affect female vulnerability to undernutrition. I have therefore adopted the SAGER guidance. Table 3 describes the principles laid out in the SAGER guidance and how these have been addressed throughout the research [47].

Table 3 SAGER guidelines general principles and how they have been addressed.

SAGER guiding principle	How this has been addressed throughout
"Authors should use the terms sex and gender carefully in order to avoid confusing both terms".	I have been careful throughout this PhD to use the terms sex and gender correctly as defined in the SAGER guidance. For example: • physiological sex differences between males and females in early infancy • gender ideals that affect the way in which male and female children might be treated differently.
"Where the subjects of research comprise organisms capable of differentiation by sex, the research should be designed and conducted in a way that can reveal sex-related differences in the results, even if these were not initially expected".	Where relevant and possible, all results have been disaggregated by sex and analysis has been conducted to determine the differences between outcomes in males and females.
"Where subjects can also be differentiated by gender (shaped by social and cultural circumstances), the research should be conducted similarly at this additional level of distinction".	In paper 2, the effects of gender are explored to determine whether it contributes towards differences in nutritional outcomes between males and females. Papers 1, 3 and 4 also consider how gender might have affected outcomes based on sex.

4 Systematic review and meta-analysis

4.1 Scope of this chapter

This chapter presents the first research paper entitled “Boys are more likely to be undernourished than girls: a systematic review and meta-analysis of sex differences in undernutrition”. This paper describes the findings of a systematic review and meta-analysis of sex differences in childhood malnutrition and explores how these differences are recognised and explained within published studies and reports.

The findings show that undernutrition is more common among boys than girls, though the extent of these differences varies and is reversed in some contexts. Both biological and social mechanisms have been proposed to be responsible for the observed differences as well as a combination of the two. The paper was published in BMJ Global Health in December 2020 as an open access article.

4.2 Figures

Figure 1 PRISMA flow diagram. PICO, Population, Intervention, Comparison, Outcome; PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses.

Figure 2 Forest plots showing the odds ratios for wasting, stunting and underweight in boys compared to girls.

4.3 Tables

Table 1 Study characteristics

Table 2 Odds of boys being undernourished compared with girls by regions and age groups

Table 3 Risk of bias assessment

4.4 Citation

Thurstans S, Opondo C, Seal A, et al. Boys are more likely to be undernourished than girls: a systematic review and meta-analysis of sex differences in undernutrition BMJ Global Health 2020;5:e004030.

4.5 Research paper 1 – BMJ

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT

T: +44 (0)20 7299 4646
F: +44 (0)20 7299 4656
www.lshtm.ac.uk

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	1802701	**Title**	Mrs
First Name(s)	Susan		
Surname/Family Name	Thurstans		
Thesis Title	Sex differences in risk and outcomes from severe malnutrition: implications for management		
Primary Supervisor	Marko Kerac		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	BMJ Global Health		
When was the work published?	December 2020		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	NA		
Have you retained the copyright for the work?*	**No**	Was the work subject to academic peer review?	**Yes**

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	NA
Please list the paper's authors in the intended authorship order:	NA
Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	The review was designed and conducted by myself with supervision from Dr Marko Kerac and Professor Rebecca Sear. The meta-analysis was led by myself with support from Dr Charles Opondo. I led the wiriting of the manuscript with contributions from all authors.

SECTION E

Student Signature	[redacted]
Date	

Supervisor Signature	
Date	

BMJ Global Health

Boys are more likely to be undernourished than girls: a systematic review and meta-analysis of sex differences in undernutrition

Susan Thurstans ,[1] Charles Opondo ,[2,3] Andrew Seal ,[4] Jonathan Wells ,[5] Tanya Khara,[6] Carmel Dolan,[6] André Briend,[7,8] Mark Myatt,[9] Michel Garenne ,[10,11,12,13] Rebecca Sear ,[1] Marko Kerac [1,14]

To cite: Thurstans S, Opondo C, Seal A, *et al*. Boys are more likely to be undernourished than girls: a systematic review and meta-analysis of sex differences in undernutrition. *BMJ Global Health* 2020;**5**:e004030. doi:10.1136/bmjgh-2020-004030

Handling editor Seye Abimbola

Received 23 September 2020
Revised 6 October 2020
Accepted 9 October 2020

For numbered affiliations see end of article.

Correspondence to
Susan Thurstans;
susan.thurstans@lshtm.ac.uk

ABSTRACT

Background Excess male morbidity and mortality is well recognised in neonatal medicine and infant health. In contrast, within global nutrition, it is commonly assumed that girls are more at risk of experiencing undernutrition. We aimed to explore evidence for any male/female differences in child undernutrition using anthropometric case definitions and the reasons for differences observed.

Methods We searched: Medline, Embase, Global health, Popline and Cochrane databases with no time limits applied. Eligible studies focused on children aged 0–59 months affected by undernutrition where sex was reported. In the meta-analysis, undernutrition-specific estimates were examined separately for wasting, stunting and underweight using a random-effects model.

Results 74 studies were identified: 44/74 studies were included in the meta-analysis. In 20 which examined wasting, boys had higher odds of being wasted than girls (pooled OR 1.26, 95% CI 1.13 to 1.40). 38 examined stunting: boys had higher odds of stunting than girls (pooled OR 1.29 95% CI 1.22 to 1.37). 23 explored underweight: boys had higher odds of being underweight than girls (pooled OR 1.14, 95% CI 1.02 to 1.26). There was some limited evidence that the female advantage, indicated by a lower risk of stunting and underweight, was weaker in South Asia than other parts of the world. 43/74 (58%) studies discussed possible reasons for boy/girl differences; 10/74 (14%) cited studies with similar findings with no further discussion; 21/74 (28%) had no sex difference discussion. 6/43 studies (14%) postulated biological causes, 21/43 (49%) social causes and 16/43 (37%) to a combination.

Conclusion Our review indicates that undernutrition in children under 5 is more likely to affect boys than girls, though the magnitude of these differences varies and is more pronounced in some contexts than others. Future research should further explore reasons for these differences and implications for nutrition policy and practice.

Key questions

What is already known?

- Undernutrition (wasting, stunting and underweight) is a public health problem affecting millions of children aged under 5 years globally.
- Although higher neonatal and infant morbidity/mortality for boys is well described, little attention has been given to sex differences in the field of undernutrition due to an assumption that girls are very often disadvantaged over boys.

What are the new findings?

- In most settings studied, undernutrition is more common among boys than girls, though the extent of these differences varies and is reversed in a few contexts.
- Both biological and social mechanisms have been proposed to be responsible for the observed differences as well as a combination of the two.

INTRODUCTION

Undernutrition is a serious public health problem affecting millions of children worldwide. Recent estimates indicate that stunting (low height-for-age) affects approximately 149 million children, with consequences for growth and cognitive development. Wasting (low weight-for-length), a life-threatening consequence of acute nutrient deficits and/or disease affects over 49 million children globally; 17 million of whom are severely wasted.[1] However, these numbers are based on prevalence estimates meaning true numbers may be considerably higher when incidence is taken into consideration.[2]

Sex (referring to biological attributes) and gender (referring to socially constructed roles, behaviours and identities)[3] are important considerations in the public health domain and receive different prominence in different academic and professional fields. Despite considerable research on childhood sex differences in neonatal and infant health, different disciplines often hold surprisingly

Key questions

What do the new findings imply?

- Greater awareness of actual sex differences is needed within the field of nutrition.
- While sex-specific data are routinely analysed and reported in nutrition surveys, it should be used in nutrition programming to better identify and understand what differences exist. Analysis should assess if the sex balance in programme admissions is reflective of the population undernutrition burden.
- Further research is needed to understand both the mechanisms behind and the reasons for that lead to sex and gender differences in undernutrition and their implications for nutrition policy and practice. Better epidemiological understanding is a priority, as is work to explore their consequent effects on morbidity and mortality.

contrary views on the relative vulnerability of male and female children.

In neonatal medicine and infant health communities, excess male morbidity and mortality is almost universally reported and is widely recognised.[4 5] Boys are known to be more vulnerable than girls, from as early as the point of conception.[6] Conditions common in childhood such as lower respiratory infections, diarrhoeal diseases, malaria and preterm birth are all more common in boys than girls, with the exception of measles, whooping cough and tuberculosis.[7] All of these are not only causes of death but also of weight loss, growth faltering or severe undernutrition among young children.[8] Boy–girl differences have not been explored in detail within the nutrition field, but girls are often widely viewed as more disadvantaged and vulnerable[9] from a gender perspective.[10–13]

How underlying biological mechanisms related to sex and social differences in gender translate into the risk of anthropometric deficits and related morbidity and mortality in the field of nutrition remains understudied. Likewise, the practical implications of these differences remain to be determined. In terms of growth and nutrition status, sex differences have long been recognised and reflected through growth charts targeted at individual sexes.[14 15] On average, boys are slightly heavier and longer at birth and throughout infancy compared with girls, and more detailed studies have shown that the extra average weight of boys is primarily lean mass, whereas fat mass is more similar between the sexes.[16 17] To evaluate growth and nutritional status therefore, raw anthropometric data are conventionally converted to indices (eg, weight-for-age; weight-for-length, length-for-age) and expressed in comparison to reference populations as z-scores (SD scores, whereby +1 and −1 z-scores are one SD above and below the reference population median, respectively). Data published by WHO in 2006 represent a 'gold standard' of how children should grow and were developed from a globally representative reference population of healthy, breastfed children. In constructing the growth standards, data for boys and girls were analysed separately[15] and the resulting growth charts should already therefore account for any sex differences. What has received little attention to date is whether sex differences reappear when z-scores are shifted away from the healthy reference range, which would indicate sex differences in susceptibility to undernutrition.

The objectives of this review were to systematically review the evidence for sex differences in undernutrition in children aged under 5 years, to explore evidence of any male/female differences in child undernutrition, and to document reasons given for any observed differences.

METHODS

This systematic review was conducted following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.[18] A protocol for the review was defined, including inclusion and exclusion criteria, and was shared among authors for consensus. The protocol was then registered with the PROSPERO International prospective register of systematic reviews (CRD42018094818). The scope of this initial protocol was broad but as the review progressed and the heterogeneity of identified studies became increasingly apparent, we made a decision to divide our work into two parts: the first (this study) focuses on prevalence and recognition of sex-related differences; and the second, which will focus on the physiological and sociological mechanisms that may account for any identified differences.

Search strategy

Our search strategy captured the concepts of undernutrition, sex and gender. Detailed search terms are in box 1.

Studies were identified by searching the Medline database using the above terms which were then adapted to Embase, Global health, Popline and Cochrane databases. No limits were applied for year of publication in order to capture historical publications on the subject. Studies were restricted to those that included terms for boy, girl, male, female, gender, or sex in the title or abstract, with the aim of filtering through the large body of literature that exists for undernutrition and capturing studies which either directly focused on sex and/or gender in the context of undernutrition or those which disaggregated and reported on it within main findings. As per the PRISMA recommendations, the search strategy was peer reviewed by a librarian.

Eligibility criteria

Studies were included in the review if they met the following criteria: human studies, age range of 0–59 months, male and female participants, outcomes related to the prevalence or determinants of undernutrition, and related morbidity and mortality. Studies were eligible for inclusion in the meta-analysis if they presented data disaggregated by sex for both the overall sample and the outcome of interest (wasting, stunting, underweight), or relevant ORs. Studies of children over 59 months, non-English language, animal studies and studies on overweight/obesity and micronutrient deficiencies were excluded. Both peer-reviewed and grey literature were

Box 1 Search terms

1. undernutrition.mp. (5708)
2. malnutrition.mp. (39279)
3. malnutrition/ or exp fetal nutrition disorders/ or exp refeeding syndrome/ or exp severe acute malnutrition/ or exp kwashiorkor/ or exp starvation/ or exp wasting syndrome/ (25202)
4. (severe adj2 malnutrition).mp. (2131)
5. stunting.mp. (3456)
6. exp Growth Disorders/ (30538)
7. chronic malnutrition.mp. (519)
8. stunt*.mp. (6655)
9. MUAC.mp. (407)
10. mid upper arm circumference.mp. (771)
11. exp Nutritional Status/ (38539)
12. marasmus.mp. or Protein-Energy Malnutrition/ (7366)
13. famine.mp. (1726)
14. exp Starvation/ (9562)
15. (failure adj2 thrive).mp. (5307)
16. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 (123406)
17. limit 16 to ("all infant (birth to 23 months)" or "newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)") (35919)
18. (boy* or girl* or male* or female* or gender or sex).ti,ab. (177252)
19. 17 and 18 (6631)

Numbers in parenthesis show the number of search results for each line.

selected. In studies that included data for children both under and over 59 months, where possible, we extracted the data for children <59 months only. Where this was not possible, studies were excluded.

Data extraction

All records identified through the search were imported into EndNote (EndNote V.X8, Clarivate Analytics). Duplicates were identified and removed. Initial screening was conducted by reading titles and abstracts to identify and remove studies which clearly did not fit our scope. Detailed review of the full text of all remaining results was conducted to determine which met the inclusion and exclusion criteria. When it was not clear how to classify an article, this was resolved through discussion and consensus with two or more authors.

A data extraction template was piloted on a small number of articles before being finalised. Data were extracted on study characteristics and outcomes of interest. These included aims and types of studies, sample size, prevalence and male/female ORs for undernutrition, and explanations offered for any differences identified.

Analysis

Due to variations in type of paper and study design, the analysis was conducted in two parts: a qualitative systematic review followed by a meta-analysis. We performed random-effects meta-analyses to pool estimates from studies that included a measurement of undernutrition prevalence, or which assessed risks and determinants of undernutrition, and stratified results by sex. Missing counts, denominators and effect estimates such as ORs, relative risk and their associated CIs were calculated from other information provided where it was possible to do so. Studies that presented only adjusted ORs or risk ratios were excluded given that studies were likely to adjust for different factors and such adjusted effect estimates were not directly comparable. Undernutrition-specific estimates were pooled separately for wasting, stunting and underweight using a random-effects model. Analysis was also stratified by age and country. Pooled effects are presented as ORs and 95% CIs. Meta-regression was conducted to assess whether study-specific factors could explain the heterogeneity of effect estimates across studies. Statistical analysis was conducted using Stata V.15.1 (StataCorp 2017, Stata Statistical Software, College Station, Texas, USA).

In all studies conducted earlier than 2006, the National Center for Health Statistics (NCHS) growth[19] references had been used. In all post-2006 studies that were included, the WHO (2006) growth standards for wasting, stunting and underweight, as measured through SD from the mean z-scores, were used. Wasting was defined by weight-for-height z-score <−2; stunting was defined by height-for-age z-score <−2; underweight was defined by weight-for-age z-score <−2.

Risk of bias assessment

We adapted the National Heart, Lung and Blood institute study quality assessment tools for Observational cohort and cross-sectional studies to assess the quality of studies,[20] and applied it to studies identified for the meta-analysis. Using this tool, we assessed data sources, a study's presentation of aims and objectives and target populations, the appropriateness of anthropometric methods and the presentation of results. We adapted the tool to assess if studies acknowledged sex differences in the discussion of results.

Patient and public involvement

The design of this review meant it was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

Study selection

The study flow chart in figure 1 summarises our process of identifying studies. The final search of Embase, Global health, Popline and Cochrane databases conducted in March 2020 identified 34 270 studies, including both peer-reviewed studies and grey literature. In addition, 21 studies were found from other sources. After removing duplicates, 22 357 studies remained. Initial screening excluded 21 925 studies as they were unrelated to our review questions. Full texts of the 432 remaining studies were reviewed in detail to assess eligibility. At this stage, a further 358 studies were discarded as they did not meet the inclusion criteria, mostly because there was no mention of sex or gender in relation to undernutrition. Seventy-four studies were therefore included

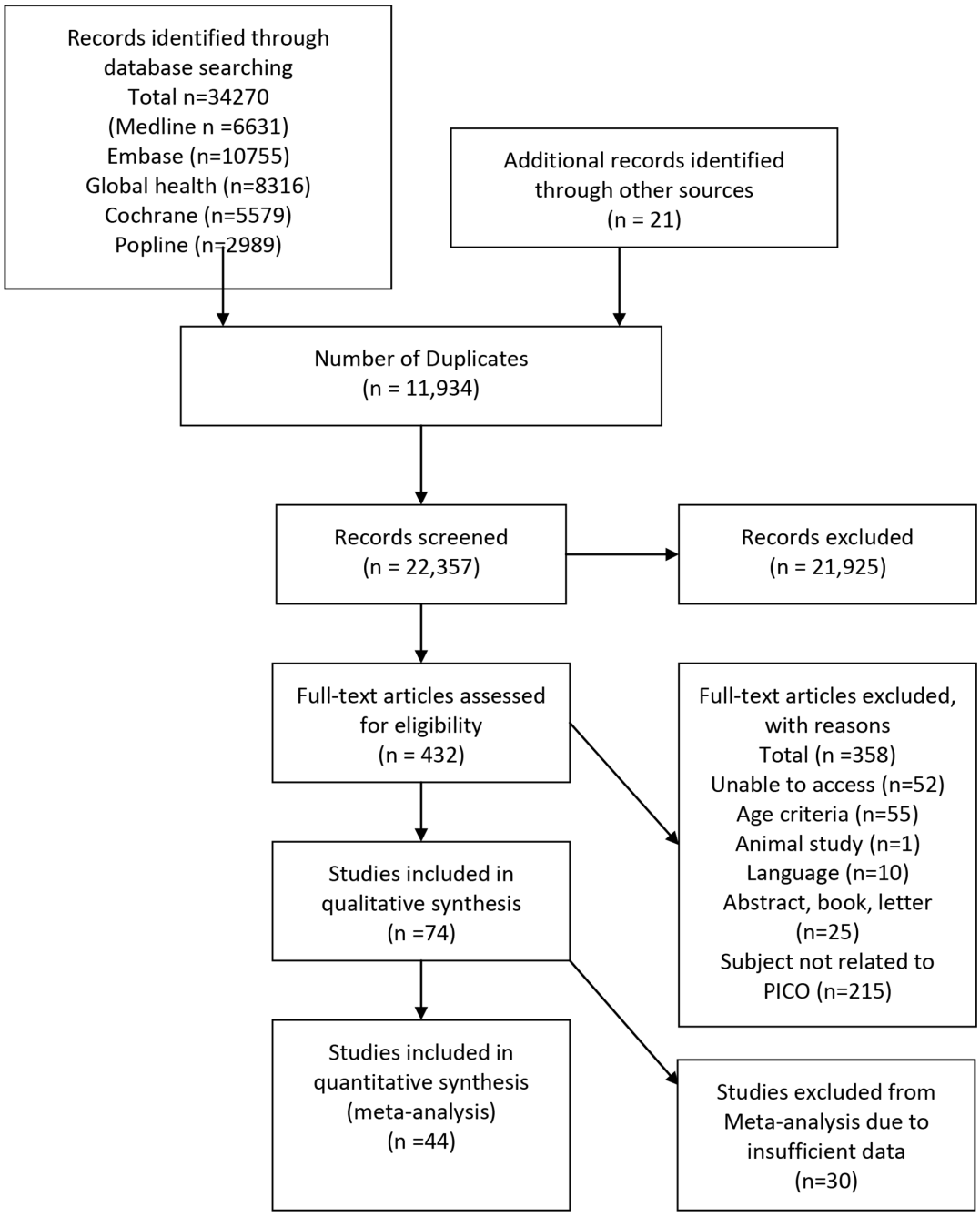


Figure 1 PRISMA flow diagram. PICO, Population, Intervention, Comparison, Outcome; PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses.

in the qualitative synthesis. Finally, we reviewed the 74 studies for inclusion in the meta-analysis and excluded 30 on the basis of insufficiently disaggregated data (which prevented the calculation of ORs). Thus, 44 studies were included in the meta-analysis.

Study characteristics

Table 1 shows the characteristics of each of the studies included in the review. The studies selected for the review varied widely in terms of aims and study design. Many were observational, assessing prevalence of undernutrition and related risk factors and many included secondary data analysis. The outcomes, both primary and secondary, also varied widely. The studies took place in more than 30 countries (some covered multiple countries). The studies were spread across Central Africa (3/74) East Africa (33/74), East Asia (1/74), North Africa (1/74), Oceania (1/74), South America (2/74), South Asia (10/74), South East Asia (9/74), South West Pacific (1/74), West Africa (8/74) and multiple countries (5/74).

Where sample size was clearly stated, the included studies involved 3 361 736 participants. Distribution of boys and girls was not provided for all studies but, where they were, results showed a total of 1 489 586 (44.3%) girls and 1 531 859 (45.6%) boys. Inclusion

Table 1 Study characteristics

Study	Study design	Country	Region	Sample size	Boy/girl difference wasting	Boy/girl difference stunting	Boy/girl difference underweight	Reasons for differences discussed
Kismul H, *et al*.[36]	Cross-sectional	DRC	Central Africa	8994	NA	More boys	NA	No
Sakisaka K, *et al*.[37]	Cross-sectional	Nicaragua	Central Africa	755	NA	More girls	More girls	Yes
Vonaesch P, *et al*.[38]	Cross-sectional	CAR	Central Africa	414	NA	More boys	NA	Other results cited
Abdulahi A. *et al*. [39]	Systematic review and meta-analysis	Ethiopia	East Africa	39 585	Not reported	More boys	Not reported	No
Abera L, Dejene T, Laelago T. [40]	Cross-sectional	Ethiopia	East Africa	398	Not reported	NA	More boys	Other results cited
Abraham D, Elifaged H, Berhanu E.[41]	Cross-sectional	Ethiopia	East Africa	50	More boys	More boys	More boys	Yes
Altare C. *et al*. [42]	Cross-sectional	Tanzania	East Africa	3264	NA	More boys	NA	Other results cited
Asfaw, M. *et al*. [43]	Cross-sectional	Ethiopia	East Africa	796	More boys	More boys	More boys	Yes
Bukusuba J, Kaaya AN, Atukwase A. [44]	Case–control	Uganda	East Africa	168	NA	More boys	NA	Yes
Chirande, L. *et al*. [45]	Cross-sectional	Tanzania	East Africa	7324	NA	More boys	NA	Yes
Chirwa EW, Ngalawa HPE.[46]	Cross-sectional	Malawi	East Africa	13 858	More boys	More boys	More boys	Yes
Condo, J. *et al*. [47]	Longitudinal	Rwanda	East Africa	480	More boys	More boys	More boys	Yes
Cruz, L. *et al*. [48]	Case–control	Mozambique	East Africa	282	NA	More boys	NA	Yes
Tosheno D, Mehretie Adinew Y, Thangavel T, et al. [49]	Cross-sectional	Ethiopia	East Africa	642	NA	NA	More boys	Yes
Eskezyiaw A, Tefera C. [50]	Cross-sectional	Ethiopia	East Africa	562	NA	More boys	NA	No
Espo M, *et al*. [51]	Cohort	Malawi	East Africa	613	NA	More boys	NA	No
Ettyang GA, Sawe CJ.[52]	Cross-sectional	Kenya and Cambodia	East Africa	10 163	NA	More boys	NA	Yes
Fentahun N, Belachew T, Lachat C. [53]	Longitudinal	Ethiopia	East Africa	1927	More girls	More girls	More girls	Yes
Geresomo N, *et al*. [54]	Cross-sectional	Malawi	East Africa	306	NA	More boys	NA	Yes
Gewa CA, Yandell N. [55]	Cross-sectional	Kenya	East Africa	3793	More boys	More boys	More boys	Yes
Medhin G, *et al*[56]	Longitudinal	Ethiopia	East Africa	1799	NA	More boys	More boys	Yes
Habtom K, *et al*. [57]	Cross-sectional	Ethiopia	East Africa	593	More boys	NA	More boys	No
Haile D, *et al*. [58]	Cross-sectional	Ethiopia	East Africa	9893	NA	More boys	NA	Yes
Kinyoki DK, *et al*. [59]	Cross-sectional	Somalia	East Africa	73 778	More boys	More boys	More boys	No
Masibo PK, Makoka D. [60]	Cross-sectional	Kenya	East Africa	19 021	NA	More boys	More boys	No

Continued

Table 1 Continued

Study	Study design	Country	Region	Sample size	Boy/girl difference wasting	Boy/girl difference stunting	Boy/girl difference underweight	Reasons for differences discussed
Matanda DJ, Mittelmark MB, Kigaru DMD.[61]	Cross-sectional	Kenya	East Africa	11 938	More boys	More boys	NA	Yes
Mgongo M, *et al*. [62]	Cross-sectional	Tanzania	East Africa	1870	More boys	More boys	More boys	Other results cited
Moges B, *et al*. [63]	Cross-sectional	Ethiopia	East Africa	734	NA	More boys	NA	No
Ndemwa M, *et al*. [64]	Cross-sectional	Kenya	East Africa	380	NA	More boys	More boys	Yes
Ndiku M, *et al*. [65]	Cross-sectional	Kenya	East Africa	629	More girls	More girls	More girls	Yes
Ntenda PAM, Chuang YC. [66]	Cross-sectional	Malawi	East Africa	6384	More boys	More boys	More boys	Yes
Olwedo MA, *et al*. [67]	Cross-sectional	Uganda	East Africa	672	More boys	More boys	NA	Yes
Rakotomanana H, *et al*. [68]	Cross-sectional	Madagascar	East Africa	4774	NA	More boys	NA	Yes
Tadesse AW, *et al*. [69]	Cross-sectional	Ethiopia	East Africa	622	NA	More boys	NA	Yes
Yisak H, Gobena T, Mesfin F. [70]	Cross-sectional	Ethiopia	East Africa	791	More boys	More boys	More boys	No
Yourkavitch J. [71]	Cross-sectional	Rwanda	East Africa	1572	More boys	More boys	More boys	Yes
Jiang Y, *et al*.[72]	Cross-sectional	China	East Asia	1115	NA	More boys	NA	Other results cited
Díez-Navarro A, *et al*. [73]	Cross-sectional	Multiple (Africa, Latin America, Asia)	Multiple	367 258	More boys	More boys	More boys	Yes
Khara T, *et al*. [28]	Cross-sectional	Multiple (global)	Multiple	570 930	More boys	More boys	NA	Yes
Keino S, *et al*.[74]	Systematic review	Multiple (sub-Saharan Africa)	Multiple	195 559	NA	More boys	NA	No
Myatt M, *et al*.[29]	Meta-analysis	Multiple (global)	Multiple	1 796 991	More boys reported with concurrent wasting and stunting	NA		Yes
Wamani H, *et al*.[21]	Cross-sectional	Multiple (sub-Saharan Africa)	Multiple	64 000	NA	More boys	NA	Yes
El-Taguri A, *et al*. [75]	Cross-sectional	Libya	North Africa	4498	NA	More boys	NA	No
Choy, C. *et al*. [76]	Cross-sectional	Samoa	Oceania	305	NA	More boys	NA	Yes
Castro B.A. *et al*. [77]	Cross-sectional	Columbia	South America	2967 under 5's	NA	More girls	NA	Yes
Correia, L. *et al*. [78]	Cross-sectional	Brazil	South America	6046	More girls	More girls	NA	No
Aguayo VM, Badgaiyan N, Paintal K. [79]	Cross-sectional	Bhutan	South Asia	2085	NA	More boys	NA	Other results cited
Aguayo VM, Badgaiyan N, Dzed L.[80]	Cross-sectional	Bhutan	South Asia	2028	More boys	NA	NA	No
Baig-Ansari, N. *et al*. [81]	Cross-sectional	Pakistan	South Asia	399	NA	More girls	NA	Yes

Continued

Table 1 Continued

Study	Study design	Country	Region	Sample size	Boy/girl difference wasting	Boy/girl difference stunting	Boy/girl difference underweight	Reasons for differences discussed
Biswas S, Bose K.[82]	Cross-sectional	India	South Asia	161	More boys	More girls	More boys	Yes
Gupta A. [83]	Cross-sectional	India	South Asia	440	NA	More girls	NA	Yes
Khan, A.T. *et al*. [84]	Cross-sectional	Pakistan	South Asia	3964	More boys	More boys	More boys	No
Kumar D, *et al*. [85]	Cross-sectional	India	South Asia	424	NA	NA	More girls	Yes
Sand A, *et al*. [86]	Cross-sectional	Pakistan	South Asia	105	More boys	NA	NA	No
Shaikh S, *et al*.[87]	Cross-sectional	India	South Asia	245	More boys	More girls	More girls	Yes
Shashank KJ, Angadi MM. [88]	Cross-sectional	India	South Asia	161	More boys	More girls	More boys	Yes
Adair LS, Guilkey DK. [89]	Longitudinal	Philippines	South East Asia	3080	NA	More boys	NA	Yes
Ahmed A.M. *et al* [90]	Cross-sectional	Bangladesh	South East Asia	8858	More boys	More boys	More boys	Other results cited
Choudhury, N. *et al*. [91]	Surveillance	Bangladesh	South East Asia	10 291	More boys	More boys	More boys	Other results cited
Chowdhury, M.R. *et al*.[92]	Cross-sectional	Bangladesh	South East Asia	7568	No difference found	More girls	More girls	Other results cited
Dancer D, Rammohan A, Smith MD.[93]	Cross-sectional	Bangladesh	South East Asia	5172	More girls	More girls	NA	Yes
Islam MM, *et al*. [94]	Cohort	Bangladesh	South East Asia	265	NA	More boys	NA	Yes
Khambalia A, *et al*. [95]	Literature review	Malaysia	South East Asia	NA	NA	More boys	No	NA
Phengxay M, *et al*. [96]	Cross-sectional	Laos	South East Asia	798	More girls	More boys	More boys	No
Ramli, A. *et al*. [97]	Cross-sectional	Indonesia	South East Asia	2168	NA	More boys	NA	No
Olita'a D, *et al*. [98]	Case–control	Papua New Guinea	South West Pacific	50	More girls	More girls	More girls	Yes
Akombi BJ, *et al*. [99]	Cross-sectional	Nigeria	West Africa	24 529	NA	More boys	NA	Yes
Amugsi DA, Mittelmark MB, Lartey A.[100]	Cross-sectional	Ghana	West Africa	7235	More boys	More boys	More boys	No
Bork KA, Diallo A.[32]	Cohort	Senegal	West Africa	7319	More boys	More boys	NA	Yes
Darteh EK, Acquah E, Kumi-Kyereme A. [101]	Cross-sectional	Ghana	West Africa	2379	NA	More boys	NA	No
Garenne M, *et al*. [102]	Longitudinal	Senegal	West Africa	12 638	More boys	More boys	NA	Yes
Miah RW, Apanga PA, Abdul-Haq Z. [103]	Cross-sectional	Ghana	West Africa	7550	More boys	More boys	More boys	Yes

Continued

Table 1 Continued

Study	Study design	Country	Region	Sample size	Boy/girl difference wasting	Boy/girl difference stunting	Boy/girl difference underweight	Reasons for differences discussed
Olusanya BO, Wirz SL, Renner JK.[104]	Cross-sectional	Nigeria	West Africa	5994	More boys	More boys	More boys	No
Poda GG, Hsu C, Chao JCJ.[105]	Cross-sectional	Burkina Faso	West Africa	6337	More boys	More boys	More boys	Other results cited

CAR, Central African Republic; DRC, Democratic Republic of the Congo; NA, not available.

criteria for age entailed a mix of studies covering all children aged 0–59 months with others focused on subsets of these children.

Meta-analysis

We identified 74 studies that had measured undernutrition in the form of wasting, stunting and underweight and reviewed them for inclusion in the meta-analysis. Forty-four studies included extractable data, fully disaggregated by sex and were therefore eligible for inclusion, 41 of these were cross-sectional and 3 were longitudinal (in which case the most recent prevalence data were used). Results from the analysis are presented in the forest plots in figure 2.

Pooled analysis by outcome

Twenty studies were included in the pooled analysis of wasting. In 17 of the 20 studies, wasting was more prevalent in boys than girls, with evidence of a difference in 11/17 of the studies. In the remaining three studies, wasting was more prevalent in girls than boys, with a significant difference in 1/3 of the studies. The pooled results of individual studies for wasting showed that boys had 26% higher odds of being wasted than girls (pooled OR 1.26, 95% CI 1.13 to 1.40, p<0.001).

Thirty-eight studies were included in the pooled analysis of stunting. In 32 of the 38 studies, stunting was more prevalent in boys than girls, with evidence of a difference in 28/32 of the studies. In the remaining six studies, stunting was more prevalent in girls than boys, with a significant difference in 3/6 of the studies. The pooled results for stunting showed that boys had 29% higher odds of being stunted than girls (pooled OR 1.29 95% CI 1.22 to 1.37, p<0.001).

Twenty-three studies were included in the pooled analysis of underweight. In 18 of the 23 studies, underweight was more prevalent in boys than in girls, with evidence of a difference in 10/18 of the studies. In the remaining five studies, girls were more likely to be underweight than boys, with a significant difference in 4/5 of the studies. The pooled results for underweight showed that boys had 14% higher odds of being underweight than girls (OR 1.14, 95% CI 1.02 to 1.26, p<0.001).

Pooled analysis by region

When organised by region, the odds of boys being malnourished were nearly always higher than for girls for wasting, stunting and underweight. For wasting, the odds were higher for boys than for girls in all regions. For stunting, the odds were higher for boys than for girls in all regions except South Asia (pooled OR 0.88, 95% CI 0.62 to 1.26, p=0.492), where there was no difference by sex. For underweight, the odds were higher for boys than for girls in all regions except Central America (OR 0.53, 95% CI 0.40 to 0.72, p<0.001), although this finding was from a single study, and South Asia (pooled OR 0.84, 95% CI 0.52 to 1.35, p=0.475). Results from the analysis are presented in table 2.

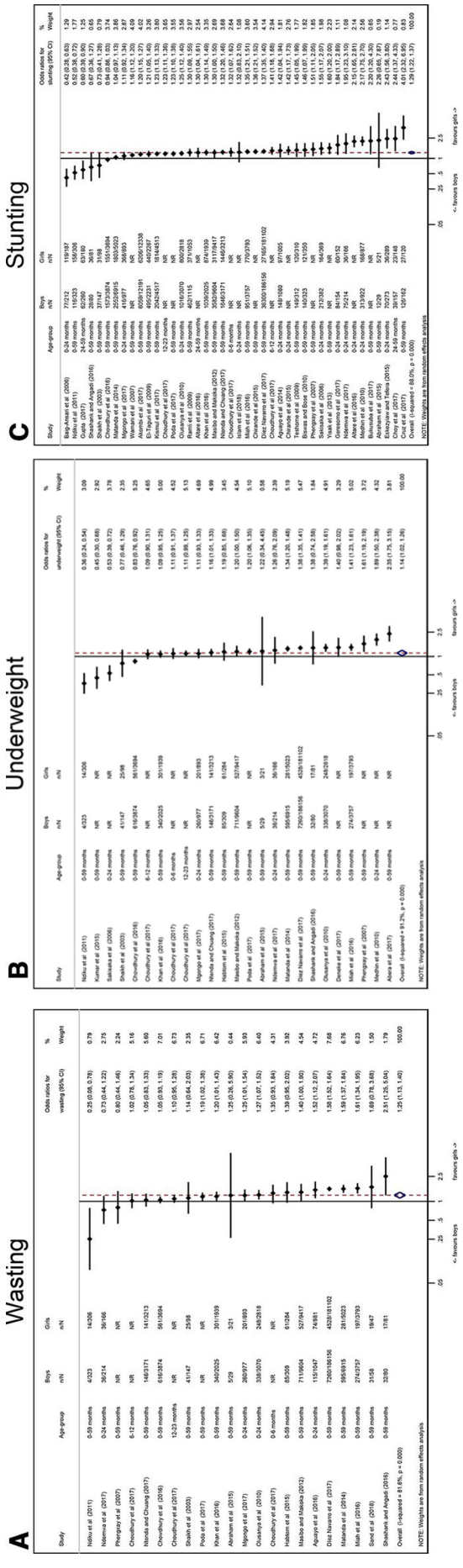


Figure 2 Forest plots showing the odds ratios for wasting, stunting and underweight in boys compared to girls.

Pooled analysis by age

When organised by age groups, the odds of boys being wasted, stunted or underweight were higher in all age categories for boys than for girls. Results from the analysis are presented in table 2.

We repeated the analysis for relative risk and found the results were consistent with results for ORs. There was strong evidence of between-study heterogeneity of effect, (wasting I^2=81.6%, p<0.001, stunting I^2=88.0%, p<0.001, underweight I^2=91.3%, p<0.001) which meta-regression by age group and region did not explain.

Risk of bias within studies

The quality assessment can be seen in table 3. All studies presented appeared to be of acceptable quality. It is worth noting however that a number of studies were excluded prior to this process due to the absence of suitable data. The main differences in quality were in the domain which assessed whether sex differences were acknowledged and explored (see Qualitative synthesis section).

Qualitative synthesis

Seventy-four studies reported on outcomes related to undernutrition—wasting, stunting and underweight. From this, 38/74 studies reported on wasting as an outcome with 31/38 (81%) reporting a higher prevalence of wasting in boys, 6/38 (16%) reporting a higher prevalence of wasting in girls, 1/38 (3%) reporting no difference in the prevalence of wasting between boys and girls. Sixty-seven of 74 studies reported on stunting as an outcome. Fifty-four of 67 (81%) reported a higher prevalence of stunting in boys and 13/67 (19%) reported higher prevalence of stunting in girls. Thirty-five of 74 studies reported on underweight as an outcome. Twenty-eight of 35 (80%) reported higher prevalence of being underweight in boys, 7/35 (20%) reported a higher prevalence of underweight in girls.

We reviewed the discussion sections of the reports to see if these findings were explicitly acknowledged and if explanations were offered. Forty-three of 74 (58%) of the studies discussed the findings, 10/74 (14%) studies cited articles with similar findings but did not speculate as to the causes of these differences and 21/74 (28%) of the studies did not discuss the findings related to sex differences at all.

Among those study reports that did offer explanations for sex differences, the reasons varied widely and were often conjectural. We coded explanations as either biological (6/43; 14%), social (21/43; 49%) or a combination of the two (16/43; 37%). Biological reasons varied from a simple statement of 'biological differences' to more detailed exploration of sex differences in the immune and endocrine system between boys and girls. Social reasons given varied widely and were almost entirely conjectural, with exceptions identified through regression analysis related to son preference and related to sibling order and sex. Other social reasons given were gender dynamics, preferential feeding practices

Table 2 Odds of boys being undernourished compared with girls by regions and age groups

Region/age groups	No. of studies of wasting	Pooled OR (95% CI)	P value	No. of studies of stunting	Pooled OR (95% CI)	P value	No. of studies of underweight	Pooled OR (95% CI)	P value
Africa									
East	8	1.18 (0.95 to 1.47)	0.126	17	1.50 (1.29 to 1.72)	<0.001	11	1.24 (1.02 to 1.50)	<0.0034
West	3	1.34 (1.12 to 1.59)	0.001	4	1.24 (1.18 to 1.30)	<0.001	3	1.32 (1.19 to 1.47)	<0.001
Central				1	1.23 (1.13 to 1.33)	<0.001			
North				1	1.21 (1.05 to 1.40)	0.009			
Oceania				1	2.44 (1.37 to 4.33)	0.002			
Asia									
South	5	1.39 (1.12 to 1.72)	0.003	7	0.88 (0.62 to 1.26)	0.492	4	0.84 (0.52 to 1.35)	0.475
South East	3	1.08 (0.99 to 1.17)	0.092	5	1.25 (1.08 to 1.45)	0.003	3	1.09 (0.91 to 1.32)	0.350
Central America				1	1.56 (1.17 to 2.07)	0.003	1	0.53 (0.40 to 0.72)	<0.001
Multiple studies	1	1.58 (1.52 to 1.64)	<0.001	2	1.26 (1.07 to 1.49)	0.006	1	1.38 (1.35 to 1.41)	<0.001
Age group (months)									
0–24	5	1.19 (1.06 to 1.34)	0.004	12	1.46 (1.20 to 1.79)	<0.001	5	1.15 (0.80 to 1.65)	0.445
24–59				3	1.21 (0.63 to 2.33)	0.572			
0–59	15	1.30 (1.13 to 1.48)	<0.001	24	1.24 (1.16 to 1.32)	<0.001	17	1.13 (0.99 to 1.29)	0.066

for either boys or girls, infant and young child feeding practices such as early weaning for boys and children's behaviours whereby girls might stay closer to the home and have more access to food being cooked, while boys play outside and in turn eat less while expending more energy.

DISCUSSION

This review offers a systematic look at sex differences over a wide geographical area. The studies included in the meta-analysis show that boys aged 0–59 months are much more likely to be wasted, stunted and underweight using anthropometric case definitions than girls. This indicates sex differences in susceptibility to undernutrition. The reasons currently provided for these differences vary and are often speculative rather than informed by direct evidence.

When stratified by region, the results also showed that boys are more likely to be wasted, stunted or underweight than girls. There were however some exceptions where ORs were reduced or reversed for boys with respect to undernutrition, in East Africa, Central America, South and South East Asia. The differences in Central America were based solely on one study, with a limited sample size and therefore need to be interpreted with caution. Our analysis potentially masks some of the complexities of regional variations in sex differences, particularly in South and South East Asia as many studies from these regions did not qualify for inclusion in the meta-analysis due to insufficient data. It is possible these differences might be under or overestimated. In reviewing the individual studies identified in the main search, results from this region are inconsistent and often conflicting compared with those coming from other regions of the world, such as Africa, which show a more consistent pattern of male disadvantage, a finding resonating with other studies.[5 21] The inconsistencies in findings for parts of South and South East Asia, however, may be explained in part by well-described social preferences for men,[22] and warrant further investigation. Such differences have also been described for under-5 mortality, with excess female child mortality for certain diseases, and according to socioeconomic status, birth order and family composition.[23–26]

These findings challenge commonly held assumptions within the nutrition community that girls are more likely to be affected by undernutrition. Recent studies focused on the relationship between wasting and stunting have also highlighted similar findings showing boys are more likely to be concurrently wasted and stunted than girls[4 27–29] and have identified this as an unexpected finding.

We found that even where sex differences are reported, they are not always acknowledged or explored. Just over a quarter of studies (28%) did not provide any discussion

Table 3 Risk of bias assessment

Study	Data source	1	2	3	4	5	6	7	8	9
Abera L t al Dejene T, Laelago T.[40]	Community-based cross-sectional study	●	●	●	●	●	●	●	Other results cited	●
Abraham D, Elifaged H, Berhanu E.[41]	Community-based cross-sectional study	●	●	●	●	◐	●	●	●	○
Aguayo VM, Badgaiyan N, Paintal K.[79]	BMIS—customised version of DHS	●	●	●	●	●	●	●	Other results cited	○
Aguayo VM, Badgaiyan N, Dzed L.[80]	BMIS—customised version of DHS	●	●	●	●	●	●	●	○	○
Akombi BJ, *et al*.[99]	DHS 2013	●	●	●	●	●	●	●	●	●
Altare C. *et al*.[42]	Cross-sectional study	●	●	●	●	●	●	●	Other results cited	●
Baig-Ansari, N. *et al*.[81]	Cross-sectional survey	●	●	●	●	●	●	●	●	●
Biswas S, Bose K.[82]	Cross-sectional study	●	●	●	●	●	●	●	●	○
Bukusuba J, Kaaya AN, Atukwase A.[44]	Case–control study	●	●	●	●	○	●	●	●	●
Chirande, L. *et al*[45]	DHS 2010	●	●	●	●	○	●	●	●	○
Choudhury, N. *et al*.[91]	Surveillance data	●	●	●	●	○	●	◐	Other results cited	●
Chowdhury, M.R. *et al*.[92]	DHS 2011	●	●	●	●	●	●	●	Other results cited	●
Choy, C. *et al*.[76]	Community-based cross-sectional study	●	●	●	●	●	●	●	●	●
Cruz, L. *et al*.[48]	Case–control study	●	●	●	●	●	●	●	●	●
Tosheno D, Mehretie Adinew Y, Thangavel T, *et al*[49]	Community-based cross-sectional study	●	●	●	●	●	●	●	●	○
Díez-Navarro A, *et al*. [73]	NGO intervention data	●	●	●	●	●	●	●	●	●
El-Taguri A, *et al*.[75]	Cross-sectional study	●	●	●	●	◐	●	●	○	●
Eskezyiaw A, Tefera C.[50]	Community-based cross-sectional study	●	●	●	●	●	●	●	○	●
Geresomo N, *et al*.[54]	Cross-sectional study	●	●	●	●	●	●	●	●	○
Gupta A.[83]	Cross-sectional study	●	●	●	●	●	●	●	●	No
Habtom K, *et al*.[57]	Community-based cross-sectional study	●	●	●	●	●	●	●	○	◐
Islam MM, *et al*.[94]	Longitudinal	●	●	●	●	●	●	●	●	●
Khan, A.T. *et al*.[84]	Cross-sectional study	●	●	●	●	●	●	●	○	○
Kismul H, *et al*.[36]	DHS 2013–2014	●	●	●	●	●	●	●	○	○
Kumar D, *et al*.[85]	Community-based cross-sectional study	●	●	●	●	●	◐	●	○	○
Masibo PK, Makoka D.[60]	DHS data—multiple years	●	●	●	●	●	●	●	○	○
Matanda DJ, Mittelmark MB, Kigaru DMD.[61]	DHS data—multiple years	●	●	●	●	●	●	●	●	●
Medhin G, *et al*.[56]	Surveillance data	●	●	●	●	●	●	●	●	●
Mgongo M, *et al*.[62]	Cross-sectional study	●	●	●	●	●	●	●	Other results cited	●
Miah RW, Apanga PA, Abdul-Haq Z. [103]	Multiple indicator cluster survey data	●	●	●	●	●	●	●	Other results cited	●
Ndemwa M, *et al*.[64]	Cross-sectional study	●	●	●	●	●	●	●	Other results cited	○
Ndiku M, *et al*.[65]	Cross-sectional study	●	●	●	●	●	●	●	●	○
Ntenda PAM, Chuang YC.[66]	DHS multiple years	●	●	●	●	●	●	●	●	●

Continued

Table 3 Continued

Study	Data source	1	2	3	4	5	6	7	8	9
Olusanya BO, Wirz SL, Renner JK.[104]	Cross-sectional study	●	●	●	●	●	●	●	○	●
Phengxay M, *et al*.[96]	Cross-sectional study	●	●	●	●	●	●	●	○	○
Poda GG, Hsu C, Chao JCJ.[105]	DHS 2010	●	●	●	●	●	●	●	Other results cited	●
Ramli, A. *et al*.[97]	Cross-sectional study	●	●	●	●	●	●	●	●	●
Sakisaka K, *et al*.[37]	Cross-sectional study	●	●	●	●	●	●	●	○	○
Sand A, *et al*.[86]	Cross-sectional study	●	●	●	●	●	●	●	○	○
Shaikh S, *et al*.[87]	Cross-sectional study	●	●	●	●	●	●	●	○	○
Shashank KJ, Angadi MM.[88]	Cross-sectional study	●	●	○	●	◐	●	●	●	◐
Tadesse AW, *et al*.[69]	Cross-sectional study	●	●	●	●	●	●	●	●	◐
Wamani H, *et al*.[21]	DHS multiple years and countries	●	●	●	●	●	●	●	●	●
Yisak H, Gobena T, Mesfin F.[70]	Community-based cross-sectional study	●	●	●	●	●	●	●	○	●

1. Were aims and objectives clearly stated?, 2. Was the target/reference population clearly described (is it clear who research is about)?, 3. Was a sample size justification, power description, or variance and effect estimates provided?, 4. Were the risk factor and outcome variables measured appropriate to the aims of the study?, 5. Were methods of anthropometric measurement and growth reference charts used well described?, 6. Is it clear what was used to determine statistical significance and/or precision estimates (eg, p values, CIs)?, 7. Results—were basic data adequately described?, 8. Were the male/female differences or non-differences discussed?, 9. Were limitations of study discussed?

●=Yes, ○=No, ◐=Partially.

BMIS, Bhutan's Multiple Indicator Survey; DHS, Demographic and Health Surveys; NGO, non-governmental organisation.

on reported differences and 14% cited similar findings but did not consider causes. Where explanations for sex differences in the prevalence of undernutrition were offered, nearly half (49%) of the studies reviewed offered explanations related to social reasons or based on speculation or preconceived supposition rather than evidence. The search criteria used (which filtered articles to those which use terms related to sex or gender in the abstract) might have introduced some bias here with a potential overestimation of studies that report and explore the issue of sex differences.

When stratified by age, the meta-analysis also shows that boys are at higher risk across all age groups, though again, our analysis potentially masks some of the complexities in age as detailed analysis of different age groups was not possible. While the results for age show that boys are more likely to be stunted than girls, the ORs are lower in the older age group compared with the younger group. Limited data in the 24–59 month age category, especially for wasting and underweight, however mean results must be interpreted with caution. These tentative results might indicate any sex-specific risks differ at different ages: further study is warranted. Two studies exploring concurrent wasting and stunting[28 29] found it to be a condition that affects children below 30 months more than it does older children, and found that sex ratios in undernourished children change with age, with a higher susceptibility for boys up to 30 months that then disappeared. Alongside other studies,[30] they suggest that sex hormones, specifically testosterone, luteinising hormone and follicle-stimulating hormones might play a role in this. Selection effects might also contribute to this, whereby if boys are more likely to die than girls, the remaining pool of boys would represent healthy survivors.

Adair and Guilkey[31] studied children in the Philippines and found men were more likely to become stunted in the first year of life (using the NCHS reference), but women were more likely than men to become stunted in the second year. They suggest differences in parental caregiving behaviours may partly account for this finding, but these were not measured in the study. Bork and Diallo[32] also found evidence of interaction between age and sex in that the deficit in boys compared with that in girls increased between the first and second years of life, regardless of the indicator used. The differences in height status were however sensitive to the growth reference chosen; they were greater when assessed using the 2006 WHO growth standards than when using the NCHS growth reference.

Sex differences in undernutrition may vary not only by geographical area, but also over time. When diseases causing undernutrition known to be more severe among girls, such as measles, whooping cough and tuberculosis, disappear because of vaccination, lower transmission and better feeding, the disadvantage of boys might increase. Conversely, if efficient nutrition programmes are conducted, the disadvantage of boys might be reduced over the years.

Interpretation of these findings into implications for practice and policy is limited at this stage but does warrant consideration and some degree of change. As a minimum, the systematic collection and reporting of disaggregated data by age and sex should be included in the design of programmes and assessments in all settings. Where differences are observed, particularly in programme admissions, these should be interpreted in light of sex differences in population burden in order to draw conclusions as to whether programmes are proving equally accessible to boys and girls, and then the potential causes of these differences should be considered and/or investigated. At present, boys' vulnerability to undernutrition is rarely a consideration in the design of nutrition programming, nor the formulation of policy. Moreover, some high-level international nutrition policies explicitly focus on the vulnerability of women and girls (eg, The Scaling Up Nutrition Movement Road Map for 2016–2020 Khara *et al*[28]). Similarly, the recent Inter-Agency Standing Committee guidance on gender in humanitarian action[33] recognises the inequity in food intake that may be faced by women and girls in crises but makes no reference to higher levels of undernutrition among boys. The absence of any reflection on gender, or the misuse of the term to highlight solely the health of women and girls, is likely to unintentionally reinforce inequalities in health.[7] In the Nutrition for Growth 2020 summit (https://nutritionforgrowth.org/) and beyond, a major focus will be on inequities in undernutrition and how they affect different groups in different locations. The emerging findings from this review have significance in ensuring consideration of these sex differences through an equity lens.

Strengths and limitations

One of the strengths of this study lies in the systematic approach that was chosen and its primary objective to review sex differences in undernutrition over a wide geographical area. However, there are areas where bias has potentially been introduced.

First, screening for studies to be included in this study was conducted by only one of the authors. While we employed systems to ensure contentious articles were discussed among two or more authors, we recognise that not using double screening is a limitation.[34]

Second, the search strategy looking for explicit mention of sex or gender in the abstract might have biased towards studies that reported on sex and gender in the abstract, or towards studies that found a significant difference, and therefore sex differences might be under-reported or over-reported in this study. Likewise, the search may have limited the analysis as there are potentially missed studies which include sex as a variable in analysis but without focusing on mention of sex in the study abstracts. Similarly, there may be a degree of publication bias whereby sex differences are simply not considered or reported.

The search criteria also encompassed a large number of studies with differing objectives meaning a limited degree of homogeneity. Few studies directly assessed the true relation between sex and undernutrition. This analysis is therefore potentially biased by healthy survivors—those children that have survived to be included in studies. We do not believe however that our results would be significantly different considering the evidence presented on male vulnerability. We also recognise the possibility of an overlap in data used from sources such as Demographic and Health Surveys (DHS). By comparing the dates and locations of included studies, we have not been able to establish any overlap. Unidentified overlap, if it occurs, is therefore likely to be minimal in our review and unlikely to affect overall conclusions. Where multiple studies are available from the same country, we have established these to be from different regions and times, therefore their inclusion as independent studies is justified. We hope that our review will stimulate future work to explore not just intercountry differences but also intracountry/regional differences as this would help understand biological versus social reasons for any difference in male/female risks.

While this analysis included some secondary DHS data, the subject in question could benefit from a systematic analysis of DHS, Multiple Indicator Cluster Surveys and or nutrition survey data. Though it is not believed that the outcome of the ORs of sex differences would be different, further analysis might help improve understanding of some of the complexities of age, context, dual burdens of undernutrition and sex differences and the implications for programmers. This might also help towards explaining some of the between-study heterogeneity that we identified but were unable to explain with our analysis.

The rigour of findings of the analysis is limited in relation to age as the grouping and degree of available data potentially masks some of the differences at various stages of the lifecycle, similarly geographical differences might be biased towards studies included through the search.

The absence of data on other anthropometric measures, such as Mid-Upper Arm Circumference (MUAC), is also a potential limitation. In considering the implications of the differences highlighted here, in addition to biological and social explanations, it is necessary to consider how we measure and define undernutrition and whether sex differences are an artefact of the indices in use. The WHO growth standards describe the physiological growth within optimal environmental conditions and are separated by sex. These reference data from healthy well-nourished populations resolve sex differences to zero by expressing data as z-scores calculated using the appropriate male and female subset of the reference population. However, it is unclear if we would expect sex differences in undernutrition expressed in this way to be zero, when the distribution of weight and height in both sexes has been shifted away from the healthy reference range. Likewise, it is unclear if the loss of the same

amount of body weight in a girl or boy would have the same physiological effect. If boys cope worse than girls when exposed to food shortages or disease and infection, this potentially highlights increased vulnerability over and above what is already accounted for by the standards.

In comparison, MUAC cut-offs are unadjusted and do not differentiate by sex or age (between 6 months and 5 years). This absence of adjustment may lead to a preferential inclusion of girls in programmes compared with what would be obtained if sex-specific standards were used as girls tend to have lower MUACs than boys. Though it has been shown to be a good predictor of mortality, sex differences in using MUAC to define undernutrition have not been widely studied.

Finally, the number of studies identified in the overall search that qualified for the meta-analysis was low. This was mainly due to a lack of presentation of disaggregated data. A recent Lancet series on gender equality, norms and health, highlighted the need for accurate disaggregated data.[35]

Implications for future research

This study is a step towards better understanding of sex differences in undernutrition and highlights the need to consider potential implications for policy and practice. Future research should aim to unpack the complexities related to age, biological and social risks (including gender norms) and context. In particular, we note that current papers are conjectural about reasons for observed differences. Any hypotheses should be more directly tested in future studies to further our understanding of sex differences in the context of undernutrition and subregional variations in order to determine the implications of these differences for programme staff and policymakers.

Future research will focus on a more detailed analysis of factors affecting outcomes for boys and girls such as epidemiological, demographic and social differences, explore the consequences of sex, age, and behavioural differences in nutritional outcomes and mortality. The impact of using differing anthropometric measurement and indices should also be explored to better understand how differing methods detect the most vulnerable children and explore how substantial sex differences are.

CONCLUSION

This review demonstrates that undernutrition defined by anthropometric case definitions is usually higher among boys than girls. While further research is needed to understand the policy and programming implications of these differences, lessons can already be drawn from this research. We call on nutrition actors to improve data collection in programmes, surveys and research through the full disaggregation and analysis of sex and age in order to identify which children are most vulnerable in specific contexts, and to allow comparison of programme data with population-level burdens. It is important to understand that the message of this study is not that boys should be prioritised over girls, rather it seeks to support all at-risk children, through improved understanding of sex differences in undernutrition. Ultimately, we believe all children under 5 years and their caregivers should be seen as a high priority group for targeted nutrition interventions, and resources and interventions should be targeted according to need.

Author affiliations
[1]Department of Population Health, London School of Hygiene and Tropical Medicine, London, UK
[2]Department of Medical Statistics, Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK
[3]National Perinatal Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK
[4]Institute for Global Health, University College London, London, UK
[5]Great Ormond Street Institute of Child Health, University College London, London, UK
[6]Emergency Nutrition Network, Kidlington, UK
[7]Department of Nutrition, Exercise and Sports, University of Copenhagen, Kobenhavn, Denmark
[8]School of Medicine, Center for Child Health Research,
[9]Brixton Health, Llwyngwril, Gwynedd, UK
[10]Institut de Recherche pour le Développement, UMI Résiliences, Bondy, France
[11]Institut Pasteur, Epidémiologie des Maladies Emergentes, Paris, France
[12]FERDI, Université d'Auvergne, Clermont-Ferrand, France
[13]MRC/Wits Rural Public Health and Health Transitions Research Unit, School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
[14]Centre for MARCH (Maternal, Adolescent & Reproductive Child Health), London School of Hygiene and Tropical Medicine, London, UK

Twitter Charles Opondo @charlesopondo and Marko Kerac @GlobalHealthNut

Acknowledgements We would like to acknowledge and thank Zoe Thomas at the London School of Hygiene and Tropical Medicine Library for her review of the search terms used in this study.

Contributors The review was designed and conducted by ST with supervision from MK and RS. The meta-analysis was led by ST supported by CO. ST led the writing of the manuscript for publication with contributions from all authors.

Funding This paper is made possible by funding from Irish Aid (grant number HQPU/2020/ENN) and the generous support of the American people through the United States Agency for International Development (USAID).

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data used were from published studies available in a public, open access repository. The datasets generated for the current study are available from the corresponding author on reasonable request.

ORCID iDs
Susan Thurstans http://orcid.org/0000-0002-7102-446X
Charles Opondo http://orcid.org/0000-0001-8155-4117
Andrew Seal http://orcid.org/0000-0003-3656-4054
Jonathan Wells http://orcid.org/0000-0003-0411-8025
Michel Garenne http://orcid.org/0000-0001-6073-7803
Rebecca Sear http://orcid.org/0000-0002-4315-0223
Marko Kerac http://orcid.org/0000-0002-3745-7317

REFERENCES

1 UNICEF/WHO/The World Bank Group. *Joint child malnutrition estimates: levels and trends in child malnutrition*, 2019.
2 Isanaka S, Boundy Ellen O'Neal, Grais RF, *et al*. Improving estimates of numbers of children with severe acute malnutrition using cohort and survey data. *Am J Epidemiol* 2016;184:861–9.
3 Heidari S, Babor TF, De Castro P, *et al*. Sex and gender equity in research: rationale for the SAGER guidelines and recommended use. *Res Integr Peer Rev* 2016;1:2.
4 Wells JC. Natural selection and sex differences in morbidity and mortality in early life. *J Theor Biol* 2000;202:65–76.
5 Garenne M. Sex differences in health indicators among children in African DHS surveys. *J Biosoc Sci* 2003;35:601–14.
6 Kraemer S. The fragile male. *BMJ* 2000;321:1609–12.
7 Hawkes S, Buse K. Gender and global health: evidence, policy, and inconvenient truths. *Lancet* 2013;381:1783–7.
8 Garenne M, Lafon M. Sexist diseases. *Perspect Biol Med* 1998;41:176–90.
9 WHO. *WHO guideline on health policy and system support to optimize community health worker programmes*, 2018.
10 FAO. *Gender and nutrition*, 2020.
11 Oniang'O R, Mukudi E. *Nutrition and gender*, 2001.
12 Institute IFPR. *Global hunger index: the inequalities of hunger*, 2017.
13 UNICEF. *UNICEF gender action plan*, 2017: 2018–21.
14 Hamill PV, Drizd TA, Johnson CL, *et al*. Physical growth: national center for health statistics percentiles. *Am J Clin Nutr* 1979;32:607–29.
15 WHO. *WHO child growth standards. growth velocity based on weight, length and head circumference methods and development*, 2006.
16 Andersen GS, Girma T, Wells JCK, *et al*. Body composition from birth to 6 Mo of age in Ethiopian infants: reference data obtained by air-displacement plethysmography. *Am J Clin Nutr* 2013;98:885–94.
17 Wells JCK, Davies PSW, Fewtrell MS, *et al*. Body composition reference charts for UK infants and children aged 6 weeks to 5 years based on measurement of total body water by isotope dilution. *Eur J Clin Nutr* 2020;74:141–8.
18 Moher D, Liberati A, Tetzlaff J, *et al*. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;339:b2535.
19 Hamill PV, Drizd TA, Johnson CL, *et al*. NCHS growth curves for children birth-18 years. United States. *Vital Health Stat 11* 1977;165:1–74.
20 NHLBI. *Quality assessment tool for observational cohort and cross-sectional studies*, 2018.
21 Wamani H, Astrøm AN, Peterson S, *et al*. Boys are more stunted than girls in sub-Saharan Africa: a meta-analysis of 16 demographic and health surveys. *BMC Pediatr* 2007;7:17.
22 Khera R, Jain S, Lodha R, *et al*. Gender bias in child care and child health: global patterns. *Arch Dis Child* 2014;99:369–74.
23 Gupta MD. Selective discrimination against female children in rural Punjab, India. *Popul Dev Rev* 1987;13:77–100.
24 Das Gupta M, Clustering D. Death clustering, mothers' education and the determinants of child mortality in rural Punjab, India. *Popul Stud* 1990;44:489–505.
25 Kuntla S, Goli S, Jain K. Explaining sex differentials in child mortality in India: trends and determinants. *Int J Popul Res* 2014;2014:1–7.
26 Wyon JB, Gordon JE. *Khanna study*, 2014.
27 Díez-Navarro A*et al*. Female eco-stability and severe malnutrition in children: evidence from humanitarian aid interventions of action against hunger in African, Asian and Latin American countries. *Nutricion Clinica y Dietetica Hospitalaria* 2017;34:127–34.
28 Khara T, Mwangome M, Ngari M, *et al*. Children concurrently wasted and stunted: A meta-analysis of prevalence data of children 6-59 months from 84 countries. *Matern Child Nutr* 2018;14:e12516.
29 Myatt M, Khara T, Schoenbuchner S, *et al*. Children who are both wasted and stunted are also underweight and have a high risk of death: a descriptive epidemiology of multiple anthropometric deficits using data from 51 countries. *Arch Public Health* 2018;76:28.
30 Schoenbuchner SM, Dolan C, Mwangome M, *et al*. The relationship between wasting and stunting: a retrospective cohort analysis of longitudinal data in Gambian children from 1976 to 2016. *Am J Clin Nutr* 2019;110:498–507.
31 Adair LS, Guilkey DK. Age-specific determinants of stunting in Filipino children. *J Nutr* 1997;127:314–20.
32 Bork KA, Diallo A. Boys are more stunted than girls from early infancy to 3 years of age in rural Senegal. *J Nutr* 2017;147:940–7.
33 IASC. *The gender handbook for humanitarian action*, 2017.
34 Gartlehner G, Affengruber L, Titscher V, *et al*. Single-reviewer abstract screening missed 13 percent of relevant studies: a crowd-based, randomized controlled trial. *J Clin Epidemiol* 2020;121:20–8.
35 Gupta GR, Oomman N, Grown C, *et al*. Gender equality and gender norms: framing the opportunities for health. *Lancet* 2019;393:2550–62.
36 Kismul H, Acharya P, Mapatano MA, *et al*. Determinants of childhood stunting in the Democratic Republic of Congo: further analysis of demographic and health survey 2013–14. *BMC Public Health* 2018;18:74.
37 Sakisaka K, Wakai S, Kuroiwa C, *et al*. Nutritional status and associated factors in children aged 0-23 months in Granada, Nicaragua. *Public Health* 2006;120:400–11.
38 Kismul H, Acharya P, Mapatano MA, *et al*. Determinants of childhood stunting in the Democratic Republic of Congo: further analysis of demographic and health survey 2013-14. *BMC Public Health* 2017;18:74.
39 Abdulahi A, Shab-Bidar S, Rezaei S, *et al*. Nutritional status of under five children in Ethiopia: a systematic review and meta-analysis. *Ethiop J Health Sci* 2017;27:175.
40 Abera L, Dejene T, Laelago T. Prevalence of malnutrition and associated factors in children aged 6-59 months among rural dwellers of damot gale district, south Ethiopia: community based cross sectional study. *Int J Equity Health* 2017;16:111.
41 Degarege A, Hailemeskel E, Erko B. Age-Related factors influencing the occurrence of undernutrition in northeastern Ethiopia. *BMC Public Health* 2015;15:108.
42 Altare C, Delbiso TD, Mutwiri GM, *et al*. Factors associated with stunting among pre-school children in southern highlands of Tanzania. *J Trop Pediatr* 2016;62:390–408.
43 Asfaw M, Wondaferash M, Taha M, *et al*. Prevalence of undernutrition and associated factors among children aged between six to fifty nine months in Bule HorA district, South Ethiopia. *BMC Public Health* 2015;15:41.
44 Bukusuba J, Kaaya AN, Atukwase A. Predictors of stunting in children aged 6 to 59 months: a case-control study in Southwest Uganda. *Food Nutr Bull* 2017;38:542–53.
45 Chirande L, Charwe D, Mbwana H, *et al*. Determinants of stunting and severe stunting among under-fives in Tanzania: evidence from the 2010 cross-sectional household survey. *BMC Pediatr* 2015;15:165.
46 chirwa ephraimw, ngalawa haroldpe, Chirwa EW, Ngalawa HPE. Determinants of child nutrition in Malawi. *South African Journal of Economics* 2008;76:628–40.
47 Condo JU, Gage A, Mock N, Condo J, et al, *et al*. Sex differences in nutritional status of HIV-exposed children in Rwanda: a longitudinal study. *Trop Med Int Health* 2015;20:17–23.
48 Cruz LMG, Azpeitia GG, Súarez DR, *et al*. Factors associated with stunting among children aged 0 to 59 months from the central region of Mozambique. *Nutrients* 2017;9. doi:10.3390/nu9050491. [Epub ahead of print: 12 May 2017].
49 Tosheno D, Mehretie Adinew Y, Thangavel T, *et al*. Risk factors of underweight in children aged 6-59 months in Ethiopia. *J Nutr Metab* 2017;2017:1–8.
50 Agedew E*et al*. Predictors of chronic under nutrition (stunting) among children aged 6-23 months in Kemba Woreda, southern Ethiopia: a community based cross-sectional study. *J Nutr Food Sci* 2015;05:4.
51 Espo M, Kulmala T, Maleta K, *et al*. Determinants of linear growth and predictors of severe stunting during infancy in rural Malawi. *Acta Paediatr* 2002;91:1364–70.
52 Ettyang GA, Sawe CJ. *Factors associated with stunting in children under age 2 in the Cambodia and Kenya 2014 demographic and health surveys*. Rockville, Maryland: ICF international, 2016. https://dhsprogram.com/pubs/pdf/WP126/WP126.pdf
53 Fentahun N, Belachew T, Lachat C. Determinants and morbidities of multiple anthropometric deficits in Southwest rural Ethiopia. *Nutrition* 2016;32:1243–9.

54 Geresomo N, Mbuthia EK, Matofari JW, *et al*. Risk factors associated with stunting among infants and young children aged 6 - 23 months in Dedza district of central Malawi. *African Journal Of Food, Agriculture, Nutrition And Development* 2017;17:12854–70.
55 Gewa CA, Yandell N. Undernutrition among Kenyan children: contribution of child, maternal and household factors. *Public Health Nutr* 2012;15:1029–38.
56 Medhin G, Hanlon C, Dewey M, *et al*. Prevalence and predictors of undernutrition among infants aged six and twelve months in Butajira, Ethiopia: the P-MaMiE birth cohort. *BMC Public Health* 2010;10:27.
57 Kelati H, Mengiste B, Alemayehu T, *et al*. Prevalence of Acute Malnutrition and its Associated Factors amongChildren aged 6-59 months in Mai-Aini Eritrean Refugees' Camp,Northern Ethiopia. *Journal of Nutrition and Food Sciences* 2015;5:1. doi:10.4172/2155-9600.1000336
58 Haile D, Azage M, Mola T, *et al*. Exploring spatial variations and factors associated with childhood stunting in Ethiopia: spatial and multilevel analysis. *BMC Pediatr* 2016;16:49.
59 Kinyoki DK, Kandala N-B, Manda SO, *et al*. Assessing comorbidity and correlates of wasting and stunting among children in Somalia using cross-sectional household surveys: 2007 to 2010. *BMJ Open* 2016;6:e009854.
60 Masibo PK, Makoka D. Trends and determinants of undernutrition among young Kenyan children: Kenya demographic and health survey; 1993, 1998, 2003 and 2008-2009. *Public Health Nutr* 2012;15:1715–27.
61 Matanda DJ, Mittelmark MB, Kigaru DMD. Child undernutrition in Kenya: trend analyses from 1993 to 2008-09. *BMC Pediatr* 2014;14:5.
62 Mgongo M, Chotta NAS, Hashim TH, *et al*. Underweight, stunting and wasting among children in Kilimanjaro region, Tanzania; a population-based cross-sectional study. *Int J Environ Res Public Health* 2017;14. doi:10.3390/ijerph14050509. [Epub ahead of print: 10 05 2017].
63 Moges B*et al*. Magnitude of stunting and associated factors among 6–59 months old children in Hossana town, southern Ethiopia. *Journal of Clinical Research and Bioethics* 2015;6. doi:10.3390/ijerph14050509
64 Ndemwa M, Wanyua S, Kaneko S, *et al*. Nutritional status and association of demographic characteristics with malnutrition among children less than 24 months in Kwale County, Kenya. *Pan Afr Med J* 2017;28:265.
65 Ndiku M, Jaceldo-Siegl K, Singh P, *et al*. Gender inequality in food intake and nutritional status of children under 5 years old in rural eastern Kenya. *Eur J Clin Nutr* 2011;65:26–31.
66 Ntenda PAM, Chuang Y-C. Analysis of individual-level and community-level effects on childhood undernutrition in Malawi. *Pediatr Neonatol* 2018;59:380–9.
67 Olwedo MA, Mworozi E, Bachou H, *et al*. Factors associated with malnutrition among children in internally displaced person's camps, Northern Uganda. *Afr Health Sci* 2008;8:244–96.
68 Rakotomanana H, Gates GE, Hildebrand D, *et al*. Determinants of stunting in children under 5 years in Madagascar. *Matern Child Nutr* 2017;13. doi:10.1111/mcn.12409. [Epub ahead of print: 28 12 2016].
69 Tadesse AW, Tadesse E, Berhane Y, *et al*. Comparison of Mid-Upper arm circumference and Weight-for-Height to diagnose severe acute malnutrition: a study in southern Ethiopia. *Nutrients* 2017;9. doi:10.3390/nu9030267. [Epub ahead of print: 11 Mar 2017].
70 Yisak H, Gobena T, Mesfin F. Prevalence and risk factors for under nutrition among children under five at Haramaya district, eastern Ethiopia. *BMC Pediatr* 2015;15:212.
71 Yourkavitch J. Trends and inequalities in young child nutrition in Rwanda: further analysis of the 2014–15 demographic and health survey, 2018. Available: https://dhsprogram.com/pubs/pdf/FA109/FA109.pdf
72 Jiang Y, Su X, Wang C, *et al*. Prevalence and risk factors for stunting and severe stunting among children under three years old in mid-western rural areas of China. *Child Care Health Dev* 2015;41:45–51.
73 Díez-Navarro A, et al. Female eco-stability and severe malnutrition in children: evidence from humanitarian aid interventions of action against hunger in African, Asian and Latin American countries. *Nutricion Clinica y Dietetica Hospitalaria* 2017;34:127–34.
74 Keino S, Plasqui G, Ettyang G, *et al*. Determinants of stunting and overweight among young children and adolescents in sub-Saharan Africa. *Food Nutr Bull* 2014;35:167–78.
75 El Taguri A, Betilmal I, Mahmud SM, *et al*. Risk factors for stunting among under-fives in Libya. *Public Health Nutr* 2009;12:1141–9.
76 Choy CC, Desai MM, Park JJ, *et al*. Child, maternal and household-level correlates of nutritional status: a cross-sectional study among young Samoan children. *Public Health Nutr* 2017;20:1235–47.
77 Castro BA, González ER, Álvarez MC, *et al*. Factors associated with stunted growth in children below 11 years of age in Antioquia, Colombia, 2004. *Colomb Med* 2011;42:204–14. doi:10.25100/cm.v42i2.772
78 Correia LL, Silva ACe, Campos JS, *et al*. Prevalence and determinants of child undernutrition and stunting in semiarid region of Brazil. *Rev Saude Publica* 2014;48:19–28.
79 Aguayo VM, Badgaiyan N, Paintal K. Determinants of child stunting in the Royal Kingdom of Bhutan: an in-depth analysis of nationally representative data. *Matern Child Nutr* 2015;11:333–78.
80 Aguayo VM, Badgaiyan N, Dzed L. Determinants of child wasting in Bhutan. insights from nationally representative data. *Public Health Nutr* 2017;20:315–24.
81 Baig-Ansari N, Rahbar MH, Bhutta ZA, *et al*. Child's gender and household food insecurity are associated with stunting among young Pakistani children residing in urban squatter settlements. *Food Nutr Bull* 2006;27:114–27.
82 Biswas S, Bose K. Sex differences in the effect of birth order and parents' educational status on stunting: a study on Bengalee preschool children from eastern India. *Homo* 2010;61:271–6.
83 Gupta A. Assessing stunting and predisposing factors among children. *Asian Journal of Pharmaceutical and Clinical Research* 2017;10:364–71.
84 Khan ATetal. Prevalence and associated factors of malnutrition among children under-five5 years in Sindh, Pakistan: a cross-sectional study. *Tropical Medicine and International Health* 2016;22:317–8.
85 Kumar D, et al. Socio-Demographic factors affecting the nutritional status of the under three children in Chandigarh, UT. *Healthline, Journal of Indian Association of Preventive and Social Medicine* 2015;6:46–52.
86 Sand A, Kumar R, Shaikh BT, *et al*. Determinants of severe acute malnutrition among children under five years in a rural remote setting: a hospital based study from district Tharparkar-Sindh, Pakistan. *Pak J Med Sci* 2018;34:260–5. doi:10.12669/pjms.342.14977
87 Shaikh S, Mahalanabis D, Chatterjee S, *et al*. Lean body mass in preschool aged urban children in India: gender difference. *Eur J Clin Nutr* 2003;57:389–93.
88 Shashank KJ, Angadi MM. Gender disparity in health and nutritional status among under-five children in a rural field practice area of Shri BM Patil medical college. *International Journal of Medical Science and Public Health* 2016;5:217–20.
89 Adair LS, Guilkey DK. Age-Specific determinants of stunting in Filipino children. *J Nutr* 1997;127:314–20.
90 Ahmed AMS, Ahmed T, Roy SK, *et al*. Determinants of undernutrition in children under 2 years of age from rural Bangladesh. *Indian Pediatr* 2012;49:821–4.
91 Choudhury N, Raihan MJ, Sultana S, *et al*. Determinants of age-specific undernutrition in children aged less than 2 years-the Bangladesh context. *Matern Child Nutr* 2017;13. doi:10.1111/mcn.12362. [Epub ahead of print: 12 10 2016].
92 Chowdhury MRK, Rahman MS, Khan MMH, *et al*. Risk factors for child malnutrition in Bangladesh: a multilevel analysis of a nationwide population-based survey. *J Pediatr* 2016;172:194–201.
93 Dancer D, Rammohan A, Smith MD. Infant mortality and child nutrition in Bangladesh. *Health Econ* 2008;17:1015–35.
94 Islam MM, Sanin KI, Mahfuz M, *et al*. Risk factors of stunting among children living in an urban slum of Bangladesh: findings of a prospective cohort study. *BMC Public Health* 2018;18:197.
95 Khambalia AZ, Lim SS, Gill T, *et al*. Prevalence and sociodemographic factors of malnutrition among children in Malaysia. *Food Nutr Bull* 2012;33:31–42.
96 Phengxay M, Ali M, Yagyu F, *et al*. Risk factors for protein-energy malnutrition in children under 5 years: study from Luangprabang Province, Laos. *Pediatr Int* 2007;49:260–5.
97 Ramli, Agho KE, Inder KJ, *et al*. Prevalence and risk factors for stunting and severe stunting among under-fives in North Maluku Province of Indonesia. *BMC Pediatr* 2009;9:64.
98 Olita'a D, Vince J, Ripa P, *et al*. Risk factors for malnutrition in children at Port Moresby General Hospital, Papua New Guinea: a case-control study. *J Trop Pediatr* 2014;60:442–8.
99 Akombi BJ, Agho KE, Hall JJ, *et al*. Stunting and severe stunting among children under-5 years in Nigeria: A multilevel analysis. *BMC Pediatr* 2017;17:15.
100 Amugsi DA, Mittelmark MB, Lartey A. An analysis of socio-demographic patterns in child malnutrition trends using Ghana

demographic and health survey data in the period 1993-2008. *BMC Public Health* 2013;13:960.
101 Darteh EKM, Acquah E, Kumi-Kyereme A. Correlates of stunting among children in Ghana. *BMC Public Health* 2014;14:504. doi:10.1186/1471-2458-14-504
102 Garenne M, Myatt M, Khara T, *et al*. Concurrent wasting and stunting among under-five children in Niakhar, Senegal. *Matern Child Nutr* 2019;15:e12736.
103 Miah RW, Apanga PA, Abdul-Haq Z, *et al*. Risk factors for undernutrition in children under five5 years old: evidence from the 2011 Ghana multiple indicator cluster survey. *Journal of AIDS and Clinical Research* 2016;7. doi:10.4172/2155-6113.1000585
104 Olusanya BO, Wirz SL, Renner JK, Prevalence RJK. Prevalence, pattern and risk factors for undernutrition in early infancy using the who multicentre growth reference: a community-based study. *Paediatr Perinat Epidemiol* 2010;24:572–83.
105 Fuchs C, Sultana T, Ahmed T, *et al*. Factors associated with acute malnutrition among children admitted to a diarrhoea treatment facility in Bangladesh. *Int J Pediatr* 2014;2014:1:5. doi:10.1155/2014/267806

5 Causes of sex differences

5.1 Scope of this chapter

This chapter presents the second research paper entitled “Understanding Sex Differences in Childhood Undernutrition: A Narrative Review”. This paper describes the findings of an extension of the systematic review and provides an in-depth narrative review of possible mechanisms and pathways behind sex differences in childhood malnutrition, from pre-conception through to childhood.

The review demonstrates that the evidence on why sex differences occur is limited but that a complex interaction of social, environmental, physiological, and genetic factors likely underlies these differences throughout the life cycle. Differences appear to be more pronounced in more severe presentations of undernutrition and in more socioeconomically deprived contexts. The paper was published in Nutrients in February 2022 as an open access article.

5.2 Figures

Figure 1. Prevalence of stunting in boys and girls by level of food insecurity.

5.3 Citation

Thurstans, S.; Opondo, C.; Seal, A.; Wells, J.C.; Khara, T.; Dolan, C.; Briend, A.; Myatt, M.; Garenne, M.; Mertens, A.; Sear, R.; Kerac, M. Understanding Sex Differences in Childhood Undernutrition: A Narrative Review. Nutrients 2022, 14, 948. https://doi.org/10.3390/nu14050948

5.4 Research paper 2 – Nutrients

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT

T: +44 (0)20 7299 4646
F: +44 (0)20 7299 4656
www.lshtm.ac.uk

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	1802701	**Title**	Mrs
First Name(s)	Susan		
Surname/Family Name	Thurstans		
Thesis Title	Sex differences in risk and outcomes from severe malnutrition: implications for management		
Primary Supervisor	Dr Marko Kerac		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	Nutrients		
When was the work published?	February 2022		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	NA		
Have you retained the copyright for the work?*	**No**	Was the work subject to academic peer review?	**Yes**

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	NA
Please list the paper's authors in the intended authorship order:	NA
Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I was responsible for the conceptualisation, design, and preparation of this review. I conducted the analysis of DHS and global food security index data with support from Dr Charles Opondo. I was responsibly for the writing of the manuscript. All co-authors reviewed and commented on draft and final versions of the paper.

SECTION E

Student Signature	[redacted]
Date	

Supervisor Signature	
Date	

nutrients

MDPI

Review

Understanding Sex Differences in Childhood Undernutrition: A Narrative Review

Susan Thurstans [1,*], Charles Opondo [2,3], Andrew Seal [4], Jonathan C. Wells [5], Tanya Khara [6], Carmel Dolan [6], André Briend [7,8], Mark Myatt [9], Michel Garenne [10,11,12,13], Andrew Mertens [14], Rebecca Sear [1] and Marko Kerac [1,15]

1 Department of Population Health, London School of Hygiene and Tropical Medicine, London WC1E 7HT, UK
2 Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London WC1E 7HT, UK
3 National Perinatal Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, Oxford OX3 7BN, UK
4 UCL Institute for Global Health, London WC1E 6BT, UK
5 Population, Policy and Practice Research and Teaching Department, UCL Great Ormond Street Institute of Child Health, London WC1N 1EH, UK
6 Emergency Nutrition Network, Oxford OX5 2DN, UK; carmel@n4d.group
7 Center for Child Health Research, School of Medicine, Tampere University, 33520 Tampere, Finland
8 Department of Nutrition, Exercise and Sports, University of Copenhagen, DK-2200 Copenhagen, Denmark
9 Brixton Health, Llwyngwril, Gwynedd LL37 2JD, Wales, UK
10 Institut de Recherche pour le Developpement, UMI Resiliences, 93140 Bondy, France
11 Institut Pasteur, Epidemiologie des Maladies Emergentes, 75015 Paris, France
12 Senior Fellow, FERDI, Universite d'Auvergne, 63000 Clermont-Ferrand, France
13 MRC/Wits Rural Public Health and Health Transitions Research Unit, School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg 2193, South Africa
14 School of Public Health, University of California, Berkeley, CA 94720-7360, USA
15 Maternal, Adolescent, Reproductive & Child Health Centre (MARCH), London School of Hygiene & Tropical Medicine, London WC1E 7HT, UK
* Correspondence: Susan.Thurstans@lshtm.ac.uk

Citation: Thurstans, S.; Opondo, C.; Seal, A.; Wells, J.C.; Khara, T.; Dolan, C.; Briend, A.; Myatt, M.; Garenne, M.; Mertens, A.; et al. Understanding Sex Differences in Childhood Undernutrition: A Narrative Review. *Nutrients* **2022**, *14*, 948. https://doi.org/10.3390/nu14050948

Academic Editors: Aamer Imdad

Received: 27 January 2022
Accepted: 17 February 2022
Published: 23 February 2022

Abstract: Complementing a recent systematic review and meta-analysis which showed that boys are more likely to be wasted, stunted, and underweight than girls, we conducted a narrative review to explore which early life mechanisms might underlie these sex differences. We addressed different themes, including maternal and newborn characteristics, immunology and endocrinology, evolutionary biology, care practices, and anthropometric indices to explore potential sources of sex differences in child undernutrition. Our review found that the evidence on why sex differences occur is limited but that a complex interaction of social, environmental, and genetic factors likely underlies these differences throughout the life cycle. Despite their bigger size at birth and during infancy, in conditions of food deprivation, boys experience more undernutrition from as early as the foetal period. Differences appear to be more pronounced in more severe presentations of undernutrition and in more socioeconomically deprived contexts. Boys are more vulnerable to infectious disease, and differing immune and endocrine systems appear to explain some of this disadvantage. Limited evidence also suggests that different sociological factors and care practices might exert influence and have the potential to exacerbate or reverse observed differences. Further research is needed to better understand sex differences in undernutrition and the implications of these for child outcomes and prevention and treatment programming.

Keywords: undernutrition; sex; age

1. Introduction

The reduction of childhood undernutrition in the form of wasting, stunting, and being underweight is key to the World Health Assembly targets and Sustainable Development Goals and is the specific focus of Goal 2, as well as being relevant to many others. Better understanding of the underlying aetiology and risk factors is key to successful prevention and management and the achievement of these goals.

In a recent systematic review and meta-analysis on sex differences in undernutrition in children aged under 5 years, [1] we found that in most settings, boys are more likely to be wasted (pooled OR 1.26, 95% CI 1.13 to 1.40), stunted (pooled OR 1.29, 95% CI 1.22 to 1.37), and underweight (pooled OR 1.14, 95% CI 1.02 to 1.26) than girls. There were regional differences, with the increase in risk being less pronounced for boys in South Asia, suggesting that social, genetic, or environmental factors may affect sex differences in nutritional status.

This finding that boys are more likely to be undernourished than girls is supported by a number of other studies. A pooled analysis of 35 longitudinal cohorts from 15 LMICs showed male sex to be a predictor of both wasting and stunting [2]. Several studies exploring concurrent wasting and stunting have also shown that, overall, boys are more likely to be affected than girls; these include population-level data [3–7], some of which contain multiple data sets, and Severe Acute Malnutrition (SAM) treatment programme data [8–10]. A recent analysis of DHS data from Africa explored sex differences in undernutrition and found that though differences were small, overall, boys were more susceptible to undernutrition than girls. The biggest differences were found in children who were concurrently wasted and stunted. Within this group, sex differences were more than the sum of sex differences in individual stunting and wasting, revealing complex layers of vulnerabilities [7]. Our review also found that sex differences tend not to be systematically reported or sometimes even recognised in studies of child undernutrition and that, where they are, explanations provided for these differences are often conjectural. Despite an abundance of literature related to sex differences in childhood in fields such as neonatal health or general morbidity and mortality patterns, to date, we have not identified a study which has specifically focused on the potential causes of sex-differences in undernutrition.

Understanding the possible origins, pathways, and consequences of sex differences in undernutrition is important for practitioners in the nutrition community and will help to refine what implications there may be for policy and practice. This paper complements our meta-analysis by presenting an in-depth exploration of potential reasons for the observed sex differences in undernutrition and considering what the pathways behind those differences may be. The aim is to synthesise data from relevant public health and biomedical domains to deepen our understanding of sex differences in undernutrition and consider their potential relevance to policy makers and practitioners in the sector.

2. Materials and Methods

This is a narrative review complementing our systematic review [1], in which we explore some of the themes identified for explaining sex differences in undernutrition in depth. The original systematic review followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [11]. The broad nature of the original protocol led to the identification of studies that were highly heterogeneous in the design and outcomes being studied, and so the study was divided into two parts. The first focuses on describing the sex-specific prevalences in undernutrition and how these varied by age and geographic region, and the second (this paper) focuses on possible explanations, exploring genetic, physiological, environmental, and sociological factors for these sex differences.

The original search strategy is reported in an earlier publication [1] and was designed to capture the concepts of malnutrition, sex, and gender. Medline, Embase, Global health, Popline, and Cochrane databases were searched. In this narrative review, we also

included studies that were considered relevant to the subject of sex differences but were not eligible for the systematic review, due to the absence of extractable prevalence data. We further searched the references included in the studies identified through the original search. Here, therefore, we have included relevant studies which discussed possible explanations or presented evidence for the possible causes of sex differences in undernutrition.

We also linked DHS data on the prevalence of stunting to FAO data on food security scores at the country level to graphically examine the relationship between the country-level prevalence of stunting and food insecurity using Stata v15 (Stata Corp., College Station, TX, USA). Countries were included in the analysis if data were available both from the DHS stat compiler and in the FAO table of food security scores.

Throughout this paper, we use the following WHO definitions: Low birthweight (LBW) refers to a birthweight < 2500 g; wasting is defined as a weight-for-height z-score < −2 or a MUAC under 125 mm; stunting and underweight are defined, respectively, as a height-for-age z-score < −2 and a weight-for-age z-score < −2.

3. Results: Potential Explanatory Factors for Sex Differences

3.1. Maternal and Newborn Factors

Differences in birth outcomes between girls and boys have been well recognised for many years. In the case of undernutrition, the fact that the greatest sex differences are found in early ages suggests that differences might originate, at least in part, in-utero [7]. Male sex has been identified as an independent risk factor for adverse pregnancy, maternal, and foetal outcomes [12,13]. Male foetuses are at increased risk of poor outcomes when compared with female foetuses and are more likely to experience complications, such as placental insufficiency, infections, and pre-term delivery [12,14,15]. Males are also less likely to survive premature birth with immature lung development, including the later development of surfactant [16]. It is estimated that a newborn female is physiologically similar to a 4–6 week old male [17], suggesting that, at birth, females are already more developed and therefore more able to withstand adverse conditions.

During the foetal period, the health and nutritional status of the mother can impact foetal growth and development and pregnancy outcomes. Poor nutritional status is associated with birth complications and poor outcomes [18,19]. Evidence has shown that the first 1000 days between conception and a child's second birthday is a critical period in which the foundations for long-term growth and development are determined [20]. The high levels of maternal undernutrition [21] in resource-limited settings have implications for meeting the needs of both the mother and the foetus. In relation to sex differences, this leads us to question if, in resource-poor settings, maternal nutritional status may have a bigger impact on infant boys than girls.

Maternal nutrition plays a pivotal role in the regulation of placental-foetal development. The role of the placenta is to provide oxygen and nutrients and facilitate the exchange of waste between the maternal and foetal circulations. Its size and function determine pre-natal growth and the infant's growth trajectory and are directly correlated. When maternal undernutrition occurs, changes in the structure of the placenta ensue, reflected in placental weight, morphology, vascular development, and transport function for amino acids, resulting in an altered nutrient supply to the foetus [22] and exacerbating the state of biological competition between a mother and foetus [19,23]. In this instance, the risk of undernutrition in the foetus is increased, [24] potentially affecting the lifelong health and productivity of offspring [22]. This might therefore suggest that boys may be in greater competition with their mothers than girls. Wells [24] suggests that in good environmental conditions, mothers physiologically invest proportionally more in a male than in a female foetus during the second half of pregnancy, resulting in a higher deposition of lean tissue.

Foetal growth in girls and boys differs from an early stage. Male foetuses have, on average, been found to be larger than female ones from the 8th to 12th week, suggesting genetic mechanisms underlying sex differences in foetal size [25]. Erikson et al. [26] describe sex differences in growth during gestation and explore the reasons and impacts of this. They suggest that boys grow faster in the womb than girls from the early stages of gestation (even before implantation). The research shows that boys' placentas may be more efficient than girls' placentas, as boys are usually longer in length than girls at any placental weight. They also suggest, however, that boys' placentas might have less reserve capacity (ability to transfer oxygen and nutrients to the foetus), increasing their vulnerability to undernutrition. Though they found both mean birthweight and placental weight to be higher in boys, when placental measurements were expressed as a ratio to birthweight, the values for placental measurements were lower in boys. This means that in situations where there is not a free flow of nutrients from the mother and where they need to be sustained by the transfer capacity of the placenta, there is less of this reserve available to a boy than to a girl of the same weight. Therefore, boys' bigger sizes and faster growth in-utero means they are at increased risk of becoming undernourished before birth. The same study also suggests that during development in the womb, boys are more responsive to a mother's gestational diet than girls, whose development seems to more closely reflect the mother's long-term nutrition and metabolic profile, a finding supported in other studies [27–30].

Recent longitudinal evidence from Nepal [31] supports these ideas. An analysis of data from a randomised controlled trial explored differences in maternal and early child nutritional status by offspring sex. Overall, the authors found that in a population with high levels of maternal undernutrition, there was minimal evidence from nutritional markers that mothers of sons could meet the extra absolute energy costs required for nourishing their sons. Sons, therefore, showed higher rates of stunting and lower head circumference z-scores in early life. However, the sex difference in undernutrition also decreased in favour of boys in the trial arm receiving food supplementation. This suggests that if the nutritional constraint on the mother is relaxed, boys capture a greater benefit than girls and can recover some of their 'lost' growth.

At birth, differences in growth mean that low birth weight (LBW), an indicator strongly linked to mortality, is higher in girls [32]. LBW is defined by an absolute weight (<2500 g) that does not take account of sex. Evidence has shown that despite the higher incidence of LBW in girls, LBW boys experience higher mortality than LBW girls [33]. In other words, it appears that smaller body size and greater adiposity from an early age favour girls in conditions of food deprivation [24,34], whilst a greater dependence on immediate maternal nutrient intake and faster growth may leave boys more vulnerable when later food shortages occur.

Finally, limited evidence suggests that there are also potential nutritional consequences for women carrying male foetuses. A small US study examined energy intake among pregnant women carrying boys compared with girls. Their study of 244 pregnant women showed that women carrying a male foetus had a higher energy intake than women carrying females (mean change in energy 796.2 kJ/day (95% CI 8.9–1583.4, p 0.05)). In agreement with the finding of higher rates of male foetal growth, the authors argue that their findings support the hypothesis that women carrying male foetuses may have higher energy requirements, and therefore, male foetuses may be more susceptible to energy restriction [35].

3.2. Endocrine/Immune Factors

Overall morbidity and mortality rates are higher throughout life in male humans compared with females [36]. Boys are generally more susceptible to infectious disease than girls, with some exceptions, notably measles, whooping cough, and tuberculosis [37]. The stronger immune response and capacity of girls for producing antibodies is one explanation for this enhanced immune reactivity [38,39]. Underlying mechanisms for these

sex differences are complex and include differences in endocrine and genetic effects on the immune system and physiology. The cycle of undernutrition and infection has been well documented [40,41]. An inadequate dietary intake leads to weight loss, growth faltering, lowered immunity, and mucosal damage, increasing the risk of disease while simultaneously resulting in increased energy and micronutrient requirements for an immune response. Infections further predispose to undernutrition through appetite loss, malabsorption, and altered metabolism and, in turn, inadequate dietary intake and further appetite loss. Hence, if males are more likely to be affected by infections, they are more likely to be affected by undernutrition. Hack et al. [42] found that LBW females achieved greater catch-up growth than LBW males and suggested this may be partly related to a lower incidence of neonatal and child infections, highlighting the importance of addressing infectious disease.

Hormonal systems differ between boys and girls, and the interactions between sex hormones and environmental factors have consequences for energy consumption, nutritional requirements, and vulnerability to infectious and noncommunicable diseases. [43,44] Testosterone, luteinizing hormone (LH), and follicle stimulating hormones (FSH) have been identified as hormones which differ between boys and girls and which might impact susceptibility to infections [45]. Leptin has also been identified as potentially playing a role in different sex responses to undernutrition. Leptin is the "satiety" hormone, responsible for the regulation of food intake and energy expenditure, and it is produced by white adipose tissue, which is higher in girls. When leptin levels are low, a feedback loop with the "hunger" hormone ghrelin is triggered, resulting in a hunger response and increased catabolism of the body's energy stores [46]. Leptin plays an important role in the generation and maintenance of immune responses [47] and has the capacity to both enhance and impede immune functions, boosting immune functions such as inflammatory cytokine production in macrophages, granulocyte chemotaxis, and increased Th17 proliferation [48].

Leptin is detectable in foetal cord blood from as early as 18 weeks of gestation, dramatically increasing after 34 weeks. A number of studies have demonstrated higher levels of leptin in girls in the last weeks of gestation and in the neonatal period [49,50] These higher levels of fat and leptin in early life for females should, in theory, increase immune protection and resistance to infections that slow growth. In newborns, the serum concentration of leptin is positively correlated with body weight and body mass and both correlated with and produced by fat mass, and it is higher in females than males [49,51]. In a sample of 82 newborns, serum leptin concentrations were found to be significantly lower in males compared with females (mean 15.3, SD 15.6 ng/mL, and range 2.0 to 79.3 ng/mL versus mean 25.0, SD 18.0 ng/mL, and range 2.1 to 84.5 ng/mL, respectively; *p*-value for test of difference = 0.011) [52].

In the case of prolonged nutritional deprivation, leptin production is suppressed by decreased energy-intake, decreasing blood insulin and possibly IGF-I concentrations [50]. A Ugandan study [53] examined the hormonal and metabolic profiles of children admitted for treatment for acute malnutrition in Uganda. As with previous studies, [54] they demonstrated the use of fatty acids as an energy source in acute malnutrition, suggesting that fatty acid metabolism plays a central role in adaptation to childhood malnutrition. They found that low baseline levels of leptin were associated with the highest risk of mortality during treatment for children with acute malnutrition. This suggests that in conditions of deprivation, girls are able to draw on their fat to increase their survival, while males will have less available due to their greater investment of energy in maintaining lean mass.

3.3. Age

Studies have noted that sex differences in undernutrition might be moderated by age [5,7]. Our systematic review showed that the male disadvantage was greater among

younger children. In the case of concurrent wasting and stunting, sex ratios change with age, with a higher susceptibility for boys up to 30 months, which then disappears [7,46].

Other studies we reviewed touched upon how the relationship between age and undernutrition differs by sex, with some inconsistencies. Adair and Guilkey [55] studied children in the Philippines and found that males were more likely to become stunted in the first year of life, but females were at a higher risk in the second year. In contrast, Bork and Diallo [56] studied children in Senegal and found a significant interaction between age and sex, in that the deficit in boys compared with that in girls increased between the first and second years of life. Moestue [57] examined the height-for-age growth curves of children aged 6–23 months in Bangladesh using the 2006 WHO growth standards. She found girls to have higher WHO z-scores than boys, with the greatest difference in the 6–11-month age group. However, she found that girls' nutritional advantage diminishes with age, with girls' Z-scores decreasing faster than boys'.

The lack of consistency across studies suggests heterogeneity in how the relationship between sex and undernutrition is affected by age. The current weight of evidence suggests that boys are more likely to be malnourished in early life but that the male disadvantage might lessen with age. This is further supported by a recent analysis of linear growth in 87 low-income countries, which showed that up to around 30 months, boys are more likely than girls to present growth faltering when compared with international growth standards, but this difference was reduced between 30–45 months, with reversal of the gap in some countries [58]. Understanding whether and how the relationship between sex and undernutrition varies by the child's age across different contexts might provide some clues to why sex differences in undernutrition exist.

3.4. Evolutionary Explanations

Theories of evolutionary biology are compatible with both the physiological and behavioural explanations discussed in this paper. This may help provide explanations for the male disadvantage, whereby even before birth, males are more vulnerable than females across several domains [59]. Greater biological vulnerability of males is common across mammalian species, and a recent paper [60] suggested that this might be linked to the nature of sex chromosomes. In mammals, males are the heterogametic sex (meaning their sex chromosomes are different (XY)), and females are the homogametic sex (meaning their sex chromosomes are the same (XX)). The 'unguarded X hypothesis' suggests that the reduced size of the Y chromosome exposes deleterious mutations on the X chromosome, leading to greater male vulnerability and to greater mortality risk. Supporting this hypothesis is the observation that in other species, such as birds, where males are the homogametic sex, it is males rather than females who have a survival advantage [60].

As well as this mechanistic explanation for the generally greater vulnerability of males, there is also a hypothesis from evolutionary biology which provides an ultimate, functional explanation for why parents may invest less in boys than girls in poor ecological conditions (e.g., under nutritional stress), which could help explain higher rates of male undernutrition in resource-stressed populations. The Trivers–Willard argument (Trivers and Willard, 1973) states that, in mammals, females almost always reproduce, while males have to compete for reproduction. Males in better conditions will be more successful at this competition than males in poor conditions. In this situation, evolutionary theory predicts that in poor conditions females will maximize their reproductive success by giving birth to more daughters, while in good conditions, they will produce more sons [61].

The same argument has been proposed to explain male disadvantage in both undernutrition of young children and under-five mortality [Wells 2000, 2016]. Here, the argument is about parental investment: in poor conditions, it is suggested that mothers biologically invest more in girls, leading to excess male under-nutrition. This hypothesis has stimulated considerable research, and some lines of evidence do provide support [62]. For example, women in Ethiopia who had recently given birth to sons had a better nutritional

status than those who had given birth to daughters [63]. Overall, however, evidence is rather mixed. Further, as discussed in the next section, while parents do sometimes treat sons and daughters differently, such parental investment behaviours are complex and not simply explained by the Trivers–Willard hypothesis.

3.5. Infant and Young Child Feeding and Care Practices

The way in which an infant is fed has consequences for their growth and development [64]. In breastfed infants, there is some evidence to suggest that the quality and quantity of milk that a mother produces or an infant takes in can vary between male and female infants. A multi-country study [65] exploring human milk intake found that male infants had human milk intakes which were 5% greater than those of female infants, although the data does not refer to exclusively breastfed infants. In a small separate US-based study [66], the breastmilk of mothers with male infants was found to have a 25% greater energy content than that of mothers of female infants. In contrast, a study of 103 Filipino mothers found no difference in milk composition of high- and low-income mothers, no difference in nursing frequency, and no difference by infant sex [67]. Important to note here is that breastmilk context is known to be highly variable from day to day and between feeds. A more recent study [68] found that the composition of milk in animal offspring was dependent on sex and suggested that adapting early nutrition intake might be one mechanism to maximise health protection and development for both sexes. The authors note, however, that the evidence for sex-specificity in human milk composition is currently limited and conflicting, and further investigation would be required to draw useful conclusions.

Some evidence also suggests that the protective effect of breastmilk in infants experiencing acute respiratory infection might differ between sexes [69]. Multivariable analysis found breastfeeding to be protective against pneumonia and hospitalisation in girls but not boys, although non-breastfed girls were at increased risk of severe acute respiratory disease compared with males. These results should be interpreted with caution, however, given the small sample size and the fact that the study did not differentiate between exclusive and non-exclusive breastfeeding.

Parental investment behaviours differ by context. A number of studies have shown that boys often receive complementary food earlier than girls, either due to boys being perceived as hungrier or because breastmilk was seen as inferior to complementary foods, and boys were prioritised for what was seen to be the superior option. This might lead to increased risk of infection. A longitudinal study in Senegal [56] explored the relationship between sex, nutritional status, and infant and young-child feeding (IYCF). They found that the stunting prevalence was higher for boys than girls in all age groups and that the mean HAZ score was lower for boys than girls in all age groups. The analysis showed sex differences in early initiation of complementary feeding, particularly in the 2–3-month age group. Boys were more likely to have consumed complementary foods (CF) in the past 24 h than girls. These differences were relatively modest and no longer apparent at 4–5 months. The authors note, however, that maternal motivations for introducing CF earlier than recommended in this setting included ‘‘a small weak infant’,’ alongside perceived breast milk insufficiency; therefore, the possibility that boys were at greater risk of early CF because they already had a lower mean HAZ than girls cannot be excluded. Similarly, a study using ethnographic interviews in Guatemala [70] found that mothers reported that male infants were hungrier and not as satisfied with breastfeeding alone compared with girls. As a result, boys were introduced earlier to complementary feeds than girls. Demographic and Health Survey (DHS) anthropometric data analysed in the same study showed a height-for-age difference in children between 6 and 17 months of 1.61cm in favour of girls ($p < 0.001$).

3.6. Sex and Socioeconomic Status

We identified some studies which show that sex differences, with increased risk among boys, are more pronounced among lower socio-economic groups. A study of 16 demographic health surveys in Sub-Saharan Africa [71] showed that sex differences in stunting were more pronounced in the lower socio-economic strata. This finding, however, was not uniform, and the authors called for more research to confirm findings. Other evidence might also point to this being a factor. Concurrent wasting and stunting has been found to be significantly higher both in males and in fragile and conflict-affected settings (FCS), [3] suggesting that in areas of deprivation and lower socio-economic conditions, the difference between girls and boys is more pronounced.

We linked stunting prevalence from DHS surveys with country-level food FAO security scores (see Figure 1) to graphically examine the relationship between the two. The results show that in most countries, as wealth decreases, the prevalence of stunting increases and that the prevalence of stunting is higher among males compared with females. There was strong evidence of a correlation between food insecurity and median prevalence of stunting (correlation coefficient −0.65, $p < 0.001$). The trend in the difference between male and female prevalence also increases as wealth decreases, suggesting the wealthier a country, the less pronounced the difference between boys and girls. Although the pattern is not uniform, and the comparison would benefit from more in-depth analysis, it does suggest that addressing inequality in socio-economic status might also help to reduce sex differences in undernutrition.

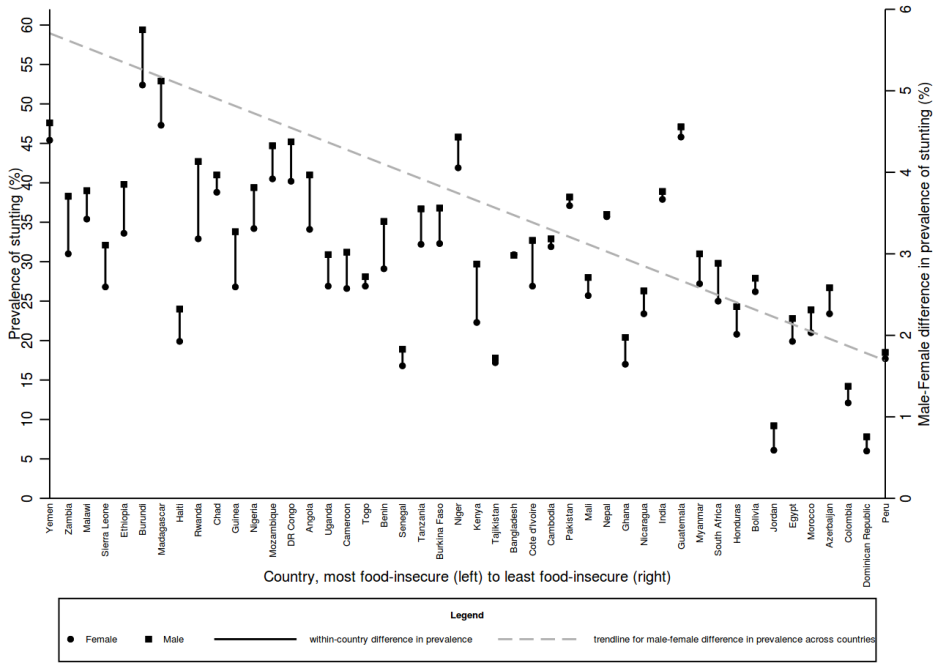


Figure 1. Prevalence of stunting in boys and girls by level of food insecurity. Data sources: Country food security scores from the global Food security index, found at https://foodsecurityindex.eiu.com/Index (accessed on 07 09 2021). Stunting prevalence data from the DHS StatCompiler https://www.statcompiler.com/en/ (accessed on 07 09 2021). The right Y-axis relates to the trendline for the male–female difference in prevalence across countries.

In contrast to the above findings, however, a recent study exploring sex differences and mortality patterns showed that whilst the overall prevalence of undernutrition declined in tandem with decreasing mortality in the population, sex differences in undernutrition increased with declining mortality [7]. This suggests that girls might benefit more than boys from general population health improvements at some levels.

3.7. Gender Perceptions

In addition to feeding and care practices, the social and economic circumstances in which families live and in which children are raised exert influences on health and nutrition outcomes through aspects such as how children are fed, what services they can access, and the wider health and disease environment to which they are exposed. This might explain some of the differences observed between data from Africa and Asia described throughout this review.

The roles that boys and girls assume within a community and the values attached to them might affect both the nutritional inputs that are made available to them and their exposure to disease and infection. For example, gender roles can influence where boys and girls spend their time and, in turn, the environment to which they are exposed and their access to food. In parts of sub-Saharan Africa, there is often a high value placed on girls because of their role in agriculture and due to the fact that they are seen as an investment, particularly in lower socio-economic groups, and a form of social security for parents [72–74]. Likewise, in early childhood, some studies suggest that the time girl children spend around the home might give them an advantage in the attention they receive from parents and increased access to food during food preparation [75]. Male children, on the other hand, might spend more time out of the house, playing with other male children, resulting in greater energy expenditure and exposure to environmental risks and sources of infection [73,75,76]. Despite these differences, a cross sectional study of African DHS data [77] found that overall, African mothers were unlikely to treat male and female infants differently; however, more in-depth mixed methods studies would be required to explore this fully.

In Asian studies, birth order and sibling sex have been found to play a role in the nutritional status of girls and boys, which might explain the differences we identified in our meta-analysis. In a study [78] observing gender differentials in childhood feeding, immunization, treatment seeking, and the nutritional status of children in Northern India, results showed that the extent of gender differentials depended on the birth order of the index child and the sex composition of older living siblings. Girls were less likely to have received solid/semi-solid food during the last 24 h, reflecting the opinion that solid/semi-solid foods are considered to be more valuable compared to liquids and breastfeeding. In contrast, a separate analysis [79] explored breastfeeding duration in India using national family health service data from 1992, 1998, and 2005 and found that girls are breastfed for a shorter duration than boys over concern of the contraceptive effects. They attributed this to both birth order and son preference, showing that duration of breastfeeding increased with birth order (younger children breastfed for longer) and was lowest for daughters, particularly those with no older brother whose parents were still trying for a son. One study documenting behaviours during famine noted that in Bangladesh, boys are given preferential treatment by parents, and girls are more likely to die [80]. These findings are in contrast to other studies which show that females are more likely to survive famine and have better long-term outcomes [81].

3.8. Indicators of Undernutrition

How undernutrition is assessed and defined has potential consequences for understanding how sex differences manifest in undernutrition. Weight and height measurements and sex-specific weight-for-height Z-scores are widely used to identify wasting. Unadjusted middle-upper-arm circumference (MUAC) measures are also widely used and have been shown to identify children with a high risk of mortality [82], providing a low cost, easy alternative, which can be used by all levels of health care professionals and mothers themselves [83].

The 2006 WHO growth standards [84] describe the growth of a "gold standard" reference group of children, from six different countries, all growing up in optimal environmental conditions and breastfed according to WHO recommendations. This reference

data was used to generate Z-scores (standard deviation scores), against which the growth and size of other children in other settings could be compared. Though sex-specific male and female growth references are always used by the WHO, what is not certain is whether sex differences observed in this original reference population are representative of sex differences in all other populations, particularly those living in situations of deprivation. In other words, it is unclear if a specific z-score (<−3, for example) in a girl or boy or the same age corresponds to the same physiological impact in both sexes and how the distribution of fat and fat-free mass affects this.

The use of MUAC, on the other hand, is based on a single cut-off point for girls and boys. The fact that boys are bigger in absolute terms and have higher energy needs to grow along given centile lines could mean that the same absolute supply of energy would only meet the requirements of a thinner arm in a boy compared to a girl, meaning boys could potentially have a predisposition to a thinner MUAC, once again as a consequence of their slightly larger size. Keeping the MUAC cut-off the same for boys and girls would then see that susceptibility expressed. It has been suggested that using a single cut-off point for MUAC may result in the overestimation of wasting in girls and the underestimation of wasting in boys [85]. Rasmussen et al. [86] compared MUAC with the MUAC Z-score as a predictor of mortality in a cohort of children in Guinea Bissau. As would be expected, they found that MUAC classified more girls and young children as moderately malnourished compared with the MUAC z-score (since z-score tables are sex-specific) but that sensitivity varied across the time-period, sex, and age groups. Overall, they found no difference in the performance of MUAC and MUAC z-score as predictors for mortality. A further analysis of mortality outcomes for older boys and girls using MUAC in different settings would be helpful to better understand risks.

4. Possible Implications of Sex Differences for Undernutrition Programming and Policy

4.1. Sex Differences in Treatment Outcomes and Mortality Implications

Though evidence clearly shows a higher risk of wasting, stunting, and being underweight for boys compared with girls, a more detailed analysis is needed to better understand the implications of these differences in relation to health and nutrition outcomes. For example, do differences in incidence and outcome follow the same direction? Evidence around diarrhoeal disease in children aged 1–5 suggests that despite slightly higher incidence rates for males, cause-specific mortality is higher amongst females, perhaps due to health-seeking behaviours [76]. Similarly, in a study of children in Senegal with concurrent wasting and stunting, sex differences in mortality were not significant after controlling for stunting and wasting [45].

In relation to treatment, evidence is limited, but it might indicate longer recovery time in boys. Data from a malnutrition treatment programme in Uganda showed that females had an increased probability of recovery compared with males, though the difference was not significant [10]. Similarly, a meta-analysis of RCTs providing small quantity lipid nutrient supplements (SQ-LNS) found that the effects of SQ-LNS on stunting, wasting, low MUAC, and small head size were greater among girls than among boys [87]. Girls were found to have a better growth status than boys. The authors suggest that the difference probably reflects a greater potential to respond to nutritional supplementation among girls.

4.2. The Policy Environment

Policy discussions and directions in the nutrition sector have rightly recognised and highlighted the importance of gender; however, the idea of sex differences is not at present widely recognised, and it is, in some cases, misrepresented. For example, our personal communication with practitioners at a 2019 international nutrition conference suggests that where male disadvantage is shown, data quality is often challenged, as it does not fit

prior assumptions. In many areas, women and girls are often identified as more vulnerable, as they may face barriers to gaining equal access to education, health care, work, and representation in both political and economic decision making. When it comes to nutrition, women and girls are also identified as the more vulnerable of the two sexes [88]. The international focus on gender concerns is well-justified. An analysis of data on mortality, wasting, and stunting from 96 countries showed that independent of gross domestic product (GDP), greater societal gender inequality is associated across countries with greater child undernutrition for both girls and boys in the next generation [89]. However, to focus solely on women and girls is not compatible with the promotion of gender equity in health, and as illustrated by our findings, it would be incompatible with public health ethics due to the requirement to focus on all groups who are at risk. Our recent systematic review and meta-analysis highlighted the importance of disaggregation of sex data in nutrition treatment programmes so that admissions can be assessed to see if they reflect the national sex distribution in the undernutrition burden between boys and girls [1]. Although there is no indication that males and females require different nutrition interventions, the recognition of sex differences in undernutrition at the policy level might support disaggregation and better understanding of data at the programme level.

5. Discussion

The concept of a sex disadvantage in neonatal and infant health is well described within some health fields, but it is less well understood in the field of nutrition. We reviewed evidence which suggests that there are different stages in the maternal and child lifecycle at which sex differences in nutritional status can manifest, although the strength of this evidence is still limited.

Boys have higher odds of being undernourished during early childhood in low resource settings, and these differences appear as early as the foetal period. Overall, differences are small but do appear to be more pronounced in more severe presentations of undernutrition, i.e., concurrent wasting and stunting and in more socio-economically deprived contexts with more severe levels of fragility and deprivation. Though genetic vulnerability might initially explain this, the sex differences observed between contexts suggests that a complex interaction of social, environmental, and genetic factors underlies these differences throughout the life cycle.

This review has demonstrated a number of possible explanations for sex differences in undernutrition, but there is more to be done in terms of fully understanding some of the complexities related to the risks of wasting, stunting, and being underweight for boys and girls. Further research is warranted to understand if sex differences impact treatment outcomes, cognitive development, long-term morbidity, and mortality risk in order to understand what the implications for policy and practice, if any, might be. Likewise, exploration of the different indices, such as MUAC, WHZ, WAZ, HAZ, and LBW, used to define undernutrition is needed. This would help to better understand the points at which differences might occur as children fall further below the reference population to determine if sex differences in outcomes are more pronounced at more severe degrees of undernutrition.

This review also highlights how complex and, at times, conflicting the evidence is. One of the main challenges encountered was that much of the work we reviewed explored sex differences as a secondary finding, rather than as the main focus of investigation, meaning that explanatory or confounding factors were not always fully accounted for. Further investigation is needed to explore, in detail, the pathways and drivers of sex differences, such as genetics, socio-economic status, infectious diseases, environmental exposures, social preferences for gender and associated practices, and geographical patterns. Understanding how these interact with other factors to impact sex differences at different points in a child's life will help to determine what actions may be appropriate from a programme or policy standpoint. Likewise, a better understanding of how these complex

factors interact to result in, enhance, or reverse sex differences is needed and of what the implications of these may be for treatment and prevention programming.

The operational implications of these findings are limited at present but do offer some possible explanations for observed sex differences in both survey and treatment data. They also highlight the importance of addressing the drivers of undernutrition, such as socio-economic inequality, and the prevention and treatment of infectious diseases. Finally, they highlight the importance of the continued collection, disaggregation, and analysis of data by age and sex to both identify and target prevention and treatment interventions toward vulnerable children.

Author Contributions: S.T. was responsible for the conceptualization, design, and preparation of this review, under the supervision of M.K. and R.S. C.O and S.T conducted the analysis of DHS and global food security index data. C.O, A.S, J.W, T.K, C.D, A.B, M.M, M.G, A.M, R.S, and M.K reviewed and commented on draft and final versions of the paper. All authors have read and agreed to the published version of the manuscript.

Funding: This paper is made possible by funding from Irish Aid (grant number HQPU/2021/ENN). The ideas, opinions and comments therein are entirely the responsibility of its authors and do not necessarily represent or reflect Irish Aid policy'.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data used were from published studies. In addition to published studies, we sourced data from the global Food security index, found at https://foodsecurityindex.eiu.com/Index (accessed on 07 09 2021), and from the DHS StatCompiler https://www.statcompiler.com/en/ (accessed on 07 09 2021)

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Thurstans, S.; Opondo, C.; Seal, A.; Wells, J.; Khara, T.; Dolan, C.; Briend, A.; Myatt, M.; Garenne, M.; Sear, R.; et al. Boys are more likely to be undernourished than girls: a systematic review and meta-analysis of sex differences in undernutrition. *BMJ Glob. Heal*. **2020**, 5, e004030, https://doi.org/10.1136/bmjgh-2020-004030.
2. Mertens, A.; Benjamin-Chung, J.; Colford, J.M., Jr.; Coyle, J.; van der Laan, M.J.; Hubbard, E.; Dayal, S.; Malenica, I.; Hejazi, N.; Sofrygin, O.; et al. Causes and consequences of child growth failure in low- and middle-income countries. **2020**. doi:10.1101/2020.06.09.20127100.
3. Khara, T.; Mwangome, M.; Ngari, M.; Dolan, C. Children concurrently wasted and stunted: A meta-analysis of prevalence data of children 6–59 months from 84 countries. *Matern. Child Nutr*. **2017**, 14, e12516, https://doi.org/10.1111/mcn.12516.
4. Obeng-Amoako, G. A. O.; Sunday Karamagi, C. A.;Nangendo, J.; Okiring, J.; Kiirya, Y.; Aryeetey, R.; Mupere, E.; Myatt, M.; Briend, A.; Kalyango, J. N.; et al. Factors associated with concurrent wasting and stunting among children 6-59 months in Karamoja, Uganda. *Matern. Child Nutr*. **2020**, 17, e13074.
5. Myatt, M.; Khara, T.; Schoenbuchner, S.; Pietzsch, S.; Dolan, C.; Lelijveld, N.; Briend, A. Children who are both wasted and stunted are also underweight and have a high risk of death: a descriptive epidemiology of multiple anthropometric deficits using data from 51 countries. *Arch. Public Heal*. **2018**, 76, 1–11, https://doi.org/10.1186/s13690-018-0277-1.
6. Obeng-Amoako, G. A. O.; Myatt, M.; Conkle, J.; Muwaga, B. K.; Aryeetey, R.; Okwi, A. L.; Okullo, I.; Mupere, E.; Wamani, H.; Briend,.A.; et al. Concurrently wasted and stunted children 6-59 months in Karamoja, Uganda: Prevalence and case detection. *Matern. Child Nutr*. **2020**, 16, e13000.
7. Garenne, M.; Thurstans, S.; Briend, A.; Dolan, C.; Khara, T.; Myatt, M.; Seal, A.; Wells, J.C. Changing sex differences in undernutrition of African children: findings from Demographic and Health Surveys. *J. Biosoc. Sci*. **2021**, 1–11, https://doi.org/10.1017/s0021932021000468.

8. Isanaka, S.; Hitchings, M.D.; Berthé, F.; Briend, A.; Grais, R.F. Linear growth faltering and the role of weight attainment: Prospective analysis of young children recovering from severe wasting in Niger. *Matern. Child Nutr*. **2019**, 15, e12817, https://doi.org/10.1111/mcn.12817.
9. Imam, A.; Hassan-Hanga, F.; Sallahdeen, A.; Farouket Z. L.. A cross-sectional study of prevalence and risk factors for stunting among under-fives attending acute malnutrition treatment programmes in north-western Nigeria: Should these programmes be adapted to also manage stunting? *Int. Health.* **2020**, 13, 262–271.
10. Obeng-Amoako, G.A.O.; Wamani, H.; Conkle, J.; Aryeetey, R.; Nangendo, J.; Mupere, E.; Kalyango, J.N.; Myatt, M.; Briend, A.; Karamagi, C.A.S. Concurrently wasted and stunted 6–59 months children admitted to the outpatient therapeutic feeding programme in Karamoja, Uganda: Prevalence, characteristics, treatment outcomes and response. *PLoS ONE.* **2020**, 15, e0230480, https://doi.org/10.1371/journal.pone.0230480.
11. Page, M.J.; McKenzie, J. E.; Bossuyt, P. M.; Boutron, I.; Hoffmann, T. C.; Mulrow, C. D.; Shamseer, L.; Tetzlaff, J. M.; Akl, E.A.; et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ.* **2021**, 372, n71.
12. Di Renzo, G.C.; Rosati, A.; Sarti, R. D.; Cruciani, L.; Cutuli, A. M. Does fetal sex affect pregnancy outcome? *Gend. Med.* **2007**, 4, 19–30.
13. Broere-Brown, Z.A.; Adank, M.C.; Benschop, L.; Tielemans, M.; Muka, T.; Gonçalves, R.; Bramer, W.M.; Schoufour, J.D.; Voortman, T.; Steegers, E.A.P.; et al. Fetal sex and maternal pregnancy outcomes: a systematic review and meta-analysis. *Biol. Sex Differ*. **2020**, 11, 1–20, https://doi.org/10.1186/s13293-020-00299-3.
14. Marino, M.; Masella, R.; Bulzomi, P.; Campesi, I.; Malorni, W.; Franconi, F. Nutrition and human health from a sex–gender perspective. *Mol. Asp. Med*. **2011**, 32, 1–70, https://doi.org/10.1016/j.mam.2011.02.001.
15. Ingemarsson, I. Gender aspects of preterm birth. *BJOG Int. J. Obstet. Gynaecol*. **2003**, 110, 34–38.
16. Townsel, C.D.; Emmer, S.F.; Campbell, W.A.; Hussain, N. Gender Differences in Respiratory Morbidity and Mortality of Preterm Neonates. *Front. Pediatr*. **2017**, 5, 6, https://doi.org/10.3389/fped.2017.00006.
17. Hutt, C. Sex Differences in Human Development. *Hum. Dev*. **1972**, 15, 153–170, https://doi.org/10.1159/000271239.
18. Victora, C.G.; Adair, L.; Fall, C.; Hallal, P.C.; Martorell, R.; Richter, L.; Sachdev, H.S.; Maternal and Child Undernutrition Study Group. Maternal and child undernutrition: Consequences for adult health and human capital. *Lancet* **2008**, 371, 340–357, https://doi.org/10.1016/s0140-6736(07)61692-4.
19. King, J.C. The Risk of Maternal Nutritional Depletion and Poor Outcomes Increases in Early or Closely Spaced Pregnancies. *J. Nutr*. **2003**, 133, 1732S–1736S, https://doi.org/10.1093/jn/133.5.1732s.
20. Bhutta, Z.A.; Ahmed, T.; Black, R.E.; Cousens, S.; Dewey, K.G.; Giugliani, E.R.J.; Haider, B.A.; Kirkwood, B.R.; Morris, S.S.; Sachdev, H.P.S.; et al. What works? Interventions for maternal and child undernutrition and survival. *Lancet*. **2008**, 371, 417–440, https://doi.org/10.1016/s0140-6736(07)61693-6.
21. GNR. *2020 Global Nutrition Report: Action on Equity to End Malnutrition*; Development Initiatives: Bristol, UK, **2020**.
22. Belkacemi, L.; Nelson, D.M.; Desai, M.; Ross, M.G. Maternal Undernutrition Influences Placental-Fetal Development. *Biol. Reprod*. **2010**, 83, 325–331, https://doi.org/10.1095/biolreprod.110.084517.
23. Haig, D. Genetic Conflicts in Human Pregnancy. *Q. Rev. Biol.* **1993**, *68*, 495–532.
24. Wells, J.C. Natural selection and sex differences in morbidity and mortality in early life. *J. Theor. Biol.* **2000**, *202*, 65–76.
25. Pedersen, J.F. Ultrasound evidence of sexual difference in fetal size in first trimester. *Br. Med. J.* **1980**, *281*, 1253–1253.
26. Eriksson, J.G.; Kajantie, E.; Osmond, C.; Thornburg, K.; Barker, D.J. Boys live dangerously in the womb. *Am. J. Hum. Biol*. **2009**, 22, 330–335, https://doi.org/10.1002/ajhb.20995.
27. O Mora, J.; De Paredes, B.; Wagner, M.; De Navarro, L.; Suescun, J.; Christiansen, N.; Herrera, M.G. Nutritional supplementation and the outcome of pregnancy. I. Birth weight. *Am. J. Clin. Nutr*. **1979**, 32, 455–462, https://doi.org/10.1093/ajcn/32.2.455.
28. Macaulay, S.; Munthali, R.J.; Dunger, D.B.; Norris, S.A. The effects of gestational diabetes mellitus on fetal growth and neonatal birth measures in an African cohort. *Diabet. Med*. **2018**, 35, 1425–1433, https://doi.org/10.1111/dme.13668.
29. Wrottesley, S. V.; Prioreschi, A.; Kehoe, S. H.; Ward, K. A.; Norris S. A. A maternal "mixed, high sugar" dietary pattern is associated with fetal growth. *Matern. Child Nutr.* **2020**, 16, e12912.

30. Prioreschi, A.; Wrottesley, S.V.; Said-Mohamed, R.; Nyati, L.; Newell, M.-L.; Norris, S.A. Understanding how maternal social and biological factors are related to fetal growth in an urban South African cohort. *J. Dev. Orig. Heal. Dis*. **2020**, 12, 79–87, https://doi.org/10.1017/s2040174420000045.
31. Saville, N.M.; Harris-Fry, H.; Marphatia, A.; Reid, A.; Cortina-Borja, M.; Manandhar, D.S.; Wells, J.C. Differences in maternal and early child nutritional status by offspring sex in lowland Nepal. *Am. J. Hum. Biol*. **2021**, e23637, https://doi.org/10.1002/ajhb.23637.
32. Amosu, A.M.; et al. Retrospective study of some factors influencing delivery of low birth weight babies in Ibadan, Oyo state, Nigeria. *Sci. Res. Essays* **2011**, 6, 236–240.
33. Vu, H.D.; Dickinson, C.; Kandasamy, Y. Sex Difference in Mortality for Premature and Low Birth Weight Neonates: A Systematic Review. *Am. J. Perinatol*. **2018**, *35*, 707–715.
34. Navarro, A.D. Female eco-stability and severe malnutrition in children: Evidence from humanitarian aid interventions of Action Against Hunger in African, Asian and Latin American countries. *Nutricion Clinica y Dietetica Hospitalaria* **2018**, 127–134, https://doi.org/10.12873/374DNAVARRO.
35. Tamini, R.M.; Lagiou, P.; Mucci, L. A.; Chung-Cheng Hsieh, C. C.; Hans-Olov Adami, H. O.; Trichopoulos, D. Average energy intake among pregnant women carrying a boy compared with a girl. *BMJ* **2003**, *326*, 1245–1246.
36. Lozano, R.; Naghavi, M.; Foreman, K.; Lim, S.; Shibuya, K.; Aboyans, V.; Abraham, J.; Adair, T.; Aggarwal, R.; Ahn, S.Y.; et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: A systematic analysis for the Global Burden of Disease Study 2010. *Lancet* **2012**, 380, 2095–2128, https://doi.org/10.1016/s0140-6736(12)61728-0.
37. Garenne, M.; Lafon, M. Sexist diseases. *Perspect. Biol. Med*. **1998**, *41*, 176–189.
38. Butterworth, M.; McClellan, B.; Aklansmith, M. Influence of Sex on Immunoglobulin Levels. *Nature* **1967**, *214*, 1224–1225.
39. Fish, E. The X-files in immunity: Sex-based differences predispose immune responses. *Nat. Rev.* **2008**, *8*, 737–744.
40. Tomkins, A.; Watson, F. Malnutrition and Infection. A review, Andrew Tomkins and Fiona Watson. United Nations Administrative Committee on Coordination/Sub Committee on Nutrition, 1989. 136 pp. Copies available from: Dr. J. B. Mason, Technical Secretary ACC/SCN, c/o WHO, 20 Avenue Appia, CH-1211 Geneva 27, Switzerland. *Trans. R. Soc. Trop. Med. Hyg*. **1990**, *84*, 446–446.
41. Rodriguez-Morales, A.; Bolivar-Mejía, A.; Alarcón-Olave, C.; Calvo-Betancourt, L. *Nutr. Infect.* **2016**, 98–103, https://doi.org/10.1016/b978-0-12-384947-2.00491-8.
42. Hack, M.B.; Schluchter, M.; Cartar, L.; Rahman, M.; Cuttler, L.; Borawski, E. Growth of Very Low Birth Weight Infants to Age 20 Years. *Pediatrics* **2003**, 112, e30–e38, https://doi.org/10.1542/peds.112.1.e30.
43. Taneja, V. Sex Hormones Determine Immune Response. *Front. Immunol*. **2018**, *9*, 1931.
44. Garenne, M. Demographic evidence of sex differences in vulnerability to infectious diseases. *J. Infect. Dis*. **2015**, *211*, 331–332.
45. Garenne, M.; Myatt, M.; Khara, T.; Dolan, C.; Briend, A. Concurrent wasting and stunting among under-five children in Niakhar, Senegal. *Matern. Child Nutr*. **2019**, *15*, e12736.
46. Klok, M.D.; Jakobsdottir, S.; Drent, M.L. The role of leptin and ghrelin in the regulation of food intake and body weight in humans: A review. *Obes. Rev*. **2007**, *8*, 21–34.
47. Lord, G. Role of Leptin in Immunology. *Nutr. Rev.* **2002**, *60* (Suppl. 10), S35–S38.
48. Naylor, C.; Petri, W.A., Jr. Leptin Regulation of Immune Responses. *Trends Mol. Med*. **2016**, *22*, 88–98.
49. Jaquet, D.; Leger, J.; Levy-Marchal, C.; Oury, J. F.; Czernichow, P. Ontogeny of leptin in human fetuses and newborns: Effect of intrauterine growth retardation on serum leptin concentrations. J. Clin. *Endocrinol. Metab*. **1998**, 83, 1243–1246.
50. Soliman, A.; ElZalabany, M.; Salama, M.; Ansari, B. Serum leptin concentrations during severe protein-energy malnutrition: Correlation with growth parameters and endocrine function. *Metabolism* **2000**, 49, 819–825, https://doi.org/10.1053/meta.2000.6745.
51. Bellone, S.; Rapa, A.; Petri, A.; Zavallone, A.; Strigini, L.; Chiorboli, E.; Ciardi, L.; Aguzzi, A.; Bona, G. Leptin levels as function of age, gender, auxological and hormonal parameters in 202 healthy neonates at birth and during the first month of life. *J. Endocrinol. Investig*. **2004**, 27, 18–23, https://doi.org/10.1007/bf03350905.
52. Matsuda, J.; Yokota, I.; Iida, M.; Murakami, T.; Naito, E.; Ito, M.; Shima, K.; Kuroda, Y. Serum leptin concentration in cord blood: Relationship to birth weight and gender. *J. Clin. Endocrinol. Metab.* **1997**, *82*, 1642–1644.

53. Bartz, S.; Mody, A.; Hornik, C.; Bain, J.R.; Muehlbauer, M.; Kiyimba, T.; Kiboneka, E.; Stevens, R.; Bartlett, J.; Peter, J.S.; et al. Severe Acute Malnutrition in Childhood: Hormonal and Metabolic Status at Presentation, Response to Treatment, and Predictors of Mortality. *J. Clin. Endocrinol. Metab*. **2014**, 99, 2128–2137, https://doi.org/10.1210/jc.2013-4018.
54. Kerr, D.S.; Stevens, M.C.; Robinson, H.M. Fasting metabolism in infants. I. Effect of severe undernutrition on energy and protein utilization. *Metabolism* **1978**, *27*, 411–435.
55. Adair, L.S.; Guilkey, D.K. Age-specific determinants of stunting in Filipino children. *J. Nutr.* **1997**, *127*, 314–320.
56. Bork, K.A.; Diallo, A. Boys Are More Stunted than Girls from Early Infancy to 3 Years of Age in Rural Senegal. *J. Nutr.* **2017**, *147*, 940–947.
57. Moestue, H. Can anthropometry measure gender discrimination? An analysis using WHO standards to assess the growth of Bangladeshi children. *Public Health Nutr*. **2009**, *12*, 1085–1091.
58. Costa, J.C.; Blumenberg, C.; Victora, C. Growth patterns by sex and age among under-5 children from 87 low-income and middle-income countries. *BMJ Glob. Health*, **2021**, *6*, e007152.
59. Kraemer, S. The fragile male. *Br. Med. J.* **2000**, *321*, 1609–1612.
60. Xirocostas, Z.A.; Everingham, S.E.; Moles, A.T. The sex with the reduced sex chromosome dies earlier: A comparison across the tree of life. *Biol. Lett*. **2020**, *16*, 20190867.
61. Song, S. Does famine influence sex ratio at birth? Evidence from the 1959–1961 Great Leap Forward Famine in China. *Proc. Biol. Sci.* **2012**, *279*, 2883–2890.
62. Cronk, L. Boy or girl: Gender preferences from a Darwinian point of view. *Reprod. BioMed. Online* **2007**, *15*, 23–32.
63. Gibson, M.A.; Mace, R. Strong mothers bear more sons in rural Ethiopia. *Proc. R. Soc. Lond. Ser. B Biol. Sci.* **2003**, *270* (Suppl. 1), S108–S109.
64. Bhutta, Z.A.; Das, J. K.; Rizvi, A.; Gaffey, M. F.; Walker, N.; Horton, S.; Webb, P.; Lartey, A.; Black, R. E. Evidence-based interventions for improvement of maternal and child nutrition: What can be done and at what cost? *Lancet* **2013**, *382*, 452–477.
65. da Costa, T.H.; Haisma, H.; Wells, J. C. K.; Mander, A. P.; Whitehead, R. G.; Bluck, L. J. C. How much human milk do infants consume? Data from 12 countries using a standardized stable isotope methodology. *J. Nutr*. **2010**, *140*, 2227–2232.
66. Powe, C.E.; Knott, C.D.; Conklin-Brittain, N. Infant sex predicts breast milk energy content. *Am. J. Hum. Biol.* **2010**, *22*, 50–54.
67. Quinn, E.A. No evidence for sex biases in milk macronutrients, energy, or breastfeeding frequency in a sample of filipino mothers. *Am. J. Phys. Anthropol.* **2013**, *152*, 209–216.
68. Galante, L.; Milan, A.M.; Reynolds, C.M.; Cameron-Smith, D.; Vickers, M.H.; Pundir, S. Sex-Specific Human Milk Composition: The Role of Infant Sex in Determining Early Life Nutrition. *Nutrients* **2018**, 10, 1194, https://doi.org/10.3390/nu10091194.
69. Libster, R.; Hortoneda, J.B.; Laham, F.R.; Casellas, J.M.; Israele, V.; Polack, N.R.; Delgado, M.F.; Klein, M.I.; Polack, F.P. Breastfeeding Prevents Severe Disease in Full Term Female Infants With Acute Respiratory Infection. *Pediatr. Infect. Dis. J*. **2009**, 28, 131–134, https://doi.org/10.1097/inf.0b013e31818a8a82.
70. Tumilowicz, A.; Habicht, J.-P.; Pelto, G.; Pelletier, D.L. Gender perceptions predict sex differences in growth patterns of indigenous Guatemalan infants and young children.. *Am. J. Clin. Nutr*. **2015**, 102, 1249–58, https://doi.org/10.3945/ajcn.114.100776.
71. Wamani, H.; Åstrøm, A.N.; Peterson, S.; Tumwine, J.K.; Tylleskär, T. Boys are more stunted than girls in Sub-Saharan Africa: a meta-analysis of 16 demographic and health surveys. *BMC Pediatr*. **2007**, 7, 17–17, https://doi.org/10.1186/1471-2431-7-17.
72. Cruz, L.M.G.; Azpeitia, G.G.; Súarez, D.R.; Rodríguez, A.S.; Ferrer, J.F.L.; Serra-Majem, L. Factors Associated with Stunting among Children Aged 0 to 59 Months from the Central Region of Mozambique. *Nutrients* **2017**, 9, 491, https://doi.org/10.3390/nu9050491.
73. Akombi, B.J.; Agho, K.E.; Hall, J.J.; Wali, N.; Renzaho, A.M.N.; Merom, D. Stunting, Wasting and Underweight in Sub-Saharan Africa: A Systematic Review. *Int. J. Environ. Res. Public Heal*. **2017**, 14, 863, https://doi.org/10.3390/ijerph14080863.

74. Espo, M.; Kulmala, T.; Maleta, K.; Cullinan, T.; Salin, M.-L.; Ashorn, P. Determinants of linear growth and predictors of severe stunting during infancy in rural Malawi. *Acta Paediatr.* **2007**, 91, 1364–1370, https://doi.org/10.1111/j.1651-2227.2002.tb02835.x.
75. Gewa, C.A.; Yandell, N. Undernutrition among Kenyan children: Contribution of child, maternal and household factors. *Public Health Nutr.* **2012**, *15*, 1029–1038.
76. WHO. *Addressing Sex and Gender in Epidemic-Prone Infectious Diseases*; WHO: Geneva, Switzerland, 2007.
77. Garenne, M. Sex differences in health indicators among children in African DHS surveys. *J. Biosoc. Sci.* **2003**, *35*, 601–614.
78. Abhishek, S.; Patel, S.K. Gender differentials in feeding practices, health care utilization and nutritional status of children in Northern India. *Int. J. Hum. Rights Healthc.* **2017**, *10*, 323–331.
79. Jayachandran, S. and I. Kuziemko, Why Do Mothers Breastfeed Girls Less than Boys? Evidence and Implications for Child Health in India. *Quart. J. Econ*. **2011**, *126*, 1485–1538.
80. Bairagi, R. Food crises and female children in rural Bangladesh. *Soc. Sci.* **1987**, *72*, 48–51.
81. Zarulli, V.; Jones, J.B.; Oksuzyan, A.; Lindahl-Jacobsen, R.; Christensen, K.; Vaupel, J.W. Women live longer than men even during severe famines and epidemics. *Proc. Natl. Acad. Sci*. **2018**, *115*, E832–E840, https://doi.org/10.1073/pnas.1701535115.
82. Mark Myatt, T.K.; Collins, S. A review of methods to detect cases of severely malnourished children in the community for their admission into community-based therapeutic care programs. *Food Nutr. Bull.* **2006**, *27* (Suppl. 3), S7–S23.
83. Blackwell, N.; Myatt, M.; Allafort-Duverger, T.; Balogoun, A.; Ibrahim, A.; Briend, A. Mothers Understand And Can do it (MUAC): a comparison of mothers and community health workers determining mid-upper arm circumference in 103 children aged from 6 months to 5 years. *Arch. Public Heal*. **2015**, *73*, 26–26, https://doi.org/10.1186/s13690-015-0074-z.
84. Zuguo Mei and Laurence M Grummer-Strawn. Standard deviation of anthropometric Z-scores as a data quality assessment tool using the 2006 WHO growth standards: a cross country analysis. *Bull. World Health Org.* **2007**, *85*, 441–448.
85. Tadesse, A.W.; Tadesse, E.; Berhane, Y.; Ekström, E.-C. Comparison of Mid-Upper Arm Circumference and Weight-for-Height to Diagnose Severe Acute Malnutrition: A Study in Southern Ethiopia. *Nutrients* **2017**, *9*, 267, https://doi.org/10.3390/nu9030267.
86. Rasmussen, J.; Andersen, A.; Fisker, A. B.; Ravn, H.; Sodemann, M.; Rodrigues, A.; Benn, C. S.; PAaby, P. Mid-upper-arm-circumference and mid-upper-arm circumference z-score: The best predictor of mortality? *Eur. J. Clin. Nutr*. **2012**, *66*, 998–1003.
87. Dewey, K.G.; Wessells, K.R.; Arnold, C.D.; Prado, E.L.; Abbeddou, S.; Adu-Afarwuah, S.; Ali, H.; Arnold, B.F.; Ashorn, P.; Ashorn, U.; et al. Characteristics that modify the effect of small-quantity lipid-based nutrient supplementation on child growth: an individual participant data meta-analysis of randomized controlled trials. *Am. J. Clin. Nutr*. **2021**, 114, 15S–42S, https://doi.org/10.1093/ajcn/nqab278.
88. IASC. *The Gender Handbook for Humanitarian Action;* IASC: Geneva, Switzerland, 2017.
89. Marphatia, A.A.; Cole, T.J.; Grijalva-Eternod, C.; Wells, J.C.K. Associations of gender inequality with child malnutrition and mortality across 96 countries. *Glob. Heal. Epidemiology Genom*. **2016**, 1, e6, https://doi.org/10.1017/gheg.2016.1.

6 Mortality implications

6.1 Scope of this chapter

This chapter presents the third research paper entitled “Anthropometric deficits and the associated risk of death by age and sex in children aged 6–59 months: A meta-analysis”. This paper describes a meta-analysis exploring mortality risk associated with anthropometric deficits in children 6–59 months by age and sex.

The findings demonstrate a high risk of mortality associated with child wasting, with no difference in risk between children 6–23 months and children 24–59 months. For underweight and stunting, younger children had a significantly higher risk of mortality than older children. Despite sex differences in the prevalence of wasting, stunting and underweight, no differences were identified in mortality risk between girls and boys. The paper was published in Maternal and Child Nutrition (MCN) in September 2022 as an open access article.

6.2 Figures

Figure 1. Study Flow Chart

Figure 2 Forest plots for pooled risk ratios of mortality in children 6–23 months versus 24–59 months for MUAC < 125 mm WHZ < −2, WAZ < −2 and HAZ < −2.

Figure 3 Forest plots for pooled risk ratios of absolute risk in children 6–23 months versus 24–59 months by sex for MUAC, WHZ, WAZ and HAZ.

6.3 Tables

Table 1. Study characteristics table

Table 2. Child mortality (deaths within 6 months) by anthropometric deficit according to geographic location, age and sex – moderate

Table 3. Absolute risk (AR) of mortality per 1000 children within 6 months of a contact and associated anthropometric deficits by age and relative risk (RR) of mortality in younger compared with older children

6.4 Citation

Thurstans, S., Wrottesley, S. V., Fenn, B., Khara, T., Bahwere, P., Berkley, J. A., Black, R. E., Boyd, E., Garenne, M., Isanaka, S., Lelijveld, N., McDonald, C. M., Mertens, A., Mwangome, M., O'Brien, K. S., Stobaugh, H., Taneja, S., West, K. P., Guerrero, S., … Myatt, M. (2023). Anthropometric deficits and the associated risk of death by age and sex in children aged 6–59 months: A meta-analysis. *Maternal & Child Nutrition*, 19, e13431. https://doi.org/10.1111/mcn.13431

6.5 Research paper 3 – MCN

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT

T: +44 (0)20 7299 4646
F: +44 (0)20 7299 4656
www.lshtm.ac.uk

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	1802701	**Title**	Mrs
First Name(s)	Susan		
Surname/Family Name	Thurstans		
Thesis Title	Sex differences in risk and outcomes from severe malnutrition: implications for management		
Primary Supervisor	Dr Marko Kerac		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	Maternal & Child Nutrition		
When was the work published?	August 2022		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	NA		
Have you retained the copyright for the work?*	**No**	Was the work subject to academic peer review?	**Yes**

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	NA
Please list the paper's authors in the intended authorship order:	NA
Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I designed the study in collaboration with Martha Mwangome, André Briend, Tanya Khara, Stephanie V. Wrottesley and Bridget Fenn. Data was contributed by Michel Garenne, Christine M. McDonald, Robert E. Black, Keith P. West, and Sunita Taneja. Analysis and interpretation was conducted by Stephanie V. Wrottesley, Bridget Fenn, and myself, and was discussed with and reviewed by all authors. I wrote all iterations of the paper, including the final. All authors have read and approved the final manuscript.

SECTION E

Student Signature	
Date	

Supervisor Signature	
Date	

Received: 12 March 2022 | Revised: 1 August 2022 | Accepted: 23 August 2022

DOI: 10.1111/mcn.13431

ORIGINAL ARTICLE

Maternal & Child Nutrition WILEY

Anthropometric deficits and the associated risk of death by age and sex in children aged 6–59 months: A meta-analysis

Susan Thurstans[1,2] | Stephanie V. Wrottesley[2] | Bridget Fenn[2] | Tanya Khara[2] | Paluku Bahwere[3] | James A. Berkley[4,5] | Robert E. Black[6] | Erin Boyd[7,8] | Michel Garenne[9,10,11,12] | Sheila Isanaka[13,14] | Natasha Lelijveld[2] | Christine M. McDonald[15,16] | Andrew Mertens[17] | Martha Mwangome[5] | Kieran S. O'Brien[18] | Heather Stobaugh[8,19] | Sunita Taneja[20] | Keith P. West[6] | Saul Guerrero[21] | Marko Kerac[1] | André Briend[22,23] | Mark Myatt[24]

[1]London School of Hygiene and Tropical Medicine, London, UK

[2]Emergency Nutrition Network, Kidlington, UK

[3]Epidemiology, Biostatistics and Clinical Research Centre, School of public Health, Université libre de Bruxelles, Brussels, Belgium

[4]Centre for Tropical Medicine & Global Health, University of Oxford, Oxford, UK

[5]Kenya Medical Research Institute (KEMRI), Centre for Geographic Medicine Research Coast (CGMRC) & KEMRI Wellcome Trust Research Programme, Kilifi, Kenya

[6]Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, USA

[7]USAID/Bureau of Humanitarian Assistance, Washington DC, USA

[8]Friedman School of Nutrition Science and Policy, Tufts University, Boston, Massachusetts, USA

[9]IRD, UMI Résiliences, Paris, France

[10]Institut Pasteur, Epidémiologie des Maladies Emergentes, Paris, France

[11]FERDI, Université d'Auvergne, Clermont-Ferrand, France

[12]MRC/Wits Rural Public Health and Health Transitions Research Unit, School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

[13]Harvard T. H. Chan School of Public Health, Boston, Massachusetts, USA

[14]Epicentre, Paris, France

[15]Departments of Pediatrics, and Epidemiology & Biostatistics, University of California, San Francisco, California, USA

[16]Department of Nutrition, University of California, Davis, USA

[17]Division of Epidemiology & Biostatistics, University of California, Berkeley, USA

[18]Francis I. Proctor Foundation, University of California, San Francisco, USA

[19]Action Against Hunger USA, New York, New York, USA

[20]Center for Health Research and Development, Society for Applied Studies, New Delhi, India

[21]United Nations Children's Fund (UNICEF), New York, USA

[22]Center for Child Health Research, Faculty of Medicine and Medical Technology, Tampere University, Tampere, Finland

[23]Department of Nutrition, Exercise, and Sports, University of Copenhagen, Fredericksberg, Denmark

[24]Brixton Health, Llwyngwril, Gwynedd, Wales, UK

Correspondence
Susan Thurstans, London School of Hygiene and Tropical Medicine, London, UK.
Email: susan.thurstans@lshtm.ac.uk

Funding information
United States Agency for International Development; Irish Aid, Grant/Award Number: HQPU/2021/ENN

Abstract

Risk of death from undernutrition is thought to be higher in younger than in older children, but evidence is mixed. Research also demonstrates sex differences whereby boys have a higher prevalence of undernutrition than girls. This analysis described mortality risk associated with anthropometric deficits (wasting, underweight and stunting) in children 6–59 months by age and sex. We categorised children into younger (6–23 months) and older (24–59 months) age groups. Age and sex variations in near-term (within 6 months) mortality risk, associated with individual anthropometric deficits were assessed in a secondary analysis of multi-country cohort data. A random effects meta-analysis was performed. Data from seven low-or-middle-income-countries collected between 1977 and 2013 were analysed. One thousand twenty deaths were recorded for children with anthropometric deficits. Pooled meta-analysis estimates showed no differences by age in absolute mortality risk for wasting (RR 1.08, $p = 0.826$ for MUAC < 125 mm; RR 1.35, $p = 0.272$ for WHZ < −2). For underweight and stunting, absolute risk of death was higher in younger (RR 2.57, $p < 0.001$) compared with older children (RR 2.83, $p < 0.001$). For all deficits, there were no differences in mortality risk for girls compared with boys. There were no differences in the risk of mortality between younger and older wasted children, supporting continued inclusion of all children under-five in wasting treatment programmes. The risk of mortality associated with underweight and stunting was higher among younger children, suggesting that prevention programmes might be justified in focusing on younger children where resources are limited. There were no sex differences by age in mortality risk for all deficits.

KEYWORDS
age, mortality, sex, stunting, underweight, wasting

1 | INTRODUCTION

Addressing all forms of undernutrition remains a public health priority for achieving the 2030 Sustainable Development Goals. Worldwide, 149 million children under 5 years of age are stunted (have a height-for-age z-score < −2) and 45 million are wasted (have a weight-for-height z-score < −2) (United Nations Children's Fund, World Health Organisation, The World Bank Group, 2021) with 15.9 million experiencing concurrent wasting and stunting (Global Nutrition Report, 2018). Evidence shows that, even in mild forms, anthropometric deficits are associated with increased mortality risk in children under five (Olofin et al., 2013).

The first 1000 days of life is a critical phase characterised by rapid growth and neurodevelopment, high nutrition requirements, increased susceptibility to infections, and full dependency on others to meet care, nutrition and social interaction requirements (Martorell, 2017). Younger children (0–23 months) have a

Key points

- There is a high risk of mortality associated with child wasting. We found no difference in mortality risk between children 6–23 months and children 24–59 months, indicating the need to include all children under 5 years in wasting treatment programmes.
- For underweight and stunting, younger children had a significantly higher risk of mortality than older children. Where resources are limited, prevention programmes may be justified in targeting younger children.
- Despite sex differences in the prevalence of wasting, stunting and underweight, there were no differences in mortality risk between girls and boys in both younger and older age groups.

higher incidence of undernutrition than older children (24–59 months) and may face a higher risk of death from undernutrition (Victora et al., 2021). Of the estimated 5.2 million child deaths recorded in 2019, 2.4 million (46%) occurred in newborns (infants under 28 days) and 1.5 million (29%) in children aged 1–11 months (World Health Organisation [WHO], 2020).

Few studies, however, have assessed the association between anthropometric deficits, age and mortality in children under five, largely due to insufficient data (Rice et al., 2000). Much of the work exploring the risk of death by age has compared the ability of different anthropometric criteria to identify children at highest risk of mortality (Garenne et al., 2019; Khara et al., 2021; O'Brien et al., 2020). Studies that have directly explored how age affects mortality risk in children 6–59 months with undernutrition, have suggested overall higher mortality for younger groups, but highlight increased mortality among older wasted children (Katz et al., 1989; Schwinger et al., 2019).

Research has also demonstrated sex differences in undernutrition whereby boys are often more likely to be wasted, stunted and underweight than girls (Costa et al., 2021; Garenne et al., 2019; Khara et al., 2018; Myatt et al., 2018; Thurstans et al., 2020). Evidence on the reasons for these differences is limited, and to date, the possible implications for treatment and mortality outcomes have not been well researched (Thurstans et al., 2022).

The aim of this analysis was to inform programming and policymaking by describing mortality risk associated with anthropometric deficits (wasting, underweight and stunting) in children 6–59 months by age and sex using multi-country cohort data from low- and middle-income countries (LMIC).

2 | METHODS

2.1 | Study design

This was a secondary data review and meta-analysis of multi-country cohort data following STROBE guidelines (Vandenbroucke et al., 2007). We assessed variations in mortality risk associated with individual anthropometric deficits (wasting, underweight and stunting), as well as whether these relationships differed by age and sex in children 6–59 months.

2.2 | Study setting and participants

This study followed a separate analysis exploring which anthropometric criteria best identifies children at high risk of near-term mortality (Khara et al., 2021). The same data set for 56,559 children was used for this analysis, which comprised a reduced set of variables containing basic demographic information, anthropometric measures and mortality outcomes. The data originated from 12 large, prospective community cohort studies or randomised controlled trials in LMIC. These included studies of various interventions such as vitamin A supplementation and antibiotic provision, breastfeeding and child feeding interventions and general monitoring of health and nutrition. The studies were conducted between 1977 and 2013 (Adair et al., 1993; Arifeen et al., 2001; Fawzi et al., 1997; Garenne et al., 1987; Katz et al., 1989; Martines et al., 1998; Mølbak et al., 1992; O'Brien et al., 2020; Van Den Broeck et al., 1993; West et al., 1991).

All of the original studies took place in LMIC, six in Africa (Democratic Republic of Congo, Ghana, Guinea Bissau, Niger, Senegal and Sudan), five in Asia (Bangladesh, India, Indonesia, Nepal, Philippines) and one in South America (Peru).

We focused on children aged 6–59 months old. Data were not available for children under 6 months of age in this data set.

2.3 | Variables

The primary outcome was mortality, defined as death recorded within 6 months of a contact during which anthropometry was assessed. Mortality was confirmed by verbal autopsy in all studies, with the exception of one which examined hospital records (Mølbak et al., 1992). A contact was defined as a point in time whereby a child's anthropometric status was assessed and recorded by a health worker.

Explanatory variables were wasting (measured by weight-for-length/weight-for-height z-score [WLZ/WHZ] or mid-upper arm circumference [MUAC]), underweight (measured by weight-for-age z-score [WAZ]) and stunting (measured by height-for-age z-score [HAZ]), as well as age and sex.

We used the World Health Organisation (WHO) classifications of undernutrition for each anthropometric indicator capturing both moderate and severe cases of each deficit (World Health Organisation [WHO], 2006). Wasting was defined as WLZ/WHZ < −2, or MUAC < 125 mm. Underweight was defined as weight-for-age WAZ < −2 z-score and stunting was defined as HAZ < −2 z-score. We also conducted separate analysis for severe definitions of each deficit. Severe wasting was defined as WLZ/WHZ < −3 z-score, or MUAC < 115 mm, severe underweight was defined as weight-for-age WAZ < −3 z-score and severe stunting was defined as HAZ < −3 z-score. Bilateral pitting oedema was not investigated as the relevant data was not present in the data set (Khara et al., 2021).

Children were stratified into two groups according to age at anthropometric assessment: younger children (aged 6–23 months) and older children (aged 24–59 months). As age was a key indicator of interest, we excluded countries where data were not available for children in both age groups. After this exclusion, eight countries remained in the data set (Democratic Republic of Congo (DRC), Guinea Bissau, Indonesia, Nepal, Niger, Philippines, Senegal and Sudan). MUAC data was only available from three countries (Senegal, Nepal and DRC).

2.4 | Statistical methods

Z-scores were calculated using the 2006 WHO Child Growth Standards (World Health Organisation [WHO], 2006). Records with extreme z-score values were identified and censored using the WHO "biological plausibility" criteria (Blössner et al., 2009) We did not encounter missing data as this was a previously cleaned data set.

Statistical analysis was conducted using Stata V.16 (StataCorp 2017, Stata Statistical Software). We used the following measures to examine mortality risk among children with anthropometric deficits, conducting separate analyses for moderate and severe definitions of MUAC, WHZ, WAZ and HAZ:

1. Absolute risk of mortality/1000 within each age and sex category

$$\text{Absolute risk mortality/1000} = \frac{\text{deaths in children with anthropometric deficit (age or sex group)}}{\text{total number of children with anthropometric deficit (age or sex group)}} \times 1000.$$

2. Risk ratio comparing absolute risks of mortality by age and sex categories (older versus younger children, girls versus boys).

Analysis was performed for each individual country. Significant heterogeneity was detected among the various surveys; hence a random effect model was used to take into consideration the effects of potential bias due to differences between the studies which were not due to chance.

We performed a random-effects meta-analysis to pool mortality risk estimates for each anthropometric deficit and compared by age and sex. Individual country and pooled effects are presented as risk ratios with 95% confidence intervals (CIs). We used the I^2 index to measure the degree of heterogeneity of effect estimates across cohorts.

2.5 | Ethical approval

All original data was subject to the relevant ethical approval process, and permissions were sought from all original Principal Investigators (PIs) while sourcing data. This analysis has further ethical approval from the London School of Hygiene and Tropical Medicine ethics committee (Reference 22958).

3 | RESULTS

3.1 | Study characteristics

Figure 1 shows the study flow diagram. After initial analysis we excluded Niger due to rarity of deaths (n= 4, two of which had anthropometric deficits recorded), resulting in insufficient power in this cohort following disaggregation.

Characteristics of the studies in the final analysis are presented in Table 1. The seven-country data set comprised 45,755 children, inclusive of 22,325 girls (48.8%) and 23,430 boys (51.2%). The age categories included 19,785 (43.2%) children aged 6–23 months and 25,970 (56.8%) children aged 24–59 months. A total of 166,755 follow-up contacts were recorded.

Overall, 1351 deaths were recorded. We present a breakdown of deaths by anthropometric deficit in Tables 2 and S2a. Of the total deaths, 1020 (75.6%) occurred in children with anthropometric deficits. Among the deaths, a total of 506 (49.6%) were for girls and 514 (50.4%) for boys. There were more deaths recorded within 6 months of an anthropometric deficit in children aged 6–23 months compared with those 24–59 months of age (n = 663 [65%] versus n = 357 [35%], respectively) (see Figure 1).

3.2 | Wasting measured by MUAC

Three country cohorts were included in the analysis for MUAC (Table 3 and Figure 2). We compared absolute risk of mortality in younger children with absolute risk of mortality in older children with MUAC < 125 mm. In two of the three cohorts, absolute risk of death was higher in younger children, with evidence of a difference between age groups in one cohort (DRC). In the remaining cohort (Senegal), the risk was higher for older children with borderline evidence of a difference between age groups. After meta-analysis, the combined effect size was RR 1.08 (95% CI 0.53–2.22, p = 0.826), suggesting no difference in absolute risk of death between older and younger children with MUAC < 125 mm. Our results were similar when the same analysis was performed for MUAC < 115 mm, with no observed difference in the risk of death between younger and older children (RR 0.77, 95% CI 0.47–1.26, p = 0.302; Table S4).

When assessing the risk of death for boys versus girls (reference group) in all age groups with a MUAC < 125 mm in a pooled meta-analysis, we did not observe differences in the risk of death in either the younger age group or the older age group (RR 0.93, 95% CI 0.46–1.86, p = 0.838 and RR 1.27, 95% CI 0.65–2.45, p = 0.484 respectively; Table S3a). One exception to this was Nepal, where younger boys had a lower relative risk of death than younger girls (RR 0.39, 95% CI 0.19–0.80, p = 0.008), but older boys with MUAC < 125 mm had a higher risk of mortality than older girls with MUAC < 125 mm (RR 2.97, 95% CI 1.02–8.60, p = 0.035).

3.3 | Wasting measured by WHZ

Six country cohorts were included in the analysis for WHZ < −2 as no deaths were recorded for this deficit in the older age group in the Philippines (Table 3 and Figure 2). In three of the cohorts, absolute risk of mortality was higher in younger children, with evidence of a difference in one cohort (Sudan). In the other three cohorts, absolute

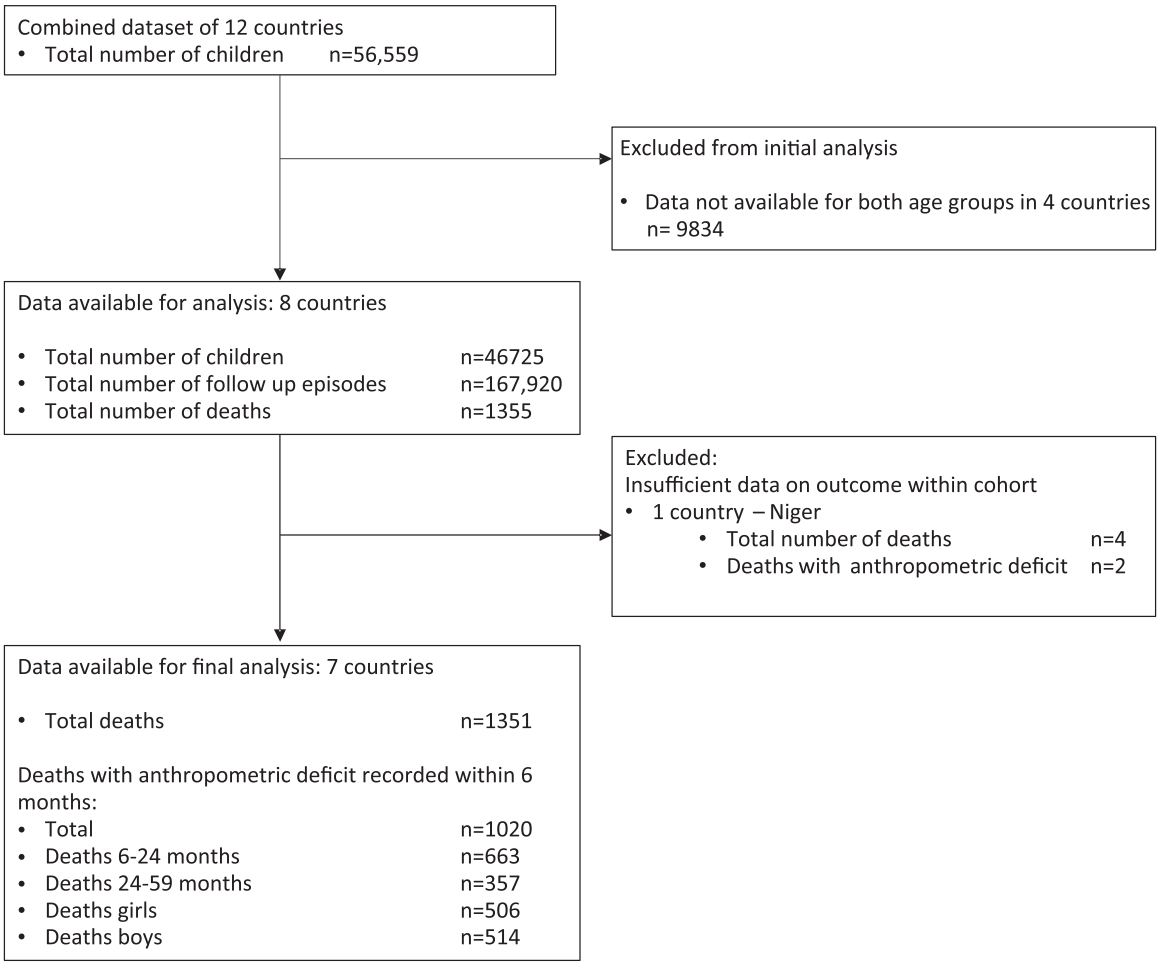


FIGURE 1 Study flow chart.

risk was higher in older children but not significantly so. The pooled meta-analysis found no significant difference in absolute mortality risk in younger compared with older children (RR 1.35, 95% CI 0.79–2.33, $p = 0.272$). Our results were similar when the meta-analysis was performed for WHZ < −3, with no observed difference in the absolute risk of death between younger and older children (RR 1.21, 95% CI 0.66–2.22, $p = 0.540$; Table S4).

Overall, after meta-analysis we did not observe a significant difference in absolute mortality risk between boys and girls (reference group) in either the younger or the older age group (RR 0.83, 95% CI 0.55–1.26, $p = 0.388$ and RR 0.84, 95% CI 0.52–1.36, $p = 0.478$ respectively). The exceptions were in Nepal and Sudan, where younger boys with WHZ < −2 had a lower absolute risk of death than younger girls with the same anthropometric deficit (RR 0.36; CI 0.18–0.75 $p = 0.004$, and RR 0.44; 95% CI 0.21–0.90, $p = 0.021$ respectively).

3.4 | Underweight

All seven country cohorts were included in our analysis of WAZ < −2 (Table 3 and Figure 2). Our results showed consistently that younger underweight children have a higher absolute risk of death within 6 months of measurements than older children in all cohorts, significantly so in Nepal and Sudan. After meta-analysis, our combined effect size was RR 2.57, (95% CI 1.65–4.00, $p < 0.001$). Results from the analysis are presented in Table 3 and Figure 2). Our results were similar when meta-analysis was performed for WAZ < −3, whereby younger children had a higher absolute risk of death when compared with older children (RR 2.05, 95% CI 1.13–3.73, $p = 0.018$; Table S4).

For sex, the pooled meta-analysis results for underweight children showed no significant difference in the absolute risk of death between girls and boys in younger and older age groups (RR 0.82, 95% CI 0.61–1.09, $p = 0.176$ and RR 1.05 95% CI 0.82–1.33, $p = 0.708$, respectively). However, we did observe a lower risk of death for younger boys compared with younger girls in Nepal (WAZ, RR 0.46, 95% CI 0.27–0.79, $p = 0.004$).

3.5 | Stunting

Seven country cohorts were included in our analysis of HAZ < −2 (Table 3 and Figure 2). Our results showed consistently that stunted

TABLE 1 Study characteristics table

Country	Study	Recruitment years	Study intervention	Children aged 6–59 months	No follow-up episodes	Duration of anthropometric follow-up in months Median (Range)	Loss to follow-up (%)	Total deaths (with or without anthropometric deficit)	Deaths (girls) *N* (%)	Deaths (boys) *N* (%)	Deaths 6–23 m age group *N* (%)	Deaths 24–59 m age group *N* (%)
DRC	Van Den Broeck (1993)	1989–1993	Longitudinal health and nutrition monitoring	4584	17,918	11 [0–10]	No info	196	91 (46.4)	105 (53.6)	122 (62.2)	74 (38.8)
Guinea-Bissau	Mølbak (1992)	1987–1990	Child mortality audit	985	4,385	11 [0–37]	No info	118	66 (55.9)	52 (44.1)	86 (72.9)	32 (27.1)
Indonesia	Katz (1989)	1977	Longitudinal nutrition monitoring	3806	17,367	15 [0–18]	7.8%	214	104 (48.6)	110 (51.4)	121 (56.5)	93 (43.5)
Nepal	West (1991)	1989	Vitamin A RCT	5883	25,159	16 [0–25]	6%	128	70 (54.7)	58(45.3)	73 (57.0)	55 (43.0%)
Philippines	Adair (1993)	1982–1983	Longitudinal Health and nutrition survey	2823	25,031	18 [0–19]	11.9%	233	99 (42.5)	134 (57.5)	233 (100)	0 (0)
Senegal	Garenne (1987)	1983	Longitudinal nutrition survey	5142	12,615	11 [0–19]	12.2%	327	166 (50.8)	161 (49.2)	196 (59.9)	131 (40.1)
Sudan	Fawzi (1997)	1988	Longitudinal nutrition survey/ Vitamin A RCT	22532	64,280	12 [0–19]	16%	135	82 (60.7)	53 (39.3)	75 (55.6)	60 (44.4)
Total				45,755	166,755			1,351	678 (50.2)	673 (49.8)	906 (67.1)	445 (32.9)

TABLE 2 Child mortality (deaths within 6 months) by anthropometric deficit according to geographic location, age and sex – moderate

		6–23 months				24–59 months			
		Male		Female		Male		Female	
Country	Anthropometric indicator	*n* died/*n* with deficit	%	*n* died/*n* with deficit	%	*n* died/*n* with deficit	%	*n* died/*n* with deficit	%
DRC	MUAC < 125 mm	40/1341	3.0	33/1589	2.1	13/1162	1.1	16/1127	1.4
	WHZ < −2	10/251	4.0	5/169	3.0	4/184	2.2	7/116	6.0
	WAZ < −2	34/1057	3.2	19/767	2.5	23/2055	1.1	20/1735	1.2
	HAZ < −2	47/1870	2.5	24/1487	1,6	29/4504	0.6	30/3734	0.8
Guinea-Bissau	WHZ < −2	5/100	5.0	4/60	6.7	3/39	7.7	2/28	7.1
	WAZ < −2	13/243	5.4	15/211	7.1	4/108	3.7	7/196	3.6
	HAZ < −2	21/407	5.2	26/396	6.6	9/435	2.1	11/387	2.8
Indonesia	WHZ < −2	10/249	4.0	5/160	3.1	7/221	3.2	7/120	5.8
	WAZ < −2	37/859	4.3	25/616	4.1	26/2138	1.2	29/1935	1.5
	HAZ < −2	46/1461	3.2	31/1124	2.8	34/4124	0.8	46/3697	1.2
Nepal	MUAC < 125 mm	9/951	1.0	38/1566	2.4	10/325	3.1	5/482	1.0
	WHZ < −2	10/929	1.1	26/879	3.0	9/665	1.4	5/462	1.1
	WAZ < −2	19/2334	0.8	39/2202	1.8	25/4268	0.6	16/4207	0.4
	HAZ < −2	20/2812	0.7	33/2605	1.3	28/6364	0.4	23/6043	0.4
Philippines	WHZ < −2	55/1242	4.4	32/897	3.6	0/61	0.0	0/45	0.0
	WAZ < −2	87/3779	2.3	72/3072	2.3	0/379	0.0	0/374	0.0
	HAZ < −2	89/5894	1.5	74/4454	1.7	0/686	0.0	0/596	0.0
Senegal	MUAC < 125 mm	29/377	7.7	26/417	6.2	16/141	11.4	14/143	9.8
	WHZ < −2	47/665	7.1	35/533	6.6	28/394	7.1	22/438	5.0
	WAZ < −2	63/1134	5.6	57/1029	5.5	42/936	4.5	38/905	4.2
	HAZ < −2	32/562	5.7	25/378	6.6	37/1122	3.3	38/961	4.0
Sudan	WHZ < −2	12/827	1.5	19/576	3.3	8/2489	0.3	10/1767	0.6
	WAZ < −2	15/2013	0.8	30/1625	1.9	20/10,023	0.2	19/10,169	0.2
	HAZ < −2	16/2838	0.6	29/2320	1.3	19/13,849	0.1	19/13,493	0.1
Total	MUAC < 125 mm	78/2689	2.9	97/3597	2.7	39/1642	2.4	35/1767	2.0
	WHZ < −2	149/4296	3.5	126/3300	3.8	59/4089	1.4	53/3002	1.8
	WAZ < −2	268/11,486	2.3	257/9585	2.7	142/20,199	0.7	129/19,775	0.7
	HAZ < −2	271/15,925	1.7	242/12,830	1.9	158/31,473	0.5	167/29,233	0.6

younger children had a higher absolute risk of death within 6 months of measurements than older children, significantly so in Nepal and Sudan. After meta-analysis, the combined effect size for HAZ was RR 2.83 (95% CI 2.09–3.82, $p < 0.001$). Similarly, when meta-analysis was performed for HAZ < −3, younger children had a significantly higher absolute risk of death when compared with older children (RR 2.74, 95% CI 1.74–4.32, $p < 0.001$; Table S4).

For sex, the pooled meta-analysis showed no significant difference in the risk of death between stunted girls and boys in both younger and older age groups (RR 0.88, 95% CI 0.67–1.14, $p = 0.318$ and RR 0.82, 95% CI 0.66–1.02, $p = 0.070$, respectively). However, we did observe a lower risk of death for younger boys compared with younger girls in Nepal (HAZ RR 0.56, 95% CI 0.32–0.98, $p = 0.038$) and for younger boys with HAZ < −2 compared with younger girls with HAZ < −2 in Sudan (RR 0.51, 95% CI 0.25–0.83, $p = 0.008$).

Using the I^2 index from the meta-analysis results (Figures 2 and 3), we found strong evidence of heterogeneity, which was not explained by age and sex. This suggests pooled estimates should be interpreted with caution as true differences in effect are likely due to influences not measured or adjusted for in this analysis.

TABLE 3 Absolute risk (AR) of mortality per 1000 children within 6 months of a contact and associated anthropometric deficits by age and relative risk (RR) of mortality in younger compared with older children

	MUAC < 125 mm														
	Both sexes					Girls					Boys				
	AR 6–23 m	AR 24–59 m	RR 6–23 m versus 24-59 m (ref)	95% CI	*p*	AR 6–23 m	AR 24–59 m	RR 6–23 m versus 24–59 m (ref)	95% CI	*p*	AR 6–23 m	AR 24–59 m	RR 6–23 m versus 24–59 m (ref)	95% CI	*p*
DRC	24.91	12.67	1.96	1.28–3.01	0.002	20.76	14.19	1.46	0.81–2.64	0.205	29.82	11.18	2.66	1.43–4.96	0.001
Nepal	18.67	18.58	1	0.56–1.79	0.988	24.26	10.37	2.33	0.93–5.91	0.063	9.46	30.76	0.3	0.13–0.75	0.006
Senegal	69.26	105.63	0.65	0.43–1.00	0.051	62.35	97.9	0.63	0.34–1.19	0.154	76.92	113.47	0.67	0.38–1.21	0.189
Pooled estimate			**1.08**	**0.53–2.22**	**0.826**			**1.28**	**0.59–2.77**	**0.530**			**0.71**	**0.30–1.71**	**0.447**
	WHZ < −2														
	Both sexes					**Girls**					**Boys**				
	AR 6–23 m	**AR 24–59 m**	**RR 6–23 m versus 24-59 m (ref)**	**95% CI**	***p***	**AR 6–23 m**	**AR 24–59 m**	**RR 6–23 m versus 24–59 m (ref)**	**95% CI**	***p***	**AR 6–23 m**	**AR 24–59 m**	**RR 6–23 m versus 24–59 m (ref)**	**95% CI**	***p***
DRC	35.71	36.66	0.97	0.45–2.09	0.946	29.58	60.34	0.49	0.16–1.51	0.204	39.84	21.73	1.83	0.58–5.75	0.291
Guinea Bissau	56.25	74.62	0.75	0.26–2.17	0.600	66.66	71.42	0.93	0.18–4.80	0.934	50	76.92	0.65	0.16–2.59	0.540
Indonesia	36.67	41.05	0.89	0.44–1.82	0.757	31.25	58.33	0.53	0.17–1.65	0.268	40.16	31.67	1.26	0.49–3.27	0.623
Nepal	19.91	12.42	1.6	0.87–2.96	0.127	29.57	10.82	2.73	1.06–7.07	0.030	10.76	13.53	0.79	0.32–1.95	0.615
Philippines	40.67	0				35.67	0				44.28	0			
Senegal	68.44	60.09	1.13	0.81–1.60	0.453	65.66	50.22	1.3	0.78–2.19	0.309	70.67	71.06	0.99	0.63–1.56	0.981
Sudan	22.09	4.22	5.23	2.93–9.31	<0.001	32.98	5.65	5.83	2.73–12.46	<0.001	14.51	3.21	4.52	1.85–11.01	<0.001
Pooled estimate			**1.35**	**0.79–2.33**	**0.272**			**1.32**	**0.66–2.65**	**0.430**			**1.32**	**0.83; 2.12**	**0.245**
	WAZ < −2														
	Both sexes					**Girls**					**Boys**				
	AR 6–23 m	**AR 24–59 m**	**RR 6–23 m versus 24-59 m (ref)**	**95% CI**	***p***	**AR 6–23 m**	**AR 24–59 m**	**RR 6–23 m versus 24–59 m (ref)**	**95% CI**	***p***	**AR 6–23 m**	**AR 24–59 m**	**RR 6–23 m versus 24–59 m (ref)**	**95% CI**	***p***
DRC	29.05	11.34	2.56	1.72–3.81	<0.001	24.77	11.52	2.15	1.15–4.00	0.014	32.16	11.19	2.87	1.70–4.85	<0.001

TABLE 3 (Continued)

	WAZ < −2														
	Both sexes					Girls					Boys				
	AR 6–23 m	AR 24–59 m	RR 6–23 m versus 24-59 m (ref)	95% CI	*p*	AR 6–23 m	AR 24–59 m	RR 6–23 m versus 24–59 m (ref)	95% CI	*p*	AR 6–23 m	AR 24–59 m	RR 6–23 m versus 24–59 m (ref)	95% CI	*p*
Guinea Bissau	61.67	36.18	1.7	0.86–3.37	0.119	71.09	35.71	1.99	0.83–4.78	0.115	53.49	37.03	1.44	0.48–4.33	0.507
Indonesia	42.03	13.5	3.11	2.18–4.45	<0.001	40.58	14.98	2.7	1.60–4.59	<0.001	43.07	12.16	3.54	2.16–5.81	<0.001
Nepal	12.78	4.83	2.64	1.77–3.93	<0.001	17.71	3.8	4.66	2.61–8.31	<0.001	8.14	5.85	1.39	0.77–2.52	0.276
Philippines	23.2	0				23.43	0				23.02	0			
Senegal	55.47	43.45	1.27	0.97–1.68	0.082	55.39	41.98	1.31	0.88–1.97	0.174	55.55	44.87	1.23	0.85–1.81	0.270
Sudan	12.36	1.93	6.4	4.18–9.82	<0.001	18.46	1.86	9.92	5.58–17.51	<0.001	7.45	1.99	3.74	1.92–7.28	<0.001
Pooled estimate			**2.57**	**1.65–4.00**	**<0.001**			**2.97**	**1.65–5.36**	**<0.001**			**2.13**	**1.40–3.24**	**<0.001**
	HAZ < −2														
	Both sexes					Girls					Boys				
	AR 6–23 m	AR 24–59 m	RR 6–23 m versus 24-59 m (ref)	95% CI	*p*	AR 6–23 m	AR 24–59 m	RR 6–23 m versus 24-59 m (ref)	95% CI	*p*	AR 6–23 m	AR 24–59 m	RR 6–23 m versus 24-59 m (ref)	95% CI	*p*
DRC	21.14	7.16	2.95	2.09–4.16	<0.001	16.13	8.03	2	1.18–3.42	0.009	25.13	6.43	3.9	2.47–6.18	<0.001
Guinea Bissau	58.53	24.33	2.4	1.44–4.02	0.001	65.65	28.42	2.3	1.16–4.61	0.014	51.59	20.68	2.49	1.16–5.38	0.016
Indonesia	29.78	10.22	2.91	2.14–3.97	<0.001	27.58	12.44	2.21	1.41–3.48	<0.001	31.48	8.24	3.82	2.46–5.93	<0.001
Nepal	9.78	4.11	2.37	1.62–3.49	<0.001	12.66	3.8	3.33	1.96–5.66	<0.001	7.11	4.39	1.61	0.91–2.86	0.097
Philippines	15.75	0				16.61	0				15.1	0			
Senegal	60.63	36	1.68	1.20–2.36	0.002	66.13	39.54	1.67	1.02–2.73	0.039	56.93	32.97	1.72	1.09–2.74	0.019
Sudan	8.72	1.38	6.31	4.08–9.66	<0.001	12.5	1.4	8.92	4.99–15.80	<0.001	5.63	1.37	4.1	2.12–7.98	<0.001
Pooled estimate			**2.83**	**2.09; 3.82**	**<0.001**			**2.82**	**1.87–4.24**	**<0.001**			**2.75**	**1.97–3.85**	**<0.001**

Note: AR represents the absolute risk of death in the exposed group per 1000 children; RR represents the relative risk of death in young (6–23 months) versus older (24–59 months; reference group) age group; pooled estimate represents the weighted pooled estimates from the meta-analysis.

4 | DISCUSSION

This analysis aimed to evaluate mortality risk associated with anthropometric deficits in children aged 6–59 months by age and sex. Our findings suggest that in wasted children, as measured by MUAC or WHZ, there is no significant difference in absolute mortality risk between older and younger age groups. For underweight and stunting, the absolute mortality risk is higher in younger compared with older children. Our findings were similar when the analysis was repeated for severe deficits. In terms of sex, our results suggest that girls and boys have a similar absolute mortality risk associated with each of the four anthropometric deficits, regardless of age.

Wasting is known to be associated with high mortality (McDonald et al., 2013) and is more common in younger than older children (Karlsson et al., 2022; Mertens et al., 2020). Here, we similarly found higher numbers of wasted children under 2 years old and a higher proportion of deaths in that age group compared with children older than 2 years. However, there were no differences in mortality risk between age groups. This suggests that, while a higher proportion of younger children may be targeted by wasting treatment programmes, older children with anthropometric deficits are similarly vulnerable to mortality and should not be neglected.

Some previous studies have suggested that the risk of death from wasting (as measured by WHZ) might be higher in older children. A multi-country pooled analysis (DRC, Senegal and Nepal) of

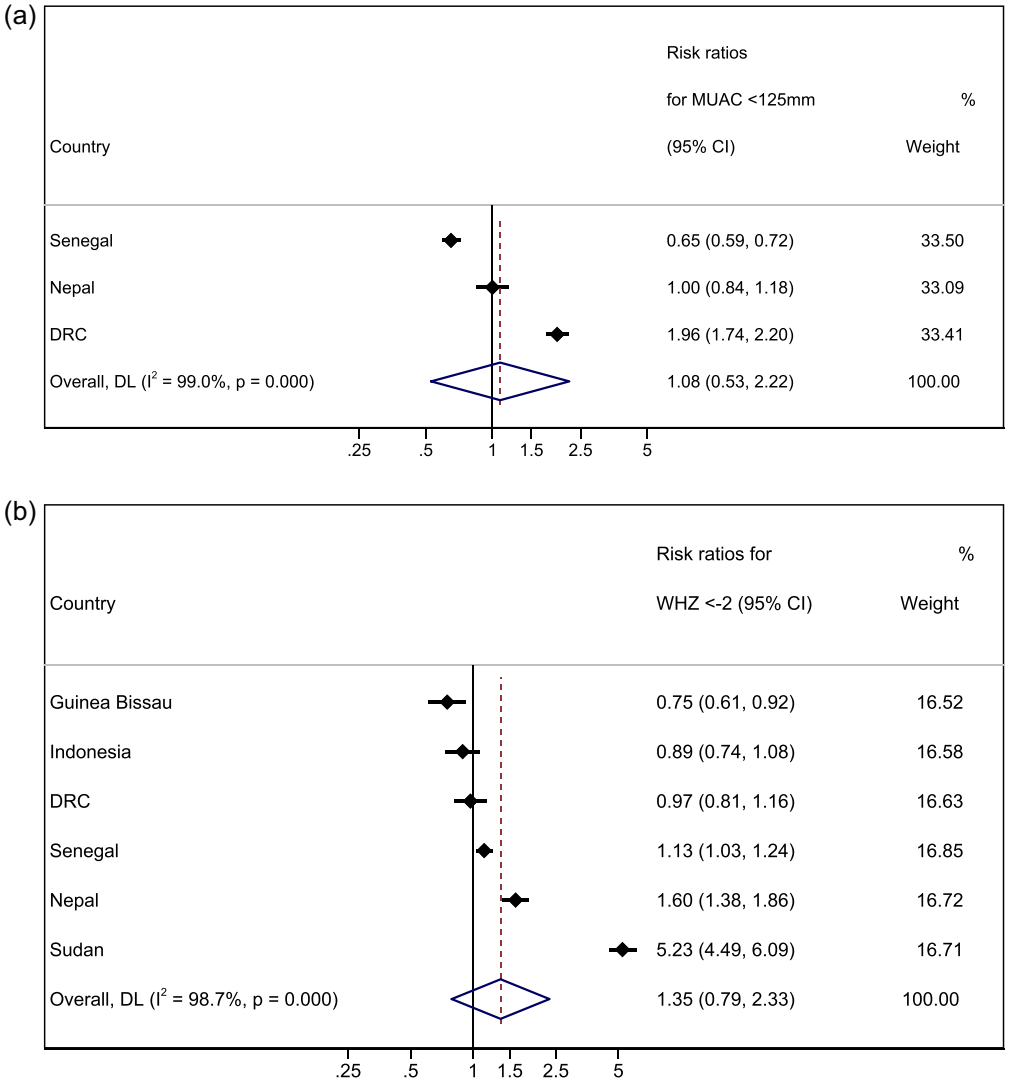


FIGURE 2 Forest plots for pooled risk ratios of mortality in children 6–23 months versus 24–59 months for MUAC < 125 mm WHZ < −2, WAZ < −2 and HAZ < −2. (a) Mortality risk ratio between younger and older (reference group) age group for MUAC < 125 mm. (b) Mortality risk ratio between younger and older (reference group) age group for WHZ < −2. (c) Mortality risk ratio between younger and older (reference group) age group for WAZ < −2. (d) Mortality risk ratio between younger and older (reference group) age group for HAZ < −2. Estimates on the left part of the axis suggest a higher mortality in older children, and estimates on the right part of the axis suggest a higher mortality among younger children.

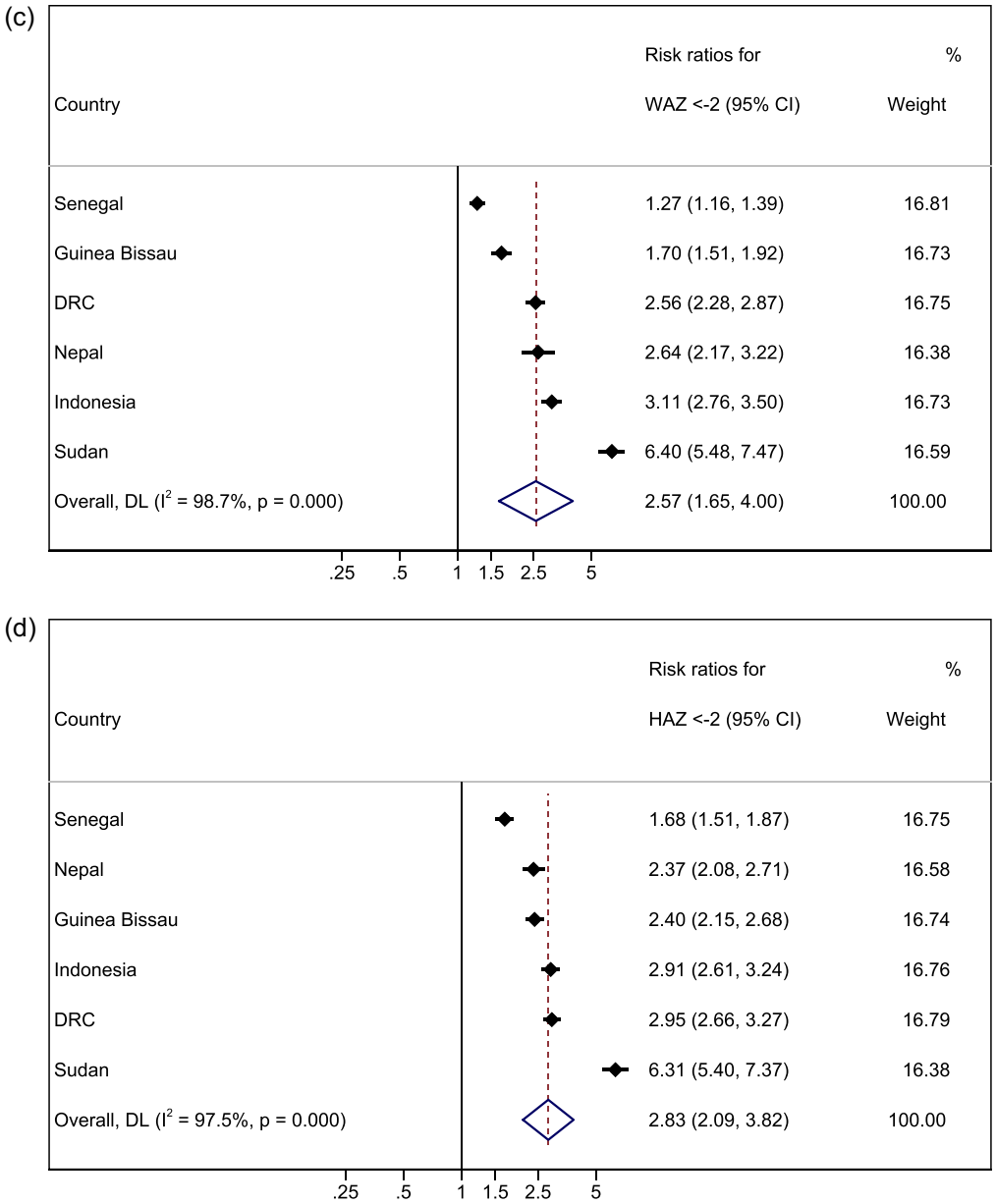


FIGURE 2 (Continued)

children aged 6–59 months found hazard ratios for children with wasting (WHZ) to be higher in older children (≥2 years), though not significantly so [10]. This was also reported in a study from Indonesia, whereby moderate to severe wasting was associated with increased mortality risk, more so in older children than in younger children [20]. However, the sample sizes in this study were very small and statistical testing was not reported. Future research looking at z-scores and age as continuous rather than binary variables might help to clarify the association between age and mortality risk associated with wasting.

Overall our results showed a higher proportion of deaths in younger children compared with older children, a finding consistent with previous research (Pelletier et al., 1994). We found higher absolute mortality risk for younger children who are underweight or stunted. This suggests that, in resource-limited settings, programmes which use these measures to target nutrition interventions may be justified in prioritising younger children. WAZ is increasingly recognised as a composite indicator of multiple anthropometric deficits and increased mortality risk (McDonald et al., 2013; Myatt et al., 2018). Evidence shows that the peak incidence of both wasting and stunting is between 0–3 months (Mertens et al., 2020), so early interventions to prevent the accumulation of anthropometric deficits (Thurstans et al., 2021) are essential, especially with the greater risk of mortality from being stunted or underweight in younger children. Evidence around the importance of meeting nutrition requirements in the first 1000 days, and the presence of wasting and stunting at birth, supports extension of nutrition programming to include the preconception and prenatal periods (Victora et al., 2021).

In relation to sex, while studies have shown that boys are more likely to be wasted, stunted and underweight than girls (Khara et al., 2018; Myatt et al., 2018; Myatt et al., 2019; Odei Obeng-Amoako et al., 2020; Thurstans et al., 2020). Our findings suggest that mortality risk is similar between the sexes. Studies of diarrhoeal disease in children aged between 12 and 59 months have found similar results, indicating that despite slightly higher incidence rates for boys, cause-specific mortality is higher amongst girls, perhaps due to health-seeking behaviours such as later presentation to professional health settings or later provision of ORS for girls (World Health Organisation [WHO], 2007). Despite there being no difference in the relative risk of mortality between boys and girls, the greater number

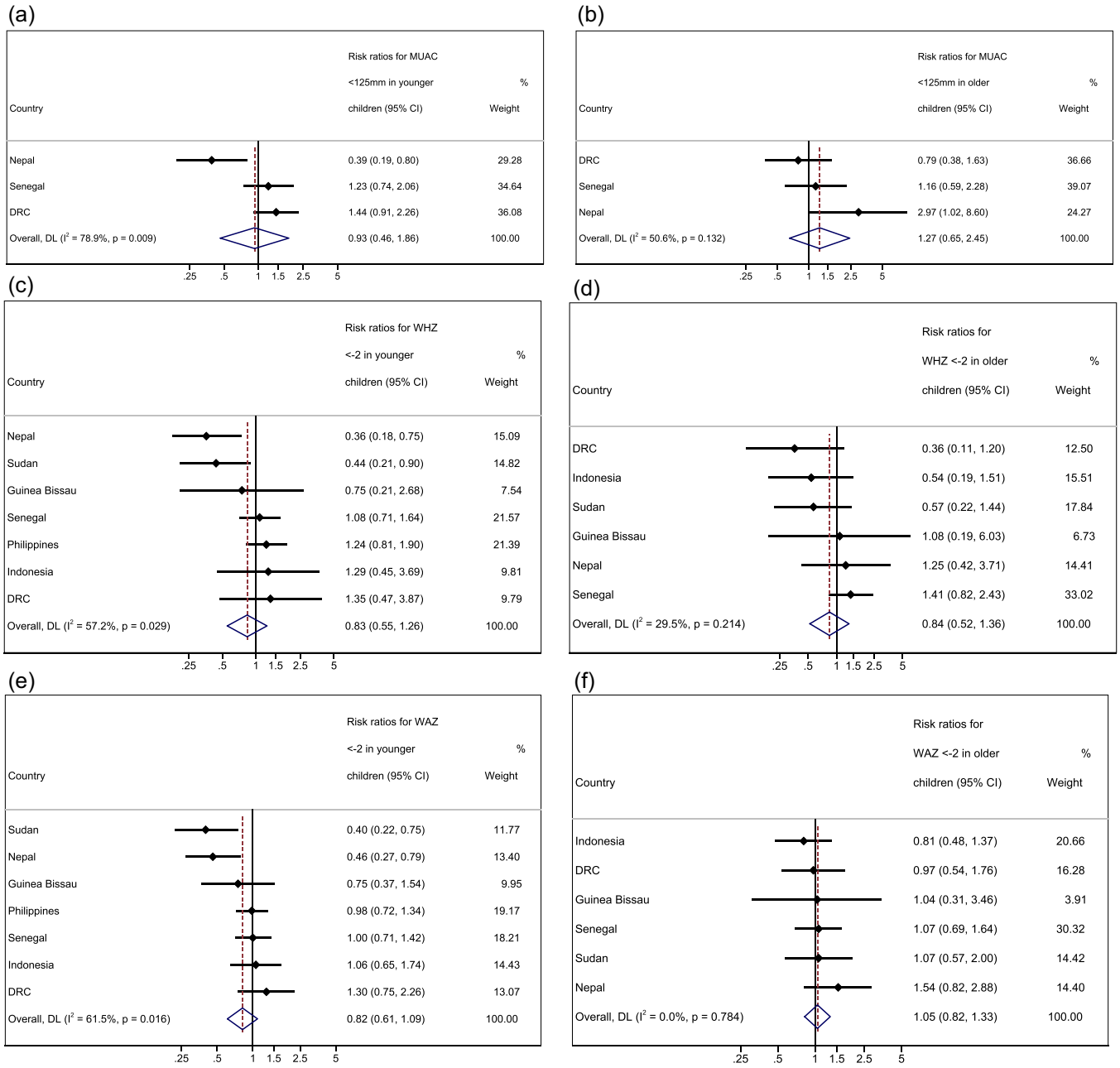


FIGURE 3 Forest plots for pooled risk ratios of absolute risk in children 6–23 months versus 24–59 months by sex for MUAC, WHZ, WAZ and HAZ. (a) Mortality risk ratio between younger boys and girls (reference group) for MUAC < 125 mm. (b) Mortality risk ratio between older boys and girls (reference group) for MUAC < 125 mm. (c) Mortality risk ratio between younger boys and girls (reference group) for WHZ < −2. (d) Mortality risk ratio between older boys and girls (reference group) for WHZ < −2. (e) Mortality risk ratio between younger boys and girls (reference group) for WAZ < −2. (f) Mortality risk ratio between older boys and girls (reference group) for WAZ < −2. (g) Mortality risk ratio between younger boys and girls (reference group) for HAZ < −2. (h) Mortality risk ratio between older boys and girls (reference group) for HAZ < −2. Estimates on the left part of the axis suggest a higher mortality in girls, and estimates on the right part of the axis suggest a higher mortality among boys.

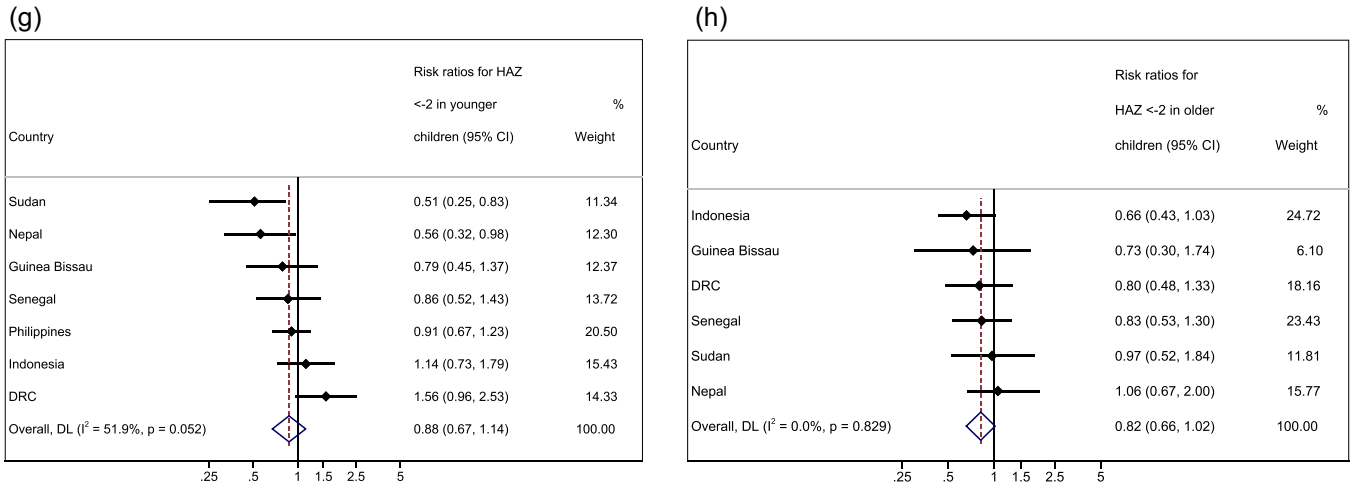


FIGURE 3 (Continued)

of boys affected by wasting, stunting and underweight, suggests that greater numbers of boys will die of undernutrition than girls in absolute terms. In our study, we did observe a difference in Nepal, whereby girls had a significantly higher risk of death than boys for each of the anthropometric deficits. Previous research has suggested that sex differences in undernutrition might be age and context-specific (Costa et al., 2021; Thurstans et al., 2020) and influenced by environmental and social factors. For example, the disadvantage in linear growth for boys is most evident in the first years, but by the age of 4 years, the sex gap has mostly disappeared, and in some countries, the gap has been reversed (Costa et al., 2021). Programme data should be analysed by both age and sex to understand geographic, environmental, and social context-specific differences in growth-failure-associated mortality risk.

4.1 | Strengths and limitations

One of the key strengths of this study is the unique nature of the data. We analysed community cohorts with information recorded on anthropometric indices and mortality and were able to pool cohort data from multiple countries. The large sample sizes provided by this approach enabled us to examine mortality risk by age and sex, as mortality is a rare outcome in individual cohorts. However, we do recognise some limitations.

The first is the absence of data for infants under 6 months, likely resulting in an underestimation of the impacts of anthropometric deficits in children under two. There is increased recognition of the importance of including infants under 6 months within nutrition programmes and surveys, alongside evidence that undernutrition often occurs before 6 months and is associated with high mortality (Mwangome et al., 2017; Victora et al., 2021). Though this is a clear limitation, our findings contribute to the evidence base for increased vulnerability before age two.

Second, there is potential for the introduction of bias from loss to follow-up in the original studies (see Table 1), leading to survivor bias if deaths were higher amongst those lost to follow-up. It was not possible to quantify this from the original studies (Khara et al., 2021). The age of the cohorts might also be a factor to consider. Much has changed since the data was collected on these cohorts, especially with respect to the availability of programmes targeting these age groups, which limits the generalisability of these results.

A further limitation is that we did not have data on potential confounders such as, socioeconomic status, health indicators such as diarrhoea, HIV, respiratory illnesses, breastfeeding status, complementary feeding, and care practices, or seasonal indicators. It was therefore not possible to explain the heterogeneity between studies or elucidate on contextual differences that might directly or indirectly influence the relationships between anthropometric deficits and mortality risk. Similarly, two of the datasets (Sudan and Nepal) were from RCTs of vitamin A supplementation and we could not adjust for the treatment group in the analysis of these datasets. In the Sudan trial, vitamin A supplementation did not have an effect on child growth or mortality (Fawzi et al., 1997; Herrera et al., 1992); therefore, it is unlikely that this variable would influence the association between anthropometric deficits and mortality in a substantial way. However, in the Nepal trial (West et al., 1991), vitamin A significantly reduced the risk of mortality; thus, the exclusion of this variable from our analysis of this data set may have led to relative risk estimates that underestimate the risk between anthropometric deficits and mortality. Some previous analysis of these data highlighted how possible access to nutrition rehabilitation and broad-spectrum antimicrobial treatment in Niger might have protected against risk of death and might in turn explain the low number of deaths observed in this cohort (Khara et al., 2021). Further research which controls for study effects and allows for consideration of other potential explanatory factors including multiple anthropometric deficits alongside age and sex would be useful to identify any differences in results. Finally, data was only available for MUAC from 3 countries. This means a smaller sample size was available

for these analyses with potentially less power to detect differences and reduced generalisability of results.

5 | CONCLUSION

Our findings demonstrate that for wasted children there is no difference in mortality risk between younger and older children, This is also true for severely wasted children. This supports the continued inclusion of all high-risk children under five in wasting treatment programmes. The risk of mortality associated with underweight, and stunting is higher among younger children. Again, this is also true for severe stunting and underweight. This suggests that nutrition prevention programmes might be justified in focusing limited resources on younger children. There does not appear to be a difference in mortality risk between girls and boys for any anthropometric deficit, suggesting no need to adjust current approaches according to sex.

AUTHOR CONTRIBUTIONS

Susan Thurstans, Martha Mwangome, André Briend, Tanya Khara, Stephanie V. Wrottesley and Bridget Fenn designed the study. Data was contributed by Michel Garenne, Christine M. McDonald, Robert E. Black, Keith P. West, and Sunita Taneja. Analysis and interpretation was conducted by Stephanie V. Wrottesley, Bridget Fenn, and Susan Thurstans, discussed with and reviewed by all authors. Susan Thurstans wrote the paper. All authors have read and approved the final manuscript.

ACKNOWLEDGMENTS

This paper is made possible by the generous support of the American people through the United States Agency for International Development (USAID), and by funding from Irish Aid (grant number (HQPU/2021/ENN). The contents are entirely the responsibility of its authors and do not necessarily reflect the views of USAID or the United States Government or represent or reflect Irish Aid policy.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study. Data from previously published studies was sourced directly from original investigators as listed in the manuscript for this specific secondary analysis.

ORCID

Susan Thurstans http://orcid.org/0000-0002-7102-446X
James A. Berkley http://orcid.org/0000-0002-1236-849X
Martha Mwangome http://orcid.org/0000-0003-4806-1307
Sunita Taneja http://orcid.org/0000-0003-3338-9799
Marko Kerac http://orcid.org/0000-0002-3745-7317

REFERENCES

Adair, L., Popkin, B. M., VanDerslice, J., Akin, J., Guilkey, D., Black, R., Briscoe, J., & Flieger, W. (1993). Growth dynamics during the first two years of life: A prospective study in the Philippines. *European Journal of Clinical Nutrition*, *47*, 42–51.

Arifeen, S., Black, R. E., Antelman, G., Baqui, A., Caulfield, L., & Becker, S. (2001). Exclusive breastfeeding reduces acute respiratory infection and diarrhea deaths among infants in Dhaka slums. *Pediatrics*, *108*, E67.

Blössner, M., Siyam, A., Borghi, E., Onyango, A., & de Onis, M. (2009). *WHO AnthroPlus for personal computers manual: software for assessing growth of the world's children and adolescents*. World Health Organization.

Van Den Broeck, J., Eeckels, R., & Vuylsteke, J. (1993). Influence of nutritional status on child mortality in rural Zaire. *Lancet*, *341*, 1491–1495.

Costa, J. C., Blumenberg, C., & Victora, C. (2021). Growth patterns by sex and age among under-5 children from 87 low-income and middle-income countries. *BMJ Global Health*, *60*, 6.

Fawzi, W. W., Herrera, M. G., Spiegelman, D. L., el Amin, A., Nestel, P., & Mohamed, K. A. (1997). A prospective study of malnutrition in relation to child mortality in the Sudan. *American Journal of Clinical Nutrition*, *65*, 1062–1069.

Garenne, M., Maire, B., Fontaine, O., Dieng, K., & Briend, A. (1987). Risques de décès associés à différents états nutritionnels chez l'enfant d'âge préscolaire: Étude réalisée à Niakhar (Sénégal), 1983–1986. *Les Etudes du CEPED*, 17.

Garenne, M., Myatt, M., Khara, T., Dolan, C., & Briend, A. (2019). Concurrent wasting and stunting among under-five children in Niakhar, Senegal. *Maternal & child nutrition*, *15*, e12736.

Global Nutrition Report. 2018. 'Shining a light to spur action on nutrition'.

Herrera, M. G., Nestel, P., Weld, L., El Amin, A., Mohamed, K. A., & Fawzi, W. W. (1992). Vitamin A supplementation and child survival. *The Lancet*, *340*, 267–71.

Karlsson, O., Kim, R., Guerrero, S., & Subramaninan, S. V. 2022. 'Child wasting before and after age two years: A cross-sectional study of 94 countries'. *EClinicalMedicine*, *46*, 101353.

Katz, J., West, K. P., Tarwotjo, I., & Sommer, A. (1989). The importance of age in evaluating anthropometric indices for predicting mortality. *Americal Journal of Epidemiology*, *130*, 1219–1226.

Khara, T., Mwangome, M., Ngari, M., & Dolan, C. (2018). Children concurrently wasted and stunted: A meta-analysis of prevalence data of children 6-59 months from 84 countries. *Maternal & Child Nutrition*, *14*, e12516.

Khara, T., Myatt, M., Sadler, K., Bahwere James, P., Berkely, A., Black, R., Erin, M., Garenne, B., Sheila Isanaka, M., Lelijveld, N., McDonald, C. M., Mertens, A., Mwangome, M., O'Brien, K. S., Stobough, H., Taneja, S., West, K., & Briend, A. (2021). Anthropometric criteria for best identifying children at high risk of mortality: A pooled analysis of 12 cohorts. *In publication*.

Martines, J., Underwood, B., Arthur, P., Bahl, R., Bhan, M., Kirkwood, B. R., Moulton, L. H., Penny, M., Ram, M., Kholhede, C. L., Propper, L., Arthur, G. P., Morris, S., Amenga-Etego, S., Zandoh, C., Boahen, O., Bhandari, N., Wahed, M., Lanata, C. F., … Rivera, K. B. (1998). Randomised trial to assess benefits and safety of vitamin A supplementation linked to immunisation in early infancy. *Lancet*, *352*, 1257–1263.

Martorell, R. (2017). Improved nutrition in the first 1000 days and adult human capital and health. *American Journal of Human Biology*, *29*, 29.

McDonald, C. M., Olofin, I., Flaxman, S., Fawzi, W. W., Spiegelman, D., Caulfield, L. E., Black, R. E., Ezzati, M., & Danaei, G. (2013). The effect of multiple anthropometric deficits on child mortality: Meta-analysis of individual data in 10 prospective studies from developing countries. *American Journal of Clinical Nutrition*, *97*, 896–901.

Mertens, A., Benjamin-Chung, J., Colford, J. M., Coyle, J., van der Laan, M. J., Hubbard, A. E., Dayal, S., Malenica, I., Hejazi, N., Sofrygin, O., Cai, W.,

Li, H., Nguyen, A., Pokpongkiat, N., Djajadi, S., Seth, A., Chung, E. O., Jilek, W., Subramoney, V., … Arnold, B. F. (2020). Causes and consequences of child growth failure in low- and middle-income countries'.

Mwangome, M., Ngari, M., Fegan, G., Mturi, N., Shebe, M., Bauni, E., & Berkley, J. A. (2017). Diagnostic criteria for severe acute malnutrition among infants aged under 6 mo. *American Journal of Clinical Nutrition*, *105*, 1415–23.

Myatt, M., Khara, T., Dolan, C., Garenne, M., & Briend, A. (2019). Improving screening for malnourished children at high risk of death: a study of children aged 6-59 months in rural Senegal. *Public Health Nutrition*, *22*, 862–71.

Myatt, M., Khara, T., Schoenbuchner, S., Pietzsch, S., Dolan, C., Lelijveld, N., & Briend, A. (2018). Children who are both wasted and stunted are also underweight and have a high risk of death: A descriptive epidemiology of multiple anthropometric deficits using data from 51 countries. *Archives of Public Health*, *76*, 28.

Mølbak, K., Aaby, P., Ingholt, L., Højlyng, N., Gottschau, A., Andersen, H., Brink, L., Gansted, U., Permin, A., & Vollmer, A. (1992). Persistent and acute diarrhoea as the leading causes of child mortality in urban Guinea Bissau. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, *86*, 216–220.

O'Brien, K. S., Amza, A., Kadri, B., Nassirou, B., Cotter, S. Y., Stoller, N. E., West, S. K., Bailey, R. L., Porco, T. C., Keenan, J. D., Lietman, T. M., & Oldenburg, C. E. (2020). Comparison of anthropometric indicators to predict mortality in a population-based prospective study of children under 5 years in Niger. *Public Health Nutrition*, *23*, 538–43.

Odei Obeng-Amoako, G. A., Myatt, M., Conkle, J., Muwaga, B. K., Aryeetey, R., Okwi, A. L., Okullo, I., Mupere, E., Wamani, H., Briend, A., Karamagi, C. A. S., & Kalyango, J. N. (2020). Concurrently wasted and stunted children 6-59 months in karamoja, Uganda: Prevalence and case detection. *Maternal and Child Nutrition*, *16*.

Olofin, I., McDonald, C. M., Ezzati, M., Flaxman, S., Black, R. E., Fawzi, W. W., Caulfield, L. E., Danaei, G., & Study Nutrition Impact Model. (2013). Associations of suboptimal growth with all-cause and cause-specific mortality in children under five years: A pooled analysis of ten prospective studies. *PLoS ONE*, *8*, e64636.

Pelletier, D., Low, J., Johnson, C., & Msukwa, L. (1994). Child anthropometry and mortality in Malawi: Testing for effect modification by age and length of follow-up and confounding by socioeconomic Factors1. *The Journal of Nutrition*, *124*, 2082S–2105SS.

Rice, A., Sacco, L., Hyder, A., & Black, R. E. (2000). Malnutrition as an underlying cause of childhood deaths associated with infectious diseases in developing countries. *Bulletin of the World Health Organization*, *78*, 1207–1221.

Schwinger, C., Golden, M. H., Grellety, E., Roberfroid, D., & Guesdon, B. (2019). Severe acute malnutrition and mortality in children in the community: Comparison of indicators in a multi-country pooled analysis. *PLoS ONE*, *14*, e0219745.

Thurstans, S., Opondo, C., Seal, A., Wells, J., Khara, T., Dolan, C., Briend, A., Myatt, M., Garenne, M., Sear, R., & Kerac, M. (2020). Boys are more likely to be undernourished than girls: A systematic review and meta-analysis of sex differences in undernutrition. *BMJ Global Health*, *5*, 5.

Thurstans, S., Opondo, C., Seal, A., Wells, J. C., Khara, T., Dolan, C., Briend, A., Myatt, M., Garenne, M., Mertens, A., Sear, R., & Kerac, M. (2022). Understanding sex differences in childhood undernutrition: A narrative review. *Nutrients*, *14*, 14.

Thurstans, S., Sessions, N., Dolan, C., Sadler, K., Cichon, B., Isanaka, S., Roberfroid, D., Stobaugh, H., Webb, P., & Khara, T. (2021). The relationship between wasting and stunting in young children: A systematic review. *Maternal & Child Nutrition*, *18*, e13246.

United Nations Children's Fund (UNICEF), World Health Organization, The World Bank Group. (2021). *Levels and trends in child malnutrition: Key findings of the 2021 edition of the joint child malnutrition estimates* (p. 2021). World Health Organization.

Vandenbroucke, J. P., vonElm, E., Altman, D. G., Gotzsche, P. C., Mulrow, C. D., Pocock, S. J., Poole, C., Schlesselman, J. J., & Egger, M. (2007). Strengthening the reporting of observational studies in epidemiology (STROBE): Explanation and elaboration. *PLoS Medicine*, *18*, 4–835.

Victora, A., Parul Christian, C. G., Paulo Vidaletti, L., Gatica-Domínguez, G., Menon, P., & Black, R. E. (2021). Revisiting maternal and child undernutrition in low-income and middle-income countries: Variable progress towards an unfinished agenda. *The Lancet*, *397*, 1388–1399.

West Jr, K. P., Katz, J., LeClerq, S. C., Pradhan, E. K., Tielsch, J. M., Sommer, A., Pokhrel, R. P., Khatry, S. K., Shrestha, S. R., & Pandey, M. R. (1991). Efficacy of vitamin A in reducing preschool child mortality in Nepal. *The Lancet*, *338*, 67–71.

World Health Organisation (WHO). (2006). 'The WHO child growth standards [Online]'.

World Health Organisation (WHO). (2007). 'Addressing sex and gender in epidemic-prone infectious diseases'.

World Health Organisation (WHO). (2020). 'Children: improving survival and well-being'.

SUPPORTING INFORMATION

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

How to cite this article: Thurstans, S., Wrottesley, S. V., Fenn, B., Khara, T., Bahwere, P., Berkley, J. A., Black, R. E., Boyd, E., Garenne, M., Isanaka, S., Lelijveld, N., McDonald, C. M., Mertens, A., Mwangome, M., O'Brien, K. S., Stobaugh, H., Taneja, S., West, K. P., Guerrero, S., … Myatt, M. (2022). Anthropometric deficits and the associated risk of death by age and sex in children aged 6–59 months: A meta-analysis. *Maternal & Child Nutrition*, e13431. https://doi.org/10.1111/mcn.13431

7 Wasting treatment outcomes

7.1 Scope of chapter

This chapter presents the fourth research paper entitled “How age and sex affect treatment outcomes for children with severe malnutrition: a multi-country secondary data analysis”. This paper describes a secondary data analysis exploring whether age and/or sex influence treatment outcomes for children affected by wasting and, if so, what the implications might be for policy and practice.

The findings demonstrate few differences in wasting treatment outcomes by sex and age. The results do not indicate the need to change current program inclusion requirements or treatment protocols on the basis of sex or age, but we recommend further research to investigate the aetiology of sex differences in recovery and implications for treatment protocols. The paper was submitted to Maternal and Child Nutrition (MCN) journal in June 2023.

7.2 List of figures

7.3 List of tables

7.4 Research paper 4

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT

T: +44 (0)20 7299 4646
F: +44 (0)20 7299 4656
www.lshtm.ac.uk

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	1802701	**Title**	Mrs
First Name(s)	Susan		
Surname/Family Name	Thurstans		
Thesis Title	Sex differences in risk and outcomes from severe malnutrition: implications for management		
Primary Supervisor	Marko Kerac		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	Maternal and Child Nutrition		
When was the work published?	November 2023		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	**No**	Was the work subject to academic peer review?	**Yes**

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	Submitted

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	The research was designed and conducted by myself with supervision from Dr Marko Kerac and Professor Rebecca Sear. Data was contributed by IRC and MSF. The analysis was led by myself with support from Dr Charles Opondo. I led the wiriting of the manuscript with contributions from all authors.

SECTION E

Student Signature	
Date	

Supervisor Signature	
Date	

Received: 21 June 2023 | Revised: 8 November 2023 | Accepted: 9 November 2023

DOI: 10.1111/mcn.13596

ORIGINAL ARTICLE

Maternal & Child Nutrition WILEY

How age and sex affect treatment outcomes for children with severe malnutrition: A multi-country secondary data analysis

Susan Thurstans[1] | Charles Opondo[2,3] | Jeanette Bailey[4] | Heather Stobaugh[5] | Fabrizio Loddo[6] | Stephanie V. Wrottesley[7] | Andy Seal[8] | Mark Myatt[9] | André Briend[10,11] | Michel Garenne[12,13,14,15] | Andrew Mertens[16] | Jonathan Wells[17] | Rebecca Sear[1] | Marko Kerac[1,18]

[1]Department of Population Health, London School of Hygiene and Tropical Medicine, London, UK

[2]Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, UK

[3]National Perinatal Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK

[4]International Rescue Committee, New York, USA

[5]Action Against Hunger, New York, USA

[6]Médecins Sans Frontières, Paris, France

[7]Emergency Nutrition Network, Oxford, UK

[8]UCL Institute for Global Health, London, UK

[9]Brixton Health, Llwyngwril, Gwynedd, UK

[10]Tampere Center for Child, Adolescent and Maternal Health Research, Tampere University and Tampere University Hospital, Tampere, Finland

[11]Department of Nutrition, Exercise and Sports, University of Copenhagen, Copenhagen, Denmark

[12]Institut de Recherche pour le Développement, UMI Résiliences, Bondy, France

[13]Department of Statistics and Population Studies, University of the Western Cape, Cape Town, South Africa

[14]FERDI, Université d'Auvergne, Clermont-Ferrand, France

[15]MRC/Wits Rural Public Health and Health Transitions Research Unit, School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

[16]University of California, Berkeley School of Public Health, Berkeley, California, USA

[17]Population, Policy and Practice Research and Teaching Department, UCL Great Ormond Street Institute of Child Health, London, UK

[18]Maternal, Adolescent, Reproductive & Child Health Centre (MARCH), London School of Hygiene & Tropical Medicine, London, UK

Correspondence
Susan Thurstans, Department of Population Health, London School of Hygiene and Tropical Medicine, London, UK.
Email: susan.thurstans@lshtm.ac.uk

Abstract

Age and sex influence the risk of childhood wasting. We aimed to determine if wasting treatment outcomes differ by age and sex in children under 5 years, enroled in therapeutic and supplementary feeding programmes. Utilising data from stage 1 of the ComPAS trial, we used logistic regression to assess the association between age, sex and wasting treatment outcomes (recovery, death, default, non-response, and transfer), modelling the likelihood of recovery versus all other outcomes. We used linear regression to calculate differences in mean length of stay (LOS) and mean daily weight gain by age and sex. Data from 6929 children from Kenya, Chad, Yemen

and South Sudan was analysed. Girls in therapeutic feeding programmes were less likely to recover than boys (pooled odds ratio [OR]: 0.84, 95% confidence interval [CI]: 0.72–0.97, $p = 0.018$). This association was statistically significant in Chad (OR: 0.61, 95% CI: 0.39–0.95, $p = 0.030$) and Yemen (OR: 0.47, 95% CI: 0.27–0.81, $p = 0.006$), but not in Kenya and South Sudan. Multinomial analysis, however, showed no difference in recovery between sexes. There was no difference between sexes for LOS, but older children (24–59 months) had a shorter mean LOS than younger children (6–23 months). Mean daily weight gain was consistently lower in boys compared with girls. We found few differences in wasting treatment outcomes by sex and age. The results do not indicate a need to change current programme inclusion requirements or treatment protocols on the basis of sex or age, but future research in other settings should continue to investigate the aetiology of differences in recovery and implications for treatment protocols.

KEYWORDS
malnutrition, sex, treatment, undernutrition, wasting

1 | BACKGROUND

Undernutrition in all its forms remains a major contributor to child mortality. Child wasting, defined as weight-for-length or weight-for-height z-score <−2 and/or mid-upper-arm circumference (MUAC) <125 mm, affects an estimated 49.5 million children under the age of five (GNR, 2022). Severe wasting (weight-for-length or weight-for-height z-score <−3) is of particular concern since it is associated with a 12 times higher risk of mortality than experienced by well-nourished children (Olofin et al., 2013). Renewed international attention to wasting recognises the need for accelerated progress towards effective integration of wasting treatment within strengthened health systems and improved efficiency of wasting treatment services (ENN, 2021; UNICEF, 2022).

Both age and sex influence the risk of wasting in childhood. In a recent meta-analysis of 44 studies (S. Thurstans et al., 2020), we showed that boys are more likely to be wasted than girls (pooled odds ratio [OR]: 1.26, 95% confidence interval [CI]: 1.13–1.40). Other studies show similar findings; for example, a pooled analysis of 35 longitudinal cohorts (Mertens et al., 2020) from 15 low- and middle-income countries (LMICs) showed male sex to be a predictor of wasting. Several studies exploring concurrent wasting and stunting both at population level and within wasting treatment programmes have also shown that overall, boys are more likely to be affected than girls (Imam et al., 2020; Isanaka et al., 2019; Khara et al., 2018; Myatt et al., 2018; Odei Obeng-Amoako, Karamagi, et al., 2020; Odei Obeng-Amoako, Myatt, et al., 2020; Odei Obeng-Amoako, Wamani, et al., 2020). Sex differences are most likely caused by a complex interaction of social, environmental, physiological and genetic factors throughout the life cycle (S. Thurstans, 2022). Differences often begin in utero, particularly in conditions where maternal undernutrition is prevalent, and the impact of fetal growth restraint is often greater in males who are bigger than females at healthy z-scores. Males also face a higher risk of infectious disease in infancy compared with females.

Key messages

- There are few differences in recovery outcomes for wasting treatment by age and sex.
- Though differences are small, mean daily weight gain (g/kg/day) appears to be significantly lower in boys than girls. Likewise, though differences are small, younger children (6–23 months) often have a significantly longer mean length of stay compared with older children (24–59 months).
- The strength of our evidence does not indicate the need to change current inclusion criteria for wasting treatment programmes on the basis of age and sex but does suggest the need for further research to understand the effects of different confounders on treatment outcomes.

Previous studies have suggested that sex differences in undernutrition may be moderated by age (Costa et al., 2021; Myatt et al., 2018; S. Thurstans et al., 2020). The male disadvantage is greater among younger children, after which it disappears or, in some contexts, is reversed. Wasting has also been shown to peak in younger children between 0 and 3 months (Benjamin-Chung et al., 2020; Mertens et al., 2023). Despite higher levels of wasting among children under 2 years compared with children aged 2–4 years (14% and 9%, respectively) (Karlsson et al., 2022), we recently demonstrated equivalent levels of associated mortality risk for younger (6–23 months) and older (24–59 months) wasted children and equivalent levels of mortality risk between wasted girls and boys (S. Thurstans et al., 2022).

The effects of age and sex on wasting treatment outcomes such as recovery, defaulting and non-response have not, to our knowledge, been explored in depth and across multiple countries. This analysis was designed to fill that important evidence gap. Our aim is to determine whether age and/or sex influence treatment outcomes for children affected by wasting and, if associations are found, to discuss potential implications for policy and practice.

2 | METHODS

2.1 | Study design

This was a secondary analysis of multi-country cohort data following STROBE guidelines (Vandenbroucke et al., 2007). We assessed whether there were differences in wasting treatment outcomes in children under 5 years by age and sex.

2.2 | Study setting and participants

The data used for this analysis is from a multi-country cohort compiled for 'stage 1' of the ComPAS study and is described elsewhere (Chase et al., 2020). In brief, the initial aim of this dataset was to help design a simplified MUAC-based treatment protocol for children with acute malnutrition and to assess the theoretical performance of MUAC-based delivery of a standard dose of ready-to-use therapeutic food (Chase et al., 2020). The data were collected from programmes providing standard treatment for wasting in four LMICs, three in Africa (Kenya, Chad and South Sudan) and one in Western Asia (Yemen). The data from South Sudan was collected by Médecins Sans Frontières (MSF)-France in 2010. The International Rescue Committee collected data from Chad in 2013–2014, Kenya in 2012–2014 and Yemen in 2014 (Chase et al., 2020).

We focused on children aged 6–59 months in this dataset, stratified into younger (6–23 months) and older (24–59 months) age groups. Admission to either outpatient-based therapeutic feeding programmes (TFP) or supplementary feeding programmes (SFP) was recorded using a unique child ID. Children enroled in this dataset were required to be clinically well. Each follow-up visit was recorded using the same ID. Anthropometric measurements were recorded at each visit, weekly for severe wasting and every 2 weeks for moderate wasting. Treatment followed national protocols based on standard international criteria. Therapeutic rations for severe wasting were provided based on weight (200 kcal/kg/day). Supplementary rations for children with moderate wasting were provided as a standard ration which varied by country (Chase et al., 2020).

2.3 | Variables

The dataset contained information on weight and height, the presence of oedema, MUAC, age, country, and which treatment programme children were enroled in, TFP for severe wasting, or SFP for moderate wasting. Our treatment outcomes of interest were recovery (TFP recovery criteria was MUAC ≥ 11.5 cm OR WFH/L ≥ −3z-score for two consecutive weeks AND no bilateral pitting oedema, SFP recovery criteria was MUAC ≥ 12.5 cm OR WFH/L ≥ −2z-score for two consecutive weeks); death, defined as a death occurring while enroled in the programme and assessed by verbal autopsy; default, defined as absence for two consecutive visits; and non-response, defined as a child not responding to the treatment provided within 3 months (Kenya_Ministry_of_Health, 2009; Sudan, 2009, 2017; Yemen. Ministry of Public, Population. Yemen. Central Statistical, Pan Arab Programme for Family, & DHS, 2014). Transfers referred to either movement within different components of the programme or movements for further medical intervention. We were not able to determine individual reasons for transfers.

We also analysed length of stay (LOS), defined as the period of time between admission and discharge for those children who recovered, and daily weight gain g/kg/day, defined as: [*discharge weight* (*g*) *minus minimum weight* (*g*)]/[*minimum weight* (kg) × *the number of days between minimum weight and discharge day*] (MSF, 1995). Possible differences by sex and age were assessed for all outcomes. Children were stratified into two groups according to age at admission: 6–23 months and 24–59 months.

In addition to analysis by TFP and SFP enrolment, we performed the same treatment-outcomes analysis and LOS and daily weight gain analyses on two further subgroups. The first was children with WAZ < −3, in light of the recent inclusion of WAZ as a means of identifying wasted children in recently revised WHO guidance for the management of acute malnutrition. The second subgroup was formed of children who were both wasted and stunted, in light of evidence demonstrating a higher prevalence of concurrent wasting and stunting in boys compared with girls. We defined this subgroup as all children with both baseline HAZ and WHZ score ≤−2.

We used the WHO classifications of severe wasting, defined as WLZ/WHZ < −3 or MUAC < 115 mm, and moderate wasting, defined as WLZ/WHZ between −3 and −2 z-score or MUAC < 125 mm. We also included children with kwashiorkor in our analysis, defined as a child with bilateral pitting oedema.

2.4 | Statistical methods

Statistical analysis was conducted using Stata V.16 (StataCorp 2017, Stata Statistical Software). Data was cleaned and excluded if age, sex or outcome variables were missing. Children under 6 months and over 5 years of age at admission to the programmes were also excluded from the analysis. Z-scores were calculated using the 2006 WHO Child Growth Standards (WHO, 2006). We plotted data against normal distributions using quantile-normal plots for each of the admission indices or criteria (WH/LZ, WAZ, H/LAZ<, MUAC and oedema). Values identified as implausible outliers were excluded (WHO, 2019).

For the treatment outcome variables (recovery, death, default, transfer and non-response), we used logistic regression to calculate crude

odds ratios and 95% CIs for the association between age and sex and the outcome indicators of interest. For each model, all other outcomes were used as the reference category modelling the likelihood of recovery, for example, recovery versus all other outcomes (death, default, transfer and non-response). We further adjusted the analysis for baseline WH/LZ and HAZ, country, and age and sex. We also performed crude and adjusted multinomial analysis of outcomes by sex as a sensitivity test, using each of the different outcomes as the reference group.

For LOS and daily weight gain, we used linear regression to calculate differences in mean LOS and daily weight gain with 95% CIs for age and sex. Here, we also adjusted for baseline WH/LZ and HAZ, country, age and sex.

For all of the above analyses, we fit logistic regression models with interaction terms between age and sex and performed likelihood ratio (LR) tests between models with and without interactions to determine statistical significance of potential interactions.

2.5 | Ethical approval

Ethical approval for stage 1 of the ComPAS trial was from the London School of Hygiene and Tropical Medicine Ethics Committee (reference number 11826). Further permission was granted for this analysis of the data by the same committee (reference number 26401).

3 | RESULTS

3.1 | Study characteristics

Figure 1 shows the study flow diagram. Data originated from four countries, Kenya, Chad, Yemen and South Sudan, and contained information from a total of 44,375 follow-up visits for 7449 children. After data cleaning, 520 children were excluded from the analysis either due to missing data, not meeting inclusion criteria or implausible anthropometric measures. Following these exclusions, 6929 children were included in the analysis.

3.2 | Children's nutrition status and treatment outcomes

Table 1 presents the baseline characteristics of the dataset. The data includes 3299 (47.6%) girls and 3630 (52.4%) boys. A total of 4666 (67.3%) were aged 6–23 months on admission and 2263 (32.7%) were aged 24–59 months on admission. The mean age at admission was 19.4 months (*SD* 12.5) for girls and 19.4 months (*SD* 12.5) for boys. For individual countries, the average age at admission was 21.3 months (*SD* 14.2) in Kenya, 16.6 months (*SD* 9.1) in Chad, 26.1 months (*SD* 16.7) in Yemen and 17.4 months (*SD* 9.6) in South Sudan.

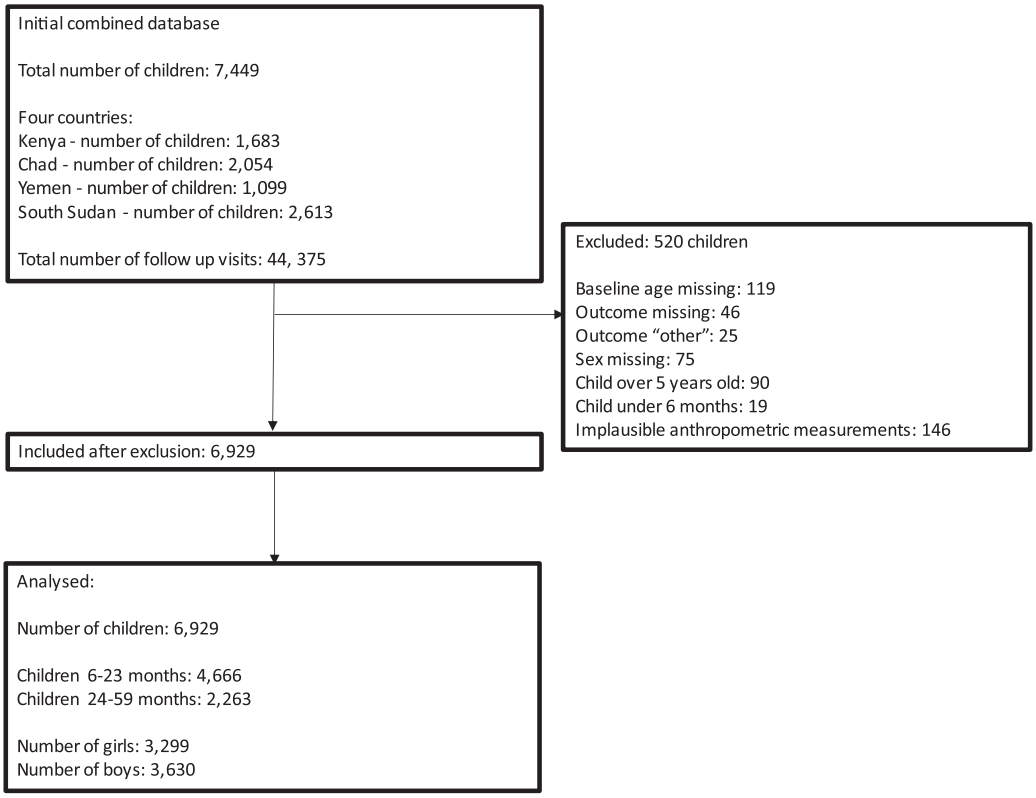


FIGURE 1 Flow diagram.

TABLE 1 Baseline characteristics.

Country	6–23 Months Female *n* (%)	6–23 Months Male *n* (%)	24–59 Months Female *n* (%)	24–59 Months Male *n* (%)	Total *n* (%)
Kenya	495 (20.2)	433 (19.6)	355 (30.2)	293 (27.0)	1576 (22.8)
Chad	878 (35.8)	695 (31.3)	223 (19.0)	194 (17.8)	1990 (28.7)
South Sudan	767 (31.2)	856 (38.7)	333 (28.3)	361 (33.2)	2317 (15.1)
Yemen	314 (12.8)	228 (10.3)	265 (22.5)	239 (22.0)	1046 (33.4)
Treatment site					
TFP[a]	1327 (54.1)	1272 (57.5)	534 (45.4)	521 (47.9)	3654 (52.7)
SFP[b]	1127 (45.9)	940 (42.5)	642 (54.6)	566 (52.1)	3275 (47.3)
Outcomes TFP					
Recovered	928 (69.9)	870 (68.4)	365 (68.4)	361 (69.3)	2524 (69.1)
Death	1 (0.1)	3 (0.2)	0 (NA)	1 (0.2)	5 (0.1)
Default	240 (18.1)	259 (20.4)	118 (22.1)	118 (22.6)	735 (20.1)
Transfer	122 (9.2)	110 (8.6)	45 (8.4)	32 (6.1)	309 (8.5)
Non-response	36 (2.7)	30 (2.4)	6 (1.1)	9 (1.7)	81 (2.2)
Outcomes SFP					
Recovered	832 (73.8)	700 (74.5)	431 (67.1)	370 (65.4)	2333 (71.2)
Death	3 (0.3)	1 (0.1)	3 (0.5)	2 (0.3)	9 (0.3)
Default	176 (15.6)	159 (16.9)	182 (28.3)	155 (27.4)	672 (20.5)
Transfer	102 (9.1)	62 (6.6)	19 (3.0)	27 (4.8)	210 (6.4)
Non-response	14 (1.2)	18 (1.9)	7 (1.1)	12 (2.1)	51 (1.6)
Totals	**2454**	**2212**	**1176**	**1087**	**6929**
No cases oedema in TFP	7 (0.5)	8 (0.6)	16 (3.0)	18 (3.5)	49 (1.3)
Mean anthropometry TFP	**Mean (*SD*)**	**Mean (*SD*)**	**Mean (*SD*)**	**Mean (*SD*)**	**Mean (*SD*)**
Baseline WHZ	−3.27 (1.04)	−3.67 (0.94)	−3.54 (0.76)	−3.80 (0.90)	−3.53 (0.97)
Baseline WAZ	−3.27 (0.98)	−3.59 (0.90)	−3.77 (1.05)	−3.78 (1.04)	−3.53 (1.00)
Baseline HAZ	−1.62 (1.60)	−1.90 (1.67)	−2.36 (1.69)	−2.46 (1.78)	−1.95 (1.69)
Baseline MUAC mm	115.0 (8.28)	117.0 (8.28)	120.5 (9.36)	121.5 (9.16)	117.4 (8.92)
Mean anthropometry SFP					
Baseline WHZ	−1.78 (0.81)	−2.27 (0.86)	−2.02 (0.95)	−2.32 (0.94)	−2.06 (0.90)
Baseline WAZ	−2.31 (0.98)	−2.79 (0.95)	−2.65 (1.05)	−2.87 (0.98)	−2.61 (1.01)
Baseline HAZ	−1.75 (1.75)	−2.13 (1.86)	−2.12 (1.92)	−2.43 (1.75)	−2.05 (1.83)
Baseline MUAC mm	122.1 (4.64)	122.8 (5.21)	126.7 (6.27)	126.9 (6.54)	124.0 (5.90)
Daily weight gain TFP g/kg/day	5.14 (4.82)	5.22 (5.42)	5.79 (7.37)	5.39 (5.79)	5.30 (5.54)
Daily weight gain SFP g/kg/day	2.93 (3.53)	2.88 (4.03)	2.91 (4.41)	2.56 (3.20)	2.85 (3.81)
Length of stay TFP days	44.8 (28.4)	45.2 (29.3)	40.1 (32.9)	42.5 (30.1)	43.9 (29.7)
Length of stay SFP days	50.0 (29.7)	51.6 (32.8)	52.2 (33.2)	51.2 (34.0)	51.0 (32.0)

Abbreviations: SFP, supplementary feeding programmes; TFP, therapeutic feeding programmes.

[a]Therapeutic feeding programme.

[b]Supplementary feeding programme, percentages may not total 100 due to rounding.

Children entered either TFP (3654; 52.7%) or SFP (3275; 47.3%) at baseline. For TFP, the mean WHZ on admission was −3.53 (*SD* 0.97), the mean WAZ was −3.53 (*SD* 1.00), the mean HAZ was −1.95 (*SD* 1.69) and the mean MUAC was 117.4 mm (*SD* 8.92). There were 54 cases of oedema. For SFP, the mean WHZ on admission was −2.06 (*SD* 0.90), the mean WAZ was −2.61 (*SD* 1.01), the mean HAZ was −2.05 (*SD* 1.83) and the mean MUAC was 124.0 mm (*SD* 5.90). For both TFP and SFP, mean z-scores were lower on average for boys compared with girls.

For TFP, the mean LOS was 43.9 days (*SD* 29.7) and the mean daily weight gain measured in g/kg/day was 5.30 (*SD* 5.54). For SFP, the mean LOS was 51.0 days (*SD* 32.0) and the mean daily weight gain measured in g/kg/day was 2.85 (*SD* 3.81).

Overall, 69.1% of children in TFP and 71.2% of children in SFP achieved recovery following wasting treatment, falling below the recommended 75% (Sphere Association, 2018). Deaths were rare in this sample and fell within the Sphere indicator of 3% for both TFP (0.1%) and SFP (0.3%). Defaulting rates were higher than recommended for both TFP (20.1%) and SFP (20.5%).

3.3 | Outcomes by sex

Tables 2a and 2b show crude and adjusted odds ratios for recovery, death, default, transfer and non-response by sex for TFP and SFP. In the crude analysis of TFP outcomes, girls were more likely to recover than boys, though this difference was not statistically significant. After adjusting for potential confounders (age, country, HAZ at baseline and WHZ at baseline), however, we found that girls were less likely to recover than boys (adjusted OR: 0.84, 95% CI: 0.72–0.97, $p = 0.018$). We further looked at the odds of recovery by sex for each country individually (see Table S1a). After adjusting for sex, age and baseline anthropometry (HAZ and WHZ), we found that for TFP there was no difference in the odds of recovery between girls and boys in Kenya and South Sudan (Kenya adjusted OR: 0.66, 95% CI: 0.39–1.13, $p = 0.130$, South Sudan adjusted OR: 0.96, 95% CI: 0.81–1.15, $p = 0.703$). In Chad and Yemen, girls were less likely to recover than boys (Chad adjusted OR: 0.61, 95% CI: 0.39–0.95, $p = 0.030$, Yemen, adjusted OR: 0.47, 95% CI: 0.27–0.81, $p = 0.006$). There was no difference in odds of recovery between girls and boys in SFP programmes in both the pooled and individual country analyses.

Girls were more likely than boys to be transferred out of the programme in the adjusted analysis for both TFP and SFP (adjusted OR: 1.34, 95% CI: 1.05–1.71, $p = 0.017$ and adjusted OR: 1.45, 95% CI: 1.07–1.96, $p = 0.017$, respectively).

We did not observe any differences between boys and girls in the odds of death, defaulting or non-response in TFP or SFP.

We performed a multinomial sensitivity analysis to further explore outcomes by sex (see Table S2). Using recovery as the reference group, there was no statistically significant difference in the risk of death, default or non-response compared with recovery between girls and boys. In the adjusted analysis, girls were more likely to be transferred out of TFP than to recover compared with boys (adjusted relative risk: 1.41, 95% CI: 1.10–1.80, $p = 0.007$). Using default or death as the reference group, there was no statistically significant difference in outcomes between girls and boys.

Table 3 shows mean crude and adjusted differences in LOS and daily weight gain by sex. For LOS, we did not observe any difference between girls and boys for either TFP or SFP. Girls had a higher mean daily weight gain than boys in TFP and SFP (mean adjusted difference: 0.61 g/kg/day, 95% CI: 0.24–1.04, $p = 0.002$ and mean adjusted difference: 0.30 g/kg/day, 95% CI: 0.00–0.61, $p = 0.049$, respectively).

3.4 | Outcomes by age

Table 2a shows crude and adjusted odds ratios for recovery, death, default, transfer and non-response by age for TFP and SFP. We found no differences in odds of recovery, death or default between the two age groupings. Older children had a lower risk of non-response to treatment compared with younger children (OR: 0.43, 95% CI: 0.24–0.77, $p = 0.005$). In the crude analysis, older children attending SFP were more likely to default compared with the younger age group (OR: 2.00, 95% CI: 1.68–2.38, $p < 0.0001$); however, this was no longer the case after adjustment (adjusted OR: 1.20, 95% CI: 0.99–1.46, $p = 0.066$).

Older children were less likely to be transferred out of the programme compared with younger children in both TFP and SFP (adjusted OR: 0.73, 95% CI: 0.55–0.97, $p = 0.027$ and adjusted OR: 0.43, 95% CI: 0.30–0.63, $p < 0.0001$, respectively).

Table 3 shows mean differences in LOS and daily weight gain by age. Older children in TFP and SFP had a significantly shorter LOS than younger children (adjusted mean difference: −7.05 days, 95% CI: −9.55 to −4.55, $p \leq 0.0001$ and −5.25 days, 95% CI: −7.94 to −2.56, $p < 0.0001$, respectively). For daily weight gain, we did not observe differences between age groups in either TFP or SFP.

3.5 | Children with WAZ < −3

Table 2b shows crude and adjusted odds ratios for recovery, death, default, transfer and non-response by age and sex for children with a WAZ < −3 at baseline. We found no difference between girls and boys for all outcomes. For age however, in both crude and adjusted analysis, older children were more likely to default (adjusted OR: 1.28, 95% CI: 1.07–1.53, $p = 0.007$), less likely to be transferred out of a programme (adjusted OR: 0.74, 95% CI: 0.58–0.96, $p = 0.022$), and had a lower risk of non-response to treatment, compared with younger children (adjusted OR: 0.46, 95% CI: 0.28–0.78, $p = 0.004$).

Table 3 shows mean differences in LOS and daily weight gain by age and sex for children with WAZ < −3 at baseline. There was no difference between girls and boys for LOS, but after adjusting for potential confounders, older children had a shorter LOS compared with younger children (adjusted difference OR: −4.88 days, 95% CI: −7.24 to −2.52, $p < 0.001$). As with TFP and SFP, girls had a higher

TABLE 2a Association between treatment outcomes and age and sex within subgroups of therapeutic and supplementary feeding.

	TFP					SFP				
Outcome	**No**	**OR (95% CI)**	***p* value**	**Adjusted OR (95% CI)[a]**	***p* value**	**No**	**OR (95% CI)**	***p* value**	**Adjusted OR (95% CI)[a]**	***p* value**
Recovery										
Male	1231/1793	REF				1070/1506	REF		REF	
Female	1293/1861	1.04 (0.90–1.20)	0.591	0.84 (0.72–0.97)	0.018	1263/1769	1.02 (0.87–1.18)	0.827	0.93 (0.79–1.10)	0.408
6–23	1798/2599	REF		REF		1532/2067	REF		REF	
24–59	726/1055	0.98 (0.84–1.15)	0.829	1.16 (0.99–1.37)	0.07	801/1208	0.69 (0.59–0.80)	0.000	1.03 (0.87–1.23)	0.711
				Interaction[b]	0.717				Interaction[b]	0.252
Death										
Male	4/1793	REF		REF		3/1506	REF		REF	
Female	1/1861	0.24 (0.03–2.15)	0.203	0.37 (0.04–3.39)	0.376	6/1769	1.71 (0.43–6.83)	0.451	1.54 (0.37–6.35)	0.550
6–23	4/2599	REF		REF		4/2067	REF		REF	
24–59	1/1055	0.62 (0.07–5.51)	0.664	0.27 (0.02–2.85)	0.275	5/1208	2.14 (0.57–8.00)	0.256	2.27 (0.54–9.45)	0.260
				Interaction[b]	NA[c]				Interaction[b]	0.666
Default										
Male	377/1793	REF		REF		314/1506	REF		REF	
Female	358/1861	0.89 (0.76–1.05)	0.178	1.05 (0.88–1.24)	0.598	358/1769	0.96 (0.81–1.14)	0.665	1.00 (0.83–1.21)	0.986
6–23	499/2599	REF		REF		335/2067	REF		REF	
24–59	236/1055	1.21 (1.02–1.44)	0.030	1.08 (0.90–1.30)	0.415	227/1208	2.00 (1.68–2.38)	<0.0001	1.20 (0.99–1.46)	0.066
				Interaction[b]	0.571				Interaction[b]	0.577
Transfer										
Male	142/1793	REF		REF		89/1506	REF		REF	
Female	167/1861	1.15 (0.91–1.45)	0.253	1.34 (1.05–1.71)	0.017	121/1769	1.17 (0.88–1.55)	0.279	1.45 (1.07–1.96)	0.017
6–23	232/2599	REF		REF		164/2067	REF		REF	
24–59	77/1055	0.80 (0.61–1.05)	0.110	0.73 (0.55–0.97)	0.027	46/1208	0.46 (0.33–0.64)	0.000	0.43 (0.30–0.63)	0.000
				Interaction[b]	0.483				Interaction[b]	0.007

(Continues)

TABLE 2a (Continued)

Outcome	TFP					SFP				
	No	OR (95% CI)	*p* value	Adjusted OR (95% CI)[a]	*p* value	No	OR (95% CI)	*p* value	Adjusted OR (95% CI)[a]	*p* value
Non-response										
Male	39/1793	REF		REF		30/1506	REF		REF	
Female	42/1861	1.04 (0.67–1.61)	0.867	1.30 (0.83–2.05)	0.255	21/1769	0.59 (0.34–1.04)	0.067	0.80 (0.42–1.52)	0.494
6–23	66/2599	REF		REF		32/2067	REF		REF	
24–59	15/1055	0.55 (0.31–0.97)	0.040	0.43 (0.24–0.77)	0.005	19/1208	1.02 (0.57–1.80)	0.956	1.22 (0.65–2.29)	0.527
				Interaction[b]	0.372				Interaction[b]	0.707

Note: This table represents results from 5 sets of logistic regression models; ORs represent the likelihood of each outcome compared with all other outcomes.

Abbreviations: CI, confidence interval; OR, odds ratio.

[a]Adjusted for sex, age, country, HAZ at baseline and WHZ at baseline.

[b]Test for interaction between age group and sex.

[c]No events, so test not comparable.

mean daily weight gain compared with boys (adjusted difference: 0.69 g/kg/day, 95% CI: 0.30–1.08, $p = 0.001$).

3.6 | Children with concurrent wasting and stunting (WaSt)

Table 2b shows crude and adjusted odds ratios for recovery, death, default, transfer and non-response by age and sex for children who were both wasted and stunted. Girls were less likely to recover than boys in both the crude and adjusted analysis (adjusted OR: 0.83, 95% CI: 0.70–1.00, $p = 0.045$). Girls were more likely to be transferred out of a programme than boys after adjusting for potential confounders (OR: 1.40, 95% CI: 1.06–1.85, $p = 0.018$). We found no difference between girls and boys for death, default and non-recovery.

Table 3 shows mean differences in LOS and daily weight gain by age and sex for children who were wasted and stunted. We found no difference between girls and boys for LOS. For daily weight gain, boys had a lower mean gain compared with girls (adjusted mean difference: 0.66 g/kg/day, 95% CI: 0.26–1.07, $p \leq 0.001$).

In terms of age (see Table 2b), as with TFP and SFP, we found that older children were less likely to be transferred out of a programme compared with younger children (adjusted OR: 0.71, 95% CI: 0.52–0.96, $p = 0.026$). We also found that older children had a lower risk of non-response to treatment compared with younger children in both crude and adjusted analysis (adjusted OR: 0.56, 95% CI: 0.33–0.97, $p = 0.038$). Finally, older children had a shorter LOS than younger children (adjusted difference: −3.53 days, 95% CI: −6.07 to −0.99, $p = 0.007$) (see Table 3).

3.7 | Interactions between age and sex

We sought to conduct subgroup analysis for the above tests to test for interaction between age and sex using LR tests. For two of the models, this was not possible (death and sex in TFP, death and sex for WaSt) due to too few events in the subgroups. We observed an interaction between age and sex in transfers out of SFP ($p = 0.007$). For all other models, we found no evidence that associations between treatment outcomes, LOS and daily weight gain varied by sex or age (see Tables 2a, 2b, 3).

4 | DISCUSSION

We explored the impact of age and sex on outcomes following treatment for wasting. Overall, our findings show few differences in treatment outcomes between girls and boys and between age groups. Based on this evidence from these settings, this suggests no need to change current programme inclusion requirements or treatment protocols on the basis of sex or age.

Our findings showed that girls in TFP have 16% lower adjusted odds of recovery than boys (OR: 0.84, 95% CI: 0.72–0.97, $p = 0.018$).

TABLE 2b Association between treatment outcomes and age and sex within subgroups of children who are wasted and stunted (WaSt) and children with WAZ < −3.

	WAZ < −3					WaSt				
Outcome	**No**	**OR (95% CI)**	***p* value**	**Adjusted OR (95% CI)[a]**	***p* value**	**No**	**OR (95% CI)**	***p* value**	**Adjusted OR (95% CI)[a]**	***p* value**
Recovery										
Male	1425/2081	REF		REF		1073/1517	REF		REF	
Female	1218/1731	1.03 (0.93–1.14)	0.546	0.91 (0.82–1.01)	0.085	811/1160	0.96 (0.81–1.14)	0.646	0.83 (0.70–1.00)	0.045
6–23	1735/2467	REF		REF		1171/1630	REF		REF	
24–59	908/1345	0.88 (0.76–1.01)	0.071	1.03 (0.92–1.16)	0.623	713/1047	0.84 (0.71–0.99)	0.039	1.08 (0.90–1.30)	0.387
				Interaction[b]	0.522				Interaction[b]	0.902
Death										
Male	4/2081	REF		REF		3/1517	REF		REF	
Female	2/1731	0.60 (0.11–3.28)	0.556	0.73 (0.13–4.13)	0.719	1/1160	0.44 (0.05–4.19)	0.472	0.63 (0.62–6.51)	0.701
6–23	3/2467	REF		REF		3/1630	REF		REF	
24–59	3/1345	1.84 (0.37–9.11)	0.457	0.85 (0.16–4.61)	0.852	1/1047	0.52 (0.05–4.99)	0.570	0.21 (0.02–2.73)	0.231
				Interaction[b]	0.751				Interaction[b]	NA[c]
Default										
Male	411/2081	REF		REF		285/1517	REF		REF	
Female	310/1731	0.89 (0.75–1.04)	0.148	0.95 (0.80–1.13)	0.552	201/1160	0.91 (0.74–1.11)	0.332	0.97 (0.79–1.20)	0.801
6–23	410/2467	REF		REF		245/1630	REF		REF	
24–59	311/1345	1.51 (1.28–1.78)	<0.001	1.28 (1.07–1.53)	0.007	241/1047	1.69 (1.39–2.06)	0.000	1.19 (0.96–1.48)	0.103
				Interaction[b]					Interaction[b]	
Transfer										
Male	190/2081	REF		REF		119/1517	REF		REF	
Female	160/1731	1.01 (0.81–1.26)	0.904	1.12 (0.89–1.40)	0.321	110/1160	1.23 (0.94–1.61)	0.134	1.40 (1.06–1.85)	0.018
6–23	247/2467	REF		REF		157/1630	REF		REF	
24–59	103/1345	0.75 (0.59–0.95)	0.016	0.74 (0.58–0.96)	0.022	72/1047	0.69 (0.52–0.93)	0.013	0.71 (0.52–0.96)	0.026
				Interaction[b]	0.727				Interaction[b]	0.768

(Continues)

TABLE 2b (Continued)

Outcome	WAZ < −3					WaSt				
	No	OR (95% CI)	*p* value	Adjusted OR (95% CI)[a]	*p* value	No	OR (95% CI)	*p* value	Adjusted OR (95% CI)[a]	*p* value
Non-response										
Male	51/2081	REF		REF		37/1517	REF		REF	
Female	41/1731	0.96 (0.64–1.46)	0.869	1.18 (0.77–1.81)	0.439	37/1160	1.32 (0.83–2.09)	0.242	1.51 (0.94–2.41)	0.087
6–23	72/2467	REF		REF		54/1630	REF		REF	
24–59	20/1345	0.50 (0.30–0.83)	0.007	0.46 (0.28–0.78)	0.004	20/1047	0.57 (0.34–0.96)	0.033	0.56 (0.33–0.97)	0.038
				Interaction[b]	0.647				Interaction[b]	0.485

Note: This table represents results from 5 sets of logistic regression models; ORs represent the likelihood of each outcome compared with all other outcomes.

Abbreviations: CI, confidence interval; OR, odds ratio.

[a]Adjusted for sex, age, country, HAZ at baseline and WHZ at baseline.

[b]Test for interaction between age group and sex.

[c]No events, so test not comparable.

Individual country analysis showed the same association to be statistically significant in Chad and Yemen, but not in Kenya or South Sudan. Girls who were both wasted and stunted were also less likely to recover compared with boys (OR: 0.83, 95% CI: 0.70–1.00, $p = 0.045$). Baseline anthropometry appeared to be the main confounding variable. There was no difference between boys and girls in recovery outcomes for SFP or in our subgroup analysis of children with WAZ < −3. We were unable to adjust for social, economic, care and feeding practices and co-morbidities, leaving the possibility of residual confounding. While changes in the magnitude of odds ratios after adjustment may indicate confounding, such changes can also occur in the absence of confounding due to the non-collapsibility property of odds ratios (Greenland, 2021a, 2021b). Further multinomial analysis, conducted as a sensitivity test, demonstrated no statistical difference between recovery by sex in TFP. The finding that girls in TFPs are less likely to recover than boys is not therefore generalisable to all settings and should be interpreted with caution. Further research is needed to understand the effect of admission and discharge criteria, baseline anthropometry and other potential confounding factors such as social, health and care indicators.

We did not observe any differences in age or sex in relation to mortality. While this sample likely lacked sufficient power for this outcome, the finding is consistent with our recent meta-analysis (S. Thurstans et al., 2022), showing no difference in the risk of mortality associated with wasting between boys and girls and between children under 2 years versus those 2–5 years. This highlights the importance of access to treatment for all children under 5 years, regardless of age and sex.

We observed lower mean weight gain in boys compared with girls in TFP, SFP, and WaSt and WAZ < −3 subgroups. Though differences are small, they might be explained by differences between girls and boys in lean and fat mass from birth onwards. Differences in body composition in infancy and early childhood have been documented whereby although girls are lighter at birth and during infancy, girls on average have less lean mass and more fat mass than males. This might then shape sex differences in weight gain (Andersen, 2013; Rodríguez, 2004). Future research into body composition and weight gain in wasting recovery and links to future health are needed. There might also be differences in the way that girls and boys respond to treatment. A recent meta-analysis of SQ-LNS supplementation demonstrated better growth in girls compared with boys in response to SQ-LNS supplementation (Dewey et al., 2021). The authors suggest that this likely reflects greater potential in girls to respond to nutritional supplementation and an effect of early vulnerability in boys to adverse conditions, which might constrain responses to nutrition interventions.

We observed that girls are transferred out of programmes more often than boys for both SFP and TFP. This was also the case in our subgroup analysis of children who were both wasted and stunted. Younger children were consistently more likely to be transferred out of a programme than older children. It is difficult to speculate as to the reasons for this pattern as the data does not distinguish between transfers to other components of programmes such as inpatient, TFP

TABLE 3 Mean differences in length of stay (LOS) and daily weight gain by age and sex within subgroups for TFP, SFP and children who are wasted and stunted or have WAZ < −3.

Outcome	Mean (*SE*)	Crude difference (95% CI)	*p* value	Adjusted difference (95% CI)[a]	*p* value
LOS TFP, mean (*SE*) days[b]					
Male	49.8 (0.81)	REF		REF	
Female	48.6 (0.81)	−1.25 (−3.50 to 1.00)	0.277	0.79 (−1.45 to 3.05)	0.486
6–23	51.0 (0.65)	REF		REF	
24–59	44.7 (1.18)	−6.28 (−8.75 to −3.80)	<0.001	−7.05 (−9.55 to −4.55)	<0.001
				Interaction	
LOS SFP, mean (*SE*) days[b]					
Male	54.1 (0.99)	REF		REF	
Female	52.9 (0.79)	−1.22 (−3.68 to 1.23)	0.329	0.33 (−2.17 to 2.83)	0.796
6–23	53.0 (0.75)	REF		REF	
24–59	54.3 (1.11)	1.26 (−1.31 to 3.84)	0.336	−5.25 (−7.94 to −2.56)	<0.001
				Interaction	0.642
LOS WaSt, mean (*SE*) days[b]					
Male	49.6 (0.86)	REF		REF	
Female	49.7 (0.86)	0.16 (−2.26 to 2.58)	0.897	1.96 (−4.48 to 4.40)	0.115
6–23	50.4 (0.77)	REF		REF	
24–59	48.4 (1.01)	−2.04 (−4.52 to 0.43)	0.106	−3.53 (−6.07 to −0.99)	0.007
				Interaction	0.778
LOS WAZ < −3, mean (*SE*) days[b]					
Male	51.1 (0.76)	REF		REF	
Female	49.9 (0.80)	−1.26 (−3.43 to 0.91)	0.255	0.24 (−1.97 to 2.45)	0.833
6–23	51.7 (0.66)	REF		REF	
24–59	48.3 (0.99)	−3.33 (−5.61 to −1.05)	0.004	−4.88 (−7.24 to −2.52)	<0.001
				Interaction	0.811
Daily weight gain, TFP, mean (*SE*) g/kg/day					
Male	5.27 (0.14)	REF		REF	
Female	5.33 (0.15)	0.05 (−0.34 to 0.46)	0.789	0.61 (0.24 to 1.04)	0.002
6–23	5.18 (0.11)	REF		REF	
24–59	5.59 (0.22)	0.41 (−0.03 to 0.86)	0.071	−0.03 (−0.47 to 0.41)	0.894
				Interaction	0.575
Daily weight gain, SFP, mean (*SE*) g/kg/day					
Male	2.77 (0.11)	REF		REF	
Female	2.92 (0.10)	0.15 (−0.14 to 0.44)	0.307	0.30 (0.00 to 0.61)	0.049
6–23	2.91 (0.09)	REF		REF	
24–59	2.74 (0.13)	−0.16 (−0.46 to 0.14)	0.288	−0.13 (−0.45 to 0.20)	0.432
				Interaction	0.404
Daily weight gain, WaSt, mean (*SE*) g/kg/day					
Male	4.31 (0.14)	REF		REF	

(Continues)

TABLE 3 (Continued)

Outcome	Mean (*SE*)	Crude difference (95% CI)	*p* value	Adjusted difference (95% CI)[a]	*p* value
Female	4.67 (0.16)	0.36 (−0.06 to 0.77)	0.091	0.66 (0.26 to 1.07)	<0.001
6–23	4.38 (0.14)	REF		REF	
24–59	4.60 (0.16)	0.22 (−0.20 to 0.65)	0.302	−0.16 (−0.58 to 0.26)	0.444
				Interaction	0.566
Daily weight gain, WAZ < −3, mean (*SE*) g/kg/day					
Male	4.65 (0.14)	REF		REF	
Female	5.00 (0.15	0.35 (−0.05 to 0.75)	0.089	0.69 (0.30 to 1.08)	0.001
6–23	4.81 (0.12)	REF		REF	
24–59	4.82 (0.19)	0.01 (−0.41 to 0.43)	0.962	−0.09 (−0.51 to 0.33)	0.671
				Interaction	0.596

[a]Adjusted for sex, age, country, HAZ at baseline and WHZ at baseline.
[b]Measured for recovered children only.

or SFP, transfers to other sites, or medical transfers. Further research is needed to better understand this. We observed longer LOS and a higher risk of non-response for younger children in TFP. We also observed a higher risk on non-response for younger children in our subgroup analyses of children with concurrent wasting and stunting and children with WAZ < −3. It is again hard to speculate as to why without understanding factors such as which discharge criteria were used for each individual child and the presence or absence of co-morbidities.

4.1 | Limitations and recommendations for future research

The strength of this analysis lies in data originating from four different countries with large numbers of children. Almost all children were wasted, which enhances the validity of pooling the data and avoids the many complexities of analysing data on oedematous severe malnutrition (especially when it comes to weight-based measures) (Frison et al., 2015). However, we also acknowledge limitations, many of which arise from the nature of the dataset. This data came from multiple locations and time periods and was collected by different non-governmental organisations. As this data does not originate from carefully controlled research programmes, there are gaps in the information needed to draw further conclusions about the findings. For example, we did not have data to say exactly how children were treated; that is, in SFP, did a child receive ready-to-use supplementary food or fortified flours, or did children switch to RUSF or fortified flours once they reached a certain anthropometric threshold. Similarly, we did not have information on precise details of entry and exit criteria for each child, that is, admitted on the basis of low MUAC or low WHZ. The absence of children less than 6 months is a limitation to fully understanding sex differences in treatment outcomes, especially given that male vulnerability is often more pronounced in infancy. Children were required to be clinically well to be enroled in this dataset so there may be a degree of survivor or selection bias introduced as children admitted for inpatient care with the most severe presentations of wasting were not included. There may also be a possibility of survivor bias in the sample as this was not a community sample, but programme data. This sample also contained a higher number of females in three of the sites, with the exception of South Sudan. This is inconsistent with other population-based figures showing higher risk of undernutrition in males (S. Thurstans et al., 2020).

The high levels of transfers and defaulters also introduce a risk of selection bias and highlight both the challenges in cohort data and the importance of ensuring allocated funding with programmes to follow-up and fully understand reasons for transfers and defaults to ensure programme quality and accurate representation of performance indicators.

Crucially, the dataset did not contain information on potential confounders such as indicators of maternal education, care and feeding indicators, socio-economic status and the presence or absence of co-morbidities. This information would not only enable better understanding of the differences that were observed in this analysis but would also enable better understanding of the possible mechanisms underlying any differences and whether addressing behaviours would impact these differences. Future research should explore such factors including whether different admission and discharge criteria, different programmes in different geographical locations, and other potential confounders (e.g., social, economic and environmental factors, all of which impact outcomes from malnutrition) might produce different results. Research should also further explore the differences we identified in LOS and weight gain between younger and older children and girls and boys to better understand the different causes of growth failure, such as nutritional intake and feeding behaviours by age and sex and to determine if different treatment or prevention strategies are needed.

5 | CONCLUSION

These findings show few differences in wasting treatment outcomes between girls and boys and between age groups. The results do not indicate any immediate case for a change in current programme inclusion requirements or treatment protocols on the basis of sex or age. Further research should use more formal study designs and more robust methods to investigate the aetiology of any sex or age differences in recovery and implications for treatment protocols.

AUTHOR CONTRIBUTIONS

Susan Thurstans was responsible for the concept and design of the study, as well as the sourcing of data. Data was contributed by the International Rescue Committee and medicines sans Frontiers. Jeanette Bailey and Fabrizio Loddo supported in developing the data sharing agreement. Susan Thurstans led in the analysis of data with support from Charles Opondo. Susan Thurstans wrote the manuscript with contributions from all authors. All authors have read and approved the final manuscript.

ACKNOWLEDGEMENTS

We thank Médecins Sans Frontières, Paris and the International Rescue Committee, New York for their support in making access to the dataset possible; and are grateful to the LSHTM data repository for releasing the data once approvals were in place.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Susan Thurstans http://orcid.org/0000-0002-7102-446X
Andy Seal http://orcid.org/0000-0003-3656-4054
Marko Kerac http://orcid.org/0000-0002-3745-7317

REFERENCES

Andersen, G. S., Girma, T., Wells, J. C., Kæstel, P., Leventi, M., Hother, A. L., Michaelsen, K. F., & Friis, H. (2013). Body composition from birth to 6 mo of age in Ethiopian infants: Reference data obtained by air-displacement plethysmography. *The American Journal of Cinical Nutrition*. *98*(4), 885–894. https://doi.org/10.3945/ajcn.113.063032

Benjamin-Chung, J., Mertens, A., Colford, J. M., Hubbard, A. E., van der Laan, M. J., Coyle, J., & Arnold, B. F. (2020). Early childhood linear growth failure in low- and middle-income countries. https://doi.org/10.1101/2020.06.09.20127001

Chase, R. P., Kerac, M., Grant, A., Manary, M., Briend, A., Opondo, C., & Bailey, J. (2020). Acute malnutrition recovery energy requirements based on mid-upper arm circumference: Secondary analysis of feeding program data from 5 countries, combined protocol for acute malnutrition study (ComPAS) stage 1. *PLoS One*, *15*(6), e0230452. https://doi.org/10.1371/journal.pone.0230452

Costa, J. C., Blumenberg, C., & Victora, C. (2021). Growth patterns by sex and age among under-5 children from 87 low-income and middle-income countries. *BMJ Global Health*, *6*(11), e007152. https://doi.org/10.1136/bmjgh-2021-007152

Dewey, K. G., Wessells, K. R., Arnold, C. D., Prado, E. L., Abbeddou, S., Adu-Afarwuah, S., Ali, H., Arnold, B. F., Ashorn, P., Ashorn, U., Ashraf, S., Becquey, E., Bendabenda, J., Brown, K. H., Christian, P., Colford, J. M., Dulience, S. J., Fernald, L. C., Galasso, E., … Stewart, C. P. (2021). Characteristics that modify the effect of small-quantity lipid-based nutrient supplementation on child growth: An individual participant data meta-analysis of randomized controlled trials. *The American Journal of Clinical Nutrition*, *114*(Suppl. 1), 15S–42S. https://doi.org/10.1093/ajcn/nqab278

ENN. (2021). Catalysing action and accountability on the prevention, early detection, and treatment of Child Wasting. *A call to action*.

Frison, S., Checchi, F., & Kerac, M. (2015). Omitting edema measurement: How much acute malnutrition are we missing? *The American Journal of Clinical Nutrition*, *102*(5), 1176–1181. https://doi.org/10.3945/ajcn.115.108282

GNR. (2022). Global Nutrition Report. *Stronger commitments for greater action*.

Greenland, S. (2021a). Noncollapsibility, confounding, and sparse-data bias. Part 1: The oddities of odds. *Journal of Clinical Epidemiology*, *138*, 178–181. https://doi.org/10.1016/j.jclinepi.2021.06.007

Greenland, S. (2021b). Noncollapsibility, confounding, and sparse-data bias. Part 2: What should researchers make of persistent controversies about the odds ratio? *Journal of Clinical Epidemiology*, *139*, 264–268. https://doi.org/10.1016/j.jclinepi.2021.06.004

Imam, A., Hassan-Hanga, F., Sallahdeen, A., & Farouk, Z. L. (2020). A cross-sectional study of prevalence and risk factors for stunting among under-fives attending acute malnutrition treatment programmes in north-Western Nigeria: Should these programmes be adapted to also manage stunting? *International Health*, *13*, 262–271. https://doi.org/10.1093/inthealth/ihaa043

Isanaka, S., Hitchings, M. D. T., Berthé, F., Briend, A., & Grais, R. F. (2019). Linear growth faltering and the role of weight attainment: Prospective analysis of young children recovering from severe wasting in Niger. *Maternal & Child Nutrition*, *15*(4), e12817. https://doi.org/10.1111/mcn.12817

Karlsson, O., Kim, R., Guerrero, S., Hasman, A., & Subramanian, S. V. (2022). Child wasting before and after age two years: A cross-sectional study of 94 countries. *eClinicalMedicine*, *46*, 101353. https://doi.org/10.1016/j.eclinm.2022.101353

Kenya_Ministry_of_Health. (2009). *National Guideline for Integrated Management of Acute Malnutrition*.

Khara, T., Mwangome, M., Ngari, M., & Dolan, C. (2018). Children concurrently wasted and stunted: A meta-analysis of prevalence data of children 6-59 months from 84 countries. *Maternal & Child Nutrition*, *14*(2), *(no pagination)* e12516. https://doi.org/10.1111/mcn.12516

Mertens, A., Benjamin-Chung, J., Colford, J. M., Coyle, J., van der Laan, M., Hubbard, A. E., & Arnold, B. F. (2020). Causes and consequences of child growth failure in low- and middle-income countries. https://doi.org/10.1101/2020.06.09.20127100

Mertens, A., Benjamin-Chung, J., Colford, J. M., Hubbard, A. E., van der Laan, M., Coyle, J., & Arnold, B. F. (2023). Child wasting and concurrent stunting in low- and middle-income countries. *Nature*, *621*, 558–567. https://doi.org/10.1038/s41586-023-06480-z

MSF. (1995). *Nutrition Guidelines*. (1st edition).

Myatt, M., Khara, T., Schoenbuchner, S., Pietzsch, S., Dolan, C., Lelijveld, N., & Briend, A. (2018). Children who are both wasted and stunted are also underweight and have a high risk of death: A descriptive epidemiology of multiple anthropometric deficits using data from 51 countries. *Archives of Public Health*, *76*, 28. https://doi.org/10.1186/s13690-018-0277-1

Odei Obeng-Amoako, G. A., Myatt, M., Conkle, J., Muwaga, B. K., Aryeetey, R., Okwi, A. L., & Kalyango, J. N. (2020). Concurrently

wasted and stunted children 6-59 months in Karamoja, Uganda: Prevalence and case detection. *Maternal and Child Nutrition*, *16*(4), 1–11. https://doi.org/10.1111/mcn.13000

Odei Obeng-Amoako, G. A., Wamani, H., Conkle, J., Aryeetey, R., Nangendo, J., Mupere, E., Kalyango, J. N., Myatt, M., Briend, A., & Karamagi, C. A. S. (2020). Concurrently wasted and stunted 6-59 months children admitted to the outpatient therapeutic feeding programme in Karamoja, Uganda: Prevalence, characteristics, treatment outcomes and response. *PLoS One*, *15*(3), e0230480. https://doi.org/10.1371/journal.pone.0230480

Odei Obeng-Amoako, G. A., Karamagi, C. A. S., Nangendo, J., Okiring, J., Kiirya, Y., Aryeetey, R., Mupere, E., Myatt, M., Briend, A., Kalyango, J. N., & Wamani, H. (2020). Factors associated with concurrent wasting and stunting among children 6-59 months in Karamoja, Uganda. *Maternal & Child Nutrition*, *17*, e13074. https://doi.org/10.1111/mcn.13074

Olofin, I., McDonald, C. M., Ezzati, M., Flaxman, S., Black, R. E., Fawzi, W. W., Caulfield, L. E., & Danaei, G. (2013). Associations of suboptimal growth with all-cause and cause-specific mortality in children under five years: A pooled analysis of ten prospective studies. *PLoS One*, *8*(5), e64636. https://doi.org/10.1371/journal.pone.0064636

Rodríguez, G., Samper, M. P., Ventura, P., Moreno, L. A., Olivares, J. L., & Pérez-González, J. M. (2004). Gender differences in newborn subcutaneous fat distribution. *European Journal of Pediatrics*, *163*(8), 457–461. https://doi.org/10.1007/s00431-004-1468-z

Sphere Association. (2018). *The sphere handbook: Humanitarian charter and minimum standards in humanitarian response* (4th ed.). www.spherestandards.org/handbook

Sudan, G. O.S. (2009). Interim guidelines integrated management of severe acute malnutrition.

Sudan, R. O. S. (2017). Guidelines for community management of acute malnutrition.

Thurstans, S. (2022). Understanding sex differences in childhood malnutrition. *Field Exchange*, *67*, 58.

Thurstans, S., Opondo, C., Seal, A., Wells, J., Khara, T., Dolan, C., Briend, A., Myatt, M., Garenne, M., Sear, R., & Kerac, M. (2020). Boys are more likely to be undernourished than girls: A systematic review and meta- analysis of sex differences in undernutrition. *BMJ Global Health*, *5*, e004030. https://doi.org/10.1136/bmjgh-2020-004030

Thurstans, S., Wrottesley, S. V., Fenn, B., Khara, T., Bahwere, P., Berkley, J. A., Black, R. E., Boyd, E., Garenne, M., Isanaka, S., Lelijveld, N., McDonald, C. M., Mertens, A., Mwangome, M., O'Brien, K. S., Stobaugh, H., Taneja, S., West, K. P., Guerrero, S., … Myatt, M. (2022). Anthropometric deficits and the associated risk of death by age and sex in children aged 6-59 months: A meta-analysis. *Maternal & child nutrition*, *19*(1), e13431. https://doi.org/10.1111/mcn.13431

UNICEF. (2022). *UNICEF Child Alert. Severe Wasting. An overlooked child survival emergency*.

Vandenbroucke, J. P., von Elm, E., Altman, D. G., Gøtzsche, P. C., Mulrow, C. D., Pocock, S. J., Poole, C., Schlesselman, J. J., & Egger, M. (2007). Strengthening the reporting of observational studies in epidemiology (STROBE): Explanation and elaboration. *PLoS Medicine*, *4*(10), e297. https://doi.org/10.1371/journal.pmed

WHO. (2006). *The WHO child growth standards* [Online].

WHO, U. (2019). *Recommendations for data collection, analysis and reporting on anthropometric indicators in children under 5 years old*.

Yemen. Ministry of Public, H., Population. Yemen. Central Statistical, O., Pan Arab Program for Family, H., & DHS, I. C. F. I. M. (2014). *Yemen National Health and Demographic Survey 2013. Preliminary report*. Retrieved from: http://dhsprogram.com/pubs/pdf/PR50/PR50.pdf

SUPPORTING INFORMATION

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

How to cite this article: Thurstans, S., Opondo, C., Bailey, J., Stobaugh, H., Loddo, F., Wrottesley, S. V., Seal, A., Myatt, M., Briend, A., Garenne, M., Mertens, A., Wells, J., Sear, R., & Kerac, M. (2023). How age and sex affect treatment outcomes for children with severe malnutrition: A multi-country secondary data analysis. *Maternal & Child Nutrition*, e13596. https://doi.org/10.1111/mcn.13596

8 Discussion

8.1 Scope of chapter

This chapter summarises the main findings of the research presented in this thesis in relation to the objectives set. The findings will be compared with evidence generated through other research. The overall strengths and limitations will be summarised. Implications for policy and practice will then be outlined in the following chapter.

8.2 Main findings of research

Considered as a whole, the findings from this research contribute to the overall aim which was to improve the assessment and treatment of undernutrition in children aged 0-5 through improved understanding of differences between the two and exploring whether and how these might need to be addressed in prevention and treatment policy and practice.

The first objective of this PhD was to review the evidence for female/male differences in the risk of developing undernutrition, determining if there is a difference in risk between girls and boys and exploring the reasons for these. The evidence presented demonstrates that boys are more likely to be wasted, stunted and underweight than girls with some variation by age and geographical region. The evidence on why these differences occur is limited but suggestive of a complex interaction of social, environmental, physiological and genetic factors throughout the life cycle as shown in Figure 9.

Figure 10 Pathways to sex differences in undernutrition

The second objective was to review the evidence for sex differences in mortality risk associated with anthropometric deficits. This addresses some of the practical questions around what sex differences mean for practitioners. The evidence presented supports existing evidence that there is a high risk of mortality associated with wasting. Our meta-analysis further demonstrates that there is a similar mortality risk between children 6–23 months and children 24–59 months, indicating the need to include all children under 5 years in wasting treatment programmes. We did note that for underweight and stunting, younger children had a significantly higher risk of mortality than older children, suggesting that where resources are limited, prevention programmes may be justified in targeting younger children. Despite our findings showing an increased risk of wasting, stunting and underweight in males, we found no differences in mortality risk between girls and boys in both younger and older age groups in our pooled analysis (see Figure 10).

The third objective was to review the evidence for sex differences in outcomes in current wasting treatment programmes, whilst considering age and geographical location. CMAM is one of the most common means of treating wasting and so understanding if sex differences are present in treatment outcomes is essential. The evidence presented shows very few differences in treatment outcomes between girls and boys (see Figure 10), and between age groups. The results suggest that there is no need to change current program inclusion requirements or treatment protocols on the basis of sex or age, but that further research is

needed to investigate the aetiology of sex differences in recovery and implications for treatment protocols.

In summary, we found that boys were more likely to be undernourished than girls, but that there were few differences in mortality or treatment outcomes between sexes.

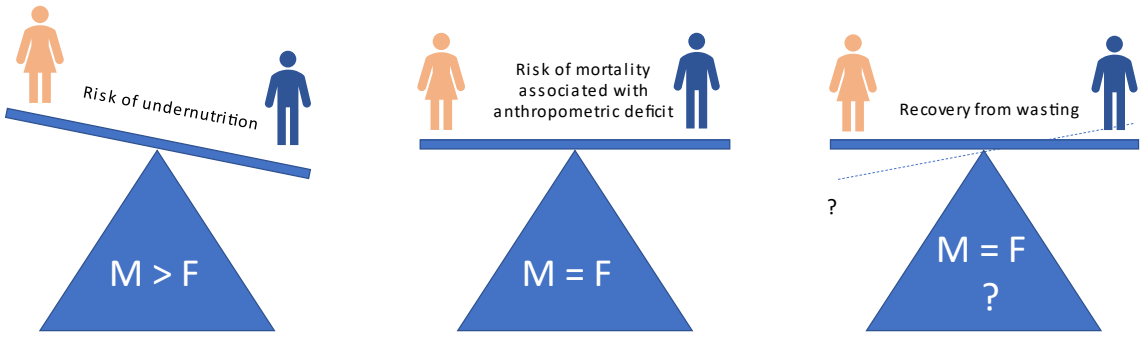


Figure 11 Summary of risk of undernutrition, mortality associated with anthropometric deficits and odds of recovery from wasting by sex

8.3 Risk of undernutrition

Our research shows that sex differences do occur in the risk of undernutrition. The ratio and direction of these differences can however vary by type of undernutrition, age, context, and region.

8.3.1 Type of undernutrition

Throughout this research, we have found that a larger body of literature exists on sex and age differences in stunting compared with wasting and underweight. Our findings therefore contribute to a growing body of evidence on stunting as well as wasting and underweight.

Our systematic review found that the biggest risk difference was for stunting whereby boys were 29% more likely to be stunted than girls, followed by wasting where boys were 26% more likely to be wasted, and then underweight where boys were 14% more likely to be affected.

A complementary paper exploring sex differences in a cohort of children from 36 African countries [59] is presented in appendix 5. In this analysis, we also found boys to be more susceptible to undernutrition compared with girls. The most pronounced differences were seen in concurrent wasting and stunting whereby boys were 29% more likely to affected and for stunting, where boys were 18% more likely to be affected. Differences were much smaller for underweight (5%) and wasting (1%), but both show boys to be at higher risk than girls. Boys heightened vulnerability to concurrent wasting and stunting has been noted elsewhere [34, 35, 60]. In our analysis, sex differences in concurrent wasting and stunting were more than the sum of sex differences for wasting and stunting alone suggesting complex layers of vulnerabilities [59].

The evidence on wasting is more inconsistent and can differ by dataset. Our systematic review showed that boys had 26% (OR1.26) higher odds of wasting compared with girls. The DHS analysis of African countries however showed a much smaller, but still statistically significant difference in sex ratios for wasting between girls and boys (OR 1.01, 95% CI 1.00–1.03, p = 0.041). This difference might be explained by heterogeneity between studies that we noted in our meta-analysis. In the DHS analysis, the sex ratio of wasting was higher than 1.0 in 60 surveys, lower than 1.0 in 68 surveys but significantly different from 1.0 in only two surveys, which could be attributed to random fluctuations. There might also be the possibility of survivor bias based on evidence of increased mortality risk for young males [61]. Further research is needed to better understand the inconsistencies observed in sex differences in wasting across studies.

8.3.2 Sex and age

Our systematic review found that the male disadvantage declined with age. In other words, as children get older, the difference in male and female risk of undernutrition becomes less pronounced and in some cases changes direction. This is consistent with recently published evidence on stunting. A meta-analysis of growth patterns by sex and age in 87 LMIC countries showed that overall boys are more stunted than girls, particularly during the first 24 months. Their pooled analysis showed that after 24 months, there was a gradual reduction in the male disadvantage which then disappeared around the age of 40 months, when growth faltering

became more common among girls than boys suggesting that the male disadvantage is most apparent in infancy and early childhood, after which point girls face a disadvantage.

Our complementary DHS analysis also supports this finding of age-related patterns. The biggest decline in heightened male risk was seen in concurrent wasting and stunting where the sex ratio declined from 1.66 at 0-5 month to 1.12 at 36-59 months. The ratio for stunting declined from 1.32 at 0-5 months to 1.16 at 36-59 months and underweight from 1.19 to 1.09. No significant change in sex ratio was seen for wasting [59]. Figure 5 shows the difference in sex ratio by 6-month intervals. The decline in male risk for concurrent wasting and stunting is most striking. Stunting also has a marked decline, whilst differences between boys and girls for underweight and wasting appear small.

The early peak in wasting and stunting is suggestive of intra-uterine origin of sex differences in nutritional deficits, supporting the idea that males are more vulnerable than females in early life [10]. Our narrative review highlights the evolution narrative that boys are more sensitive to their environment, whilst girls are more stable and resilient to environmental factors. It also considered evidence that shows in addition to increased vulnerability in males to complications such as placental insufficiency, infections, pre-eclampsia, placental abruption, and pre-term delivery [43, 44, 62], males are also more vulnerable to nutritional deficits before birth, particularly in contexts of high maternal undernutrition. Despite their larger size at birth, we reviewed evidence that suggest that males grow faster in-utero, and are more responsive to a mothers gestational diet than girls meaning they are at increased risk of becoming undernourished before birth in conditions of deprivation [63-68]. Differences in placental function between girls and boys might also explain some of these differences. Boys placentas have been shown to be less efficient and contain less reserve capacity. This is consistent with evidence looking at placental-to-birthweight ratio which has been shown to be lower in males. This means in situations where there is not a free flow of nutrients from the mother, insufficient transfer capacity of the placenta results in less reserve capacity in boys compared with girls of the same weight, resulting in intra-uterine growth restriction [36, 64].

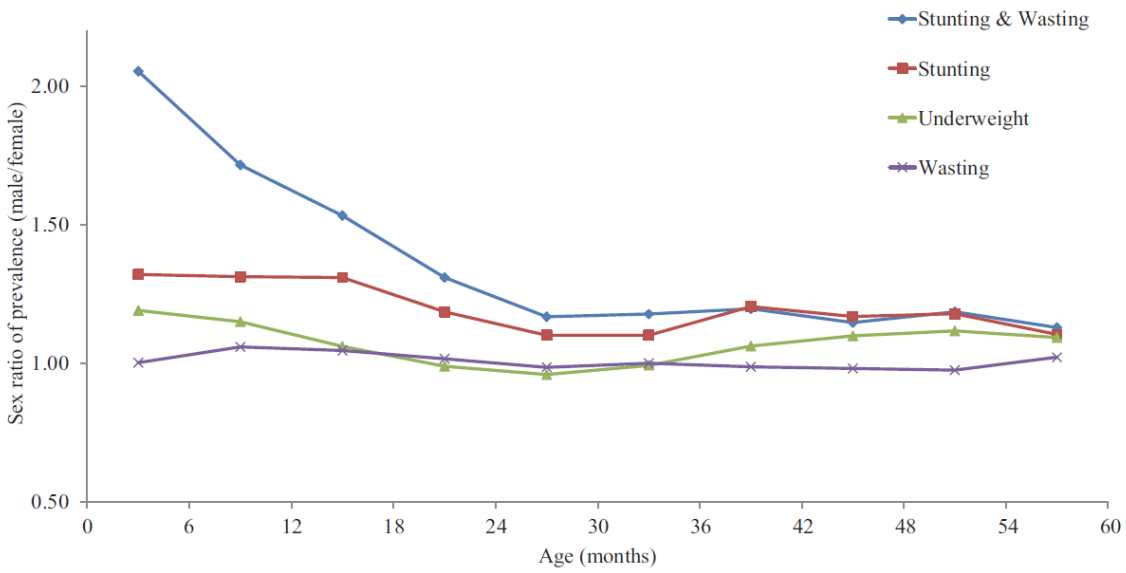


Figure 12 Sex differences in undernutrition by age for children under five in African DHS surveys (CDC-2000 reference set).

Source: Garenne, M. et al (2021) Changing sex differences in undernutrition of African children: findings from Demographic and Health Surveys [59]. CC-BY

8.3.3 Contextual and regional variations

The prevalence of wasting, stunting and underweight varies by region around the world [1]. Our systematic review indicated that the ratio and direction of sex differences might differ in some geographical regions. We found no difference in patterns for wasting between regions, the odds were consistently higher for boys than girls across all regions. For stunting and underweight however, we found that the odds were higher for boys than for girls in all regions except South Asia (stunting pooled OR 0.88, 95% CI 0.62 to 1.26, p=0.492, underweight pooled OR 0.84, 95% CI 0.52 to 1.35, p=0.475). We also found, girls to be at higher risk of underweight in Central America (OR 0.53, 95% CI 0.40 to 0.72, p<0.001), although this finding was from a single study.

Evidence published since our systematic review is consistent with our findings [13]. Figure 12 shows the association between sex and stunting incidence in a cohort of children aged 0-24 months. Boys consistently have a higher risk of stunting across regions with the exception of Asia. In Asia, cohorts from Nepal and India both show girls to have a higher risk of stunting than boys, though not significantly so.

Our narrative review explored some of the reasons for these differences in more detail, and identified that a complex interaction of care practices, gender ideals, and socio-economic factors might underlie these differences and can reduce the male advantage and/or increase the female disadvantage. Our mortality analysis also demonstrated some regional variations in Nepal and Sudan where girls have a higher risk of mortality than boys associated with some anthropometric deficits (see section 7.4). We highlight the need for further research to better understand these regional differences and which factors contribute.

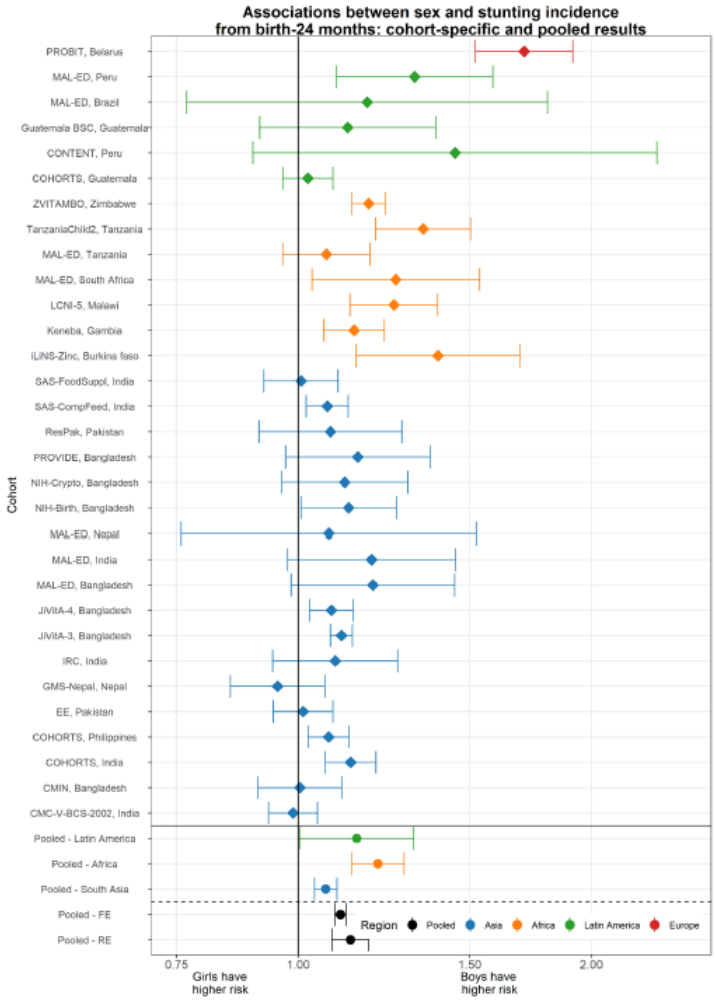


Figure 13 Associations between sex and stunting incidence from birth to 24 months: cohort specific and pooled results

Source: Benjamin-Chung, J. et al (2020) Early childhood linear growth failure in low- and middle-income countries [13]. CC-BY

8.4 Mortality risk

8.4.1 Sex differences in population level mortality trends

In circumstances where children have the same access to food and healthcare, boys tend to have higher mortality rates than girls [61]. Mortality rates differ in infancy and childhood. In infancy, girls have less vulnerability towards perinatal conditions such as birth trauma, intrauterine hypoxia and birth asphyxia, prematurity, respiratory distress syndrome and neonatal tetanus, congenital anomalies, and infectious diseases such as intestinal infections and lower respiratory infections. Beyond infancy however, this advantage lessens with infectious diseases and common causes of death in settings where mortality is high [69]. This is often referred to as the epidemiological transition (see Figure 13).

Improvements in child mortality exacerbate the male disadvantage in undernutrition as girls appear to benefit more from overall improvements in health. This also appears to be true in the case of undernutrition. In our complementary analysis of sex differences and mortality patterns , linear regression revealed increasing sex ratios with significant values ($P<0.001$) for concurrent wasting and stunting (from 1.19-1.31), stunting (1.11 to 1.23) and underweight (1.01 to 1.05), as mortality levels moved from high (300 per 1000) to low (50 per 1000) values. Sex ratios for wasting remained constant as under-five mortality levels changed.

Data from higher income countries also show this trend whereby sex difference ratios increase towards higher male mortality as health increases and under five mortality declines, suggesting that girls benefit more than boys from overall health improvements. Figure 13 shows the historical change in the sex ratio of mortality as under 5 mortality declines. This decline suggests that underlying genetic and biological differences between girls and boys are accountable for residual differences once overall health and mortality levels improve.

Whilst sex differentials in childhood mortality demonstrate a trend of more pronounced male vulnerability as the overall health picture improves, our narrative review suggests that in the case of undernutrition, male vulnerability might also be more pronounced at the opposite extreme, i.e., in fragile and conflict affected states (FCAS). We found that alongside evidence of a correlation between food insecurity and median prevalence of stunting (correlation coefficient -0.65, $p < 0.001$), there was evidence of a trend whereby the difference between male and female prevalence of stunting also increases as wealth decreases, suggesting the more fragile a context, the more pronounced the difference between boys and girls. We note that the pattern is not uniform, and would benefit from more in-depth analysis, but it does

suggest that addressing inequality in socio-economic status might also help to reduce sex differences in undernutrition. Increased sex ratios in concurrent wasting and stunting, and the high prevalence of concurrent wasting and stunting in FCAS, alongside evidence of male vulnerability and wider sex ratios in famine conditions add strength to this theory. As does a recent pooled analysis of stunting in 87 countries [70] exploring the association between GDP per capita and age and sex specific differences in mean HAZ. The early male disadvantage was shown to be more marked in low GDP countries. This suggests that the impact of suboptimal conditions in LMICs is more harmful to boys than to girls. Evidence from famine conditions as described in chapter 1 also supports the idea that the most extreme of contexts might increase the sex ratio and exacerbate male vulnerability.

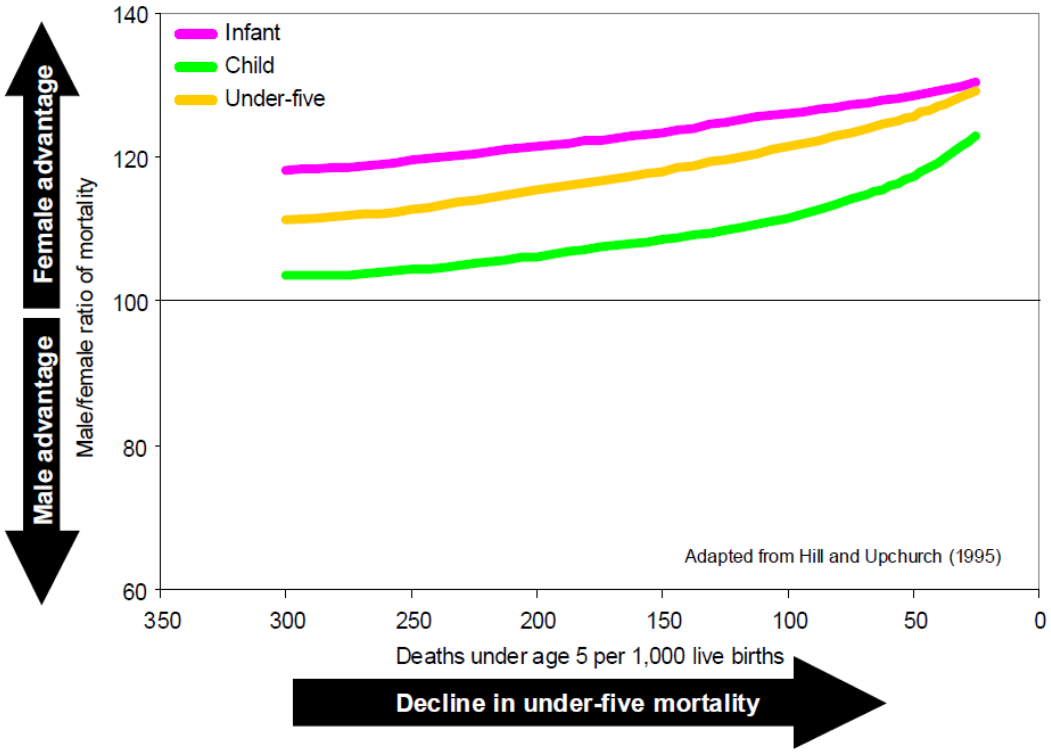


Figure 14 Historical change in the sex ratio of mortality as under-five mortality declined, selected developed countries

Source: United Nations (2011) *Sex differentials in Childhood Mortality [61].*

8.4.2 Sex differences in mortality risk associated with anthropometric deficits.

We set to determine if mortality risk associated with undernutrition is affected by sex. Our research shows that despite a higher risk of wasting, stunting and underweight in boys, once

a child becomes undernourished, their relative risk of death does not differ by sex. However, despite no difference in the relative risk of mortality between undernourished boys and girls, the higher incidence of undernutrition in boys does mean than higher numbers of boys are at risk of death compared with girls.

We did observe some small variations with significant results. The assessment of wasting measured by MUAC <125mm showed no differences between girls and boys in the risk of mortality with the exception of Nepal. Here, the relative risk of mortality was lower for younger boys compared with younger girls (RR 0.39, 95% CI 0.19–0.80, p=0.008), but higher for older boys compared with older girls (RR 2.97, 95% CI 1.02–8.60, p=0.035). Similar exceptions were seen for the younger age group when assessing wasting defined by WHZ-score in both Nepal and Sudan. Here, younger boys with WHZ <−2 had a lower absolute risk of death than younger girls with the same anthropometric deficit (Nepal - RR 0.36; 95% CI 0.18–0.75 p=0.004, and Sudan - RR 0.44; 95% CI 0.21–0.90, p=0.021 respectively).

Similar results were found for both underweight and stunting in Nepal whereby we observed a lower risk of death for boys compared with girls (Underweight WAZ <-2, RR 0.46, 95% CI 0.27–0.79, p=0.004, Stunting HAZ <-2 RR 0.56, 95% CI 0.32–0.98, p=0.038). Likewise, in Sudan, there was a lower risk of death among stunted boys than stunted girls (HAZ <−2 RR 0.51, 95% CI 0.25–0.83, p=0.008).

These findings might be a result of context specific differences as outlined in our narrative review. Evidence shows that high levels of gender inequality result in higher excess under-five female mortality [71]. Without further research however, it is difficult to speculate as to whether the differences observed in mortality risk in certain countries are a direct result of these sociological differences, or whether there are physiological differences between girls and boys that leave girls with anthropometric deficits at higher risk of mortality compared with boys.

8.4.3 Age differences in mortality risk associated with anthropometric deficits.

The evidence presented in this PhD on mortality risk associated with wasting by age is consistent with previous research , in that it demonstrates a high risk of mortality associated with child wasting. We further offer evidence that mortality risk in wasted children does not differ according to age. In other words, there is no difference in mortality risk between wasted children aged 6–23 months and wasted children aged 24–59 months. This implies that the

targeting of all wasted children under 5yrs of age is appropriate for treatment approaches aiming to achieve impact on mortality.

The large dataset used in our mortality analysis and the methods employed contribute to the strength of our evidence, but further research which considers the limitations of our own study would be beneficial to determine if similar results are replicated. This is particularly important considering some recent changes in key strategy documents from UNICEF which appear to point towards a shift in approach towards targeting wasting treatment to children under 2 years of age. Examples of this include:

- The UNICEF Nutrition strategy 2020-2030 overall refers to children under 5 but does seem to prioritise children under 2 in the result for treating wasting in early childhood: "Timely and effective detection and treatment are particularly critical for children under 2 years of age who are most vulnerable to the life-threatening consequences of wasting" [73].
- UNICEF's acceleration plan for 2022-2023, No time to waste, outlines a strategic approach to ensure that no child dies from wasting. Strategic result 4, outlines 10 innovations to prioritise to optimise and simplify treatment with the more severe forms of wasting. Innovation 1 is "Focusing early detection and treatment on children under 2 years of age" [4].
- The UNICEF child alert on severe wasting published in May 2022 states that all stakeholders should "Prioritize resources where they will save the most lives – severely wasted children under age 2" [74].

These priorities might have been informed by prevalence estimates which demonstrate higher numbers of wasted children aged under 2 compared with children 2-4 years. Karlsson et al (2022) compared prevalence estimates between children 0-2 and children 2-4 years [75]. Children under 2 were reported to have a wasting prevalence of 14% compared with 9% in children 2-4 years. Our evidence does show that younger children (under 24 months) who are stunted or underweight have a higher absolute mortality risk compared with older children (24-59 months). This finding may justify prioritising this age group where these measures are used to target nutrition interventions and where resources are limited.

8.5 Wasting treatment outcomes

We set out to determine if there are differences in wasting treatment outcomes by age and sex. Our analysis showed that there were very few differences between girls and boys in the three age categories used in all of the outcomes commonly used to measure the effectiveness of wasting treatment programmes (recovery, death, default, non-response, transfer).

Recovery is the optimal outcome following wasting treatment. Our results showed very few differences in sex and age groups with some exceptions. After controlling for potential confounders, we observed that girls were less likely to recover than boys in our pooled analysis (OR 0.84, 95%CI 0.72 to 0.97, p=0.020). We further explored this by breaking down the analysis by individual country. We found that in Kenya and South Sudan, there was no difference in the odds of recovery between girls and boys (Kenya OR 0.68, 95%CI 0.40-1.17, P=0.169, South Sudan OR 0.97, 95%CI 0.82-1.16, p=0.761). In Chad and Yemen, however, girls were less likely to recover than boys (Chad OR 0.64, 95%CI 0.41-0.99, P=0.045, Yemen, OR 0.45, 95% CI 0.26-0.79, p=0.005). Our sensitivity analysis showed that using either recovery or default as the reference group, there was no statistically significant difference in the risk of recovery death, default or non-response, between girls and boys. The differences that we did observe were specific to TFP, no differences were seen between girls and boys or different age groups for SFP. Our results are limited in their generalisability at present and further research which considers wider potential confounders is warranted.

Our study also identified that girls had a higher mean daily weight gain than boys for TFP (mean adjusted difference 0.68 g/kg/day, 95%CI 0.28-1.07, p<0.001). These variances are small, and likely explained by differences between girls and boys in lean and fat mass from birth onwards but do warrant further research into body composition and weight gain in wasting recovery.

8.6 Strengths and limitations of the research

This research has many strengths, but throughout, we recognise several limitations. Some of these have been highlighted in the relevant chapters. The following section brings those strengths and limitations together to consider what they mean for the interpretation of the overall research.

8.6.1 Strengths

One of the first strengths in this research is the choice of topic which asks a relevant question that challenges some commonly held assumptions. This is especially relevant for policy and practice as our findings contribute to a growing body of evidence in severe malnutrition, and understanding which children are most at risk and why. It also offers perspectives from other disciplines such as evolutionary biology to further understanding.

One of the strengths of our systematic review lies in the methods chosen. We followed the PRISMA guidelines for systematic reviews meaning that a methodical approach was followed for the review and meta-analysis allowing for a thorough search of the literature and covering a wide geographic area. This approach further fed into the narrative review, with an extension of inclusion criteria allowing for a more extensive review of literature to gain a better understanding of the causes of sex and age differences in undernutrition. Likewise for the cohort analyses, we adopted the STROBE guidelines allowing for consistency in our reporting.

We have used various sources of secondary data throughout this research allowing for the analysis of multi-country data, covering a wide geographic area. Our mortality analysis for example involved a unique collection of data from 12 cohorts. We were able to analyse untreated historic community cohorts with information recorded on anthropometric indices and mortality. This data also originated from multiple countries, which we pooled to create a large dataset. Mortality is a rare outcome in individual cohorts, and therefore difficult to research. The large sample sizes provided by this approach enabled us to examine mortality risk by age and sex. Similarly, our treatment analysis data originated from 4 countries and from programmes implemented by different NGOs meaning a representative sample of programme data.

Finally, our papers, have benefitted from the process of peer review during the submission process to reputable journals to determine the validity and significance of our research.

8.6.2 Limitations

Despite the strengths in this research, there are also limitations. In our systematic review screening for studies to be included was conducted by only one of the authors. While we employed systems to ensure contentious articles were discussed among two or more authors, we recognise that not using double screening is a limitation. Likewise, we recognised the bias that may have been introduced with the search strategy used (see appendix 1). The decision

to limit the search might have led to bias towards studies found a significant difference. The search might also have limited the analysis as there are potentially missed studies which include sex as a variable in analysis but without focusing on mention of sex in the study abstracts. Similarly, there may be a degree of publication bias whereby sex differences are simply not considered or reported. Despite these limitations, conducting the work that proceeded this study and having re-reviewed literature, we do not believe that our overall interpretation would change. Research that has taken place since the review also supports this with findings that are consistent with our own [10, 38, 70].

Our narrative review has several limitations. This was born to manage the large amount of literature generated through the broad search criteria used for the systematic review, and capture some of the valuable information identified through the search. Some of the literature identified did not fit within the scope of the systematic review and meta-analysis but did offer insights into the causes for sex differences, either directly related to undernutrition, or from other public health domains which could further the understanding of sex differences within undernutrition. Though the paper explored a wide range of literature, a much less formal and systematic process was followed. This means that there is a possibility that evidence was missed. Efforts were made to review the quality of evidence reviewed, but no formal critical appraisal of studies included was performed. The use of food security scores as a proxy for wealth in the analysis of stunting across countries might also be a limitation. Future analyses should explore how different indicators interact with sex differences to determine if sex differences are more or less pronounced in different socioeconomic strata's.

Whilst the use of multiple secondary data sets gives strength to this research, it also poses some limitations. One of the main limitations within this PhD is that within the mortality and treatment analyses, we did not have data on potential confounders such as, socioeconomic status, health indicators such as diarrhoea, HIV, respiratory illnesses, breastfeeding status, complementary feeding, and care practices, or seasonal indicators. This has limited our ability to explain the heterogeneity observed between studies in the mortality analysis or elucidate on contextual differences that might directly or indirectly influence the relationships between anthropometric deficits, age, sex and mortality risks and treatment outcomes. As described throughout the research, sex differences appear to be influenced by context. Despite our limitations, we have been able to make some educated assumptions and observations of patterns as to the cause of observed sex and age differences, however further research is warranted to better understand how confounding factors affect sex differences within undernutrition in difference contexts and regions.

Another limitation is the data related to MUAC. In our systematic review, we did not have data on MUAC. Similarly, within the mortality analysis, MUAC data was limited and available in only 3 of the 30 plus included countries. In our treatment analysis, we did have MUAC data but not for all children, and it was unclear from the data if admission and discharge was based on MUAC or WH/LZ score. This means a smaller sample size was available for these analyses with potentially less power to detect differences and reduced generalisability of results.

Children under 6 months of age were included in the studies presented wherever possible, but data was absent for the mortality analysis. This might have resulted in an underestimation of the impacts of anthropometric deficits in children under two. Despite this being a clear limitation given the evidence that undernutrition often occurs before 6 months and is associated with high mortality [76, 77], our findings do contribute to the evidence base for increased vulnerability before age two. They also highlight the increased vulnerability of boys in infancy and up to 2 years.

Within our treatment analysis, we used data collected between 2010-2014. Although this might be perceived as older data, the existing case definitions (i.e. 2006 WHO standards) were in use within the programmes. The treatment protocols in use during this period are also the same as those being used today to continue to treat severe malnutrition. We did not have data on cases of complicated wasting. Evidence seems to indicate that boys in poorer health are less likely to survive. It is therefore not possible be sure if a focus on children with complicated undernutrition would yield different results. Despite this, we can draw conclusions on the importance of the prevention of undernutrition in the first 1000 days regardless of sex. We were also unable to assess whether sex differences occur in the case of relapse following discharge from wasting treatment programmes.

Finally, there might have been some selection bias introduced due to loss to follow up in both the mortality and treatment datasets leading to survivor bias if deaths were higher amongst those lost to follow up. It was not possible to quantify this from the original studies in the mortality analysis [56]. This is also true for the treatment analysis. The high levels of transfers and defaulters observed in this study highlights the importance of follow up within programming to be able to truly interpret outcomes, but also infer the impact of social influences on programmes.

9 Implications and conclusions

9.1 Scope of chapter

This chapter considers both the implications for policy and practice which stem from our research. Although the findings presented go some way towards better understanding sex differences in undernutrition, the scope of this research and the limitations outlined above emphasise that questions remain. Addressing these will allow further understanding of how to interpret sex and age differences in different contexts.

9.2 Implications for understanding and preventing undernutrition

Throughout this research, our findings highlight the importance of prevention of undernutrition in all its forms and the need to address the underlying causes and determinants of undernutrition. Exposure to wasting and stunting often starts in-utero, with boy's vulnerability heightened during this period. Male sex is an independent risk factor for undernutrition; however, the influence of sex differences overall is small when compared with other factors such as birth length, birth weight, mothers' weight and height, birth order and sanitation. Mertens et al (2020) measured the population attributable fraction (PAF) of undernutrition attributable to sex and estimated that the PAF for male sex was around 4% for wasting and around 5% for stunting [10]. Whilst some of the biological pre-disposition to risk in boys is beyond the control of policy makers and programmers, evidence that risk is exacerbated in conditions of deprivation and even more so in FCAS, provides further justification to prioritise prevention efforts in a meaningful and effective way. So too does evidence that social determinants can reverse the trend in certain contexts to make girls more vulnerable. Understanding and addressing the wider determinants of undernutrition in a way that improves the overall health and nutrition is likely to impact sex differences. Future research should consider whether targeting interventions by season or population subgroups defined by sex, social indicators or maternal and childbirth characteristics might help to focus preventive interventions [10, 19].

As prevention of undernutrition from an early age is a priority, regardless of sex, addressing maternal nutrition is fundamental to breaking the cycle of undernutrition and reducing the risk of accumulating further nutrition deficits. A recent lancet series on small and vulnerable newborns highlight the effectiveness of multiple micronutrient supplementation (MMN), and

balanced protein and energy supplementation, alongside a series of interventions to support maternal and fetal health (low-dose aspirin, progesterone provided vaginally, education for smoking cessation, malaria prevention, treatment of asymptomatic bacteriuria, and treatment of syphilis), in reducing the incidence of small vulnerable newborns and associated poor outcomes [78].

What is not clear is whether interventions to prevent undernutrition need to be adapted to increase their effectiveness for the most at-risk groups. Some evidence suggests that the impact of preventative interventions might differ by sex. A meta-analysis of 14 RCTs [79] analysing the use of small quantity lipid nutrition supplement (SQ-LNS) to prevent undernutrition, found a greater effect in girls than in boys. SQ-LNS was found to reduce stunting by 16%, wasting by 21%, low MUAC by 27% and small head size by 15% in girls. For boys the reductions were smaller at 9%, 10%, 7% and 4% respectively. These differences were not explained by lower prevalence of undernutrition in the girls. When length, MUAC and head circumference were examined in units as opposed to continuous variables, mean differences were consistently greater in girls leading the authors to conclude that girls had a better growth status than boys, likely reflecting a greater potential to respond to nutritional supplementation in girls compared with boys.

Similarly, a meta-analysis [80] assessing modifiers of effect of providing maternal multiple micronutrient supplementation on stillbirth, birth outcomes, and infant mortality, found that the effect of multiple micronutrient supplementation was modified by sex. Multiple micronutrient supplementation for pregnant women led to a 15% reduction in mortality during the first year of life in females but no significant difference in mortality outcomes was observed for males. Further research is needed to better understand the mechanisms which account for the differences in response between girls and boys to supplementary interventions.

9.2.1 Implications for Social and care practices

Throughout this research, we have shown that the size and direction of sex differences vary according to different influencing factors and that these trends can be reversed or masked. As outlined in the limitations section however, further analysis is needed to better understand which factors can and do influence the risk of undernutrition by sex and age and how strong their influence is. Analysis of multi-country DHS and/or MICS data would be beneficial to assess how social indicators and feeding and care practices impact sex and age differences in different contexts. For example, countries in Asia such as Nepal and India stand out from

our analyses as having different patterns from other countries in the magnitude and direction of sex ratios, with girls often facing a disadvantage [70]. Are contextual factors responsible for this change? How much of a role do gender ideals play?

Similarly, both our mortality and treatment analyses were limited in that we could not consider confounding variables and their effect on our results. Further research should be conducted which controls for study effects (social and care practices) and allows for consideration of other potential explanatory factors including multiple anthropometric deficits alongside age and sex.

9.2.2 Pathways to sex differences in undernutrition

In addition to social, economic, behavioural and care practices, throughout this research, differences in body composition, endocrine systems, immune function, genetic disposition, environment, and maternal nutrition have been identified as potential contributary factors to sex differences in undernutrition. What is clear is that a complex interaction of these factors alongside social and behavioural determinants all contribute to sex differences. Further research is needed to better understand physiological pathways. For example, sex differences appear to be more consistent and more pronounced in stunting and concurrent wasting and stunting than in wasting alone. Does this mean that stunting accounts for more of the differences observed between boys and girls than wasting does? Further research is needed to understand how body composition and physiology contribute to differences.

9.3 Implications for malnutrition treatment programmes

9.3.1 Recognition of patterns in international and national policy & strategy

We performed a qualitative synthesis within our systematic review to assess how studies recognise, report, and explain sex differences in undernutrition. We found that sex differences are not systematically reported on and that reasons given for differences vary. 28% of studies included in our study did not provide any discussion on reported differences. Where explanations for sex differences in the prevalence of undernutrition were offered, nearly half (49%) of the studies explanations related to social reasons or were based on speculation or preconceived supposition rather than evidence.

Since this research began, our findings have often been met with different reactions. A qualitative study conducted since this research started, involving key informant interviews found that generally, stakeholders were aware of increased prevalence among males in undernutrition, but it was a surprising trend for many [81]. This is reflected in nutrition policy and strategy documents which often include a specific focus on girls. This likely stems from approaches which consider the lifecycle of undernutrition and the importance of supporting nutrition in women of reproductive age. Sex specific differences, however, are rarely a consideration. Whilst the recognition of female vulnerability linked with gender discrimination is essential, our research highlights how important it is to not to confuse gender discrimination and the negative consequences for women and girls, with sex differences. Consideration of sex differences within international nutrition policy and strategy would help improve understanding of these differences among implementors and aid in both the interpretation of programme data and planning of interventions.

9.3.2 Programme design, data collection and reporting, and research

The implications of this PhD research for front-line programmes are yet to be fully realised. But they do emphasise the need for the recognition and understanding of sex differences within nutrition policy and practice. Sex differences should also be considered in programme design alongside the national burden.

Our findings support the need for disaggregated analysis and reporting of nutrition estimates and assessment of programming outcomes by age and sex. They also support a clearer understanding of the differences between sex and gender with consideration of how data is analysed and how sex and gender should be considered as variables of importance that can explain, rather than confound research [82]. Better understanding of age and sex differences in undernutrition, at programme level and in national and regional contexts, will allow for better understanding of the determinants of undernutrition and biological, social, and economic contributors to a child's ability to grow and thrive. It will also support contextual adaptation of interventions where relevant to address differences in demographic presentations of undernutrition whilst considering biological and social factors that affect a child's risk of undernutrition.

9.3.3 Identification of undernutrition

In our narrative review we highlighted that the ways in which undernutrition is assessed has consequences for understanding how sex differences might manifest in undernutrition. Boys and girls differ in body composition with differences in fat and muscle distribution. Girls have higher levels of fat whilst boys have higher levels of muscle or lean mass. The higher energy content of fat and ability to use it for other metabolic purposes places girls at an advantage in situations of food shortages. Boys also tend to weigh more than girls. Our analysis of DHS surveys found the average weight difference between boys and girls to be around 411g, with minor variation by age [59]. Some research suggests that this indicates higher energy requirements [83]. Boys also have higher average birth weights than girls [84]. The implications of these differences for the identification of undernutrition are not fully clear.

Our narrative review highlighted the possibility that sex differences might manifest with the use of MUAC based on a single cut off. Boys are bigger than girls in absolute terms, and so the same cut off point for boys and girls might see their predisposition to thinner arms expressed. Our mortality paper included analysis of the risk of mortality associated with low MUAC by sex and age. Whilst pooled analysis showed no difference in the risk of mortality by sex in both the younger and the older age groups, an exception was noted in Nepal. Here, younger boys with MUAC <125mm had a statistically significantly lower relative risk of death than younger girls (RR 0.39, 95% CI 0.19–0.80, p=0.008), but older boys with MUAC <125mm had a higher risk of mortality than older girls with MUAC <125mm (RR 2.97, 95% CI 1.02–8.60, p=0.035). However, one of the limitations already highlighted in this analysis was that MUAC data was only available for 3 of the 12 country cohorts, another was that data was not available on potential confounders. A possible alternative to a single MUAC cut off point is the use of MUAC z-score [85]. In practice however, the simplicity of MUAC has been fundamental to its use, and the scale up of its use by families [86]. Further analysis of mortality outcomes for boys and girls using MUAC in different settings would be important to better understand risks.

WAZ is now increasingly recognised as a good indicator of increased mortality risk – in part because it captures concurrent wasting and stunting [56, 87-90]. We demonstrated no difference in the risk of mortality between underweight boys and girls. This suggests that a move towards WAZ combined with MUAC would identify both boys and girls at high risk of mortality. Further research is needed however to understand programme implications of a move towards WAZ [56, 89].

We have reviewed evidence which outlines key differences in body composition between girls and boys, and how these differences might contribute to the differences in both the risk of undernutrition and the response to wasting treatment and nutritional supplements. Evidence remains limited however and would benefit from further research. As we highlight in our narrative review, it is unclear if sex differences observed in the reference population on which the WHO 2006 standards are based are representative of sex differences in all other populations, particularly those living in situations of deprivation. In other words, do the same specific z-scores for WAZ, WHZ and HAZ in a girl or boy of the same age correspond to the same physiological impact in both sexes and the way in which the distribution of fat and fat-free mass affects this. Further research into body composition in children with anthropometric deficits would enhance understanding.

Finally, though this research did not determine if the mid-point value chosen in the development of the MOYO joint sex charts is appropriate, the evidence on differing body composition seems to suggest that joint sex charts might not account for sex differences in undernutrition and therefore single sex charts should be used until a comprehensive analysis of how body composition in boys and girls at different levels of undernutrition is conducted. The evidence on the ease of use of the MOYO format however suggests that research on the feasibility and acceptability of difference chart types is warranted. Furthermore, this should include the evaluation of easy-to-use WAZ look up charts.

9.3.4 Wasting treatment

Our treatment analysis showed few differences between boys and girls in response to wasting treatment suggesting that there is no need to change current program inclusion requirements or treatment protocols based on sex or age. Our findings and the limitations highlighted in our paper and limitations sections, however, suggest that further research is warranted to determine whether the decreased chance of recovery seen for girls in some parts of our analysis are true differences or specific to each country. Likewise, the impact of confounding variables on these outcomes should be explored.

Throughout this research, we have shown that males have a disadvantage in-utero and in early infancy compared with girls. Combined with the onset of wasting and stunting from as early as in-utero, the importance of addressing infants under six months within wasting treatment programmes is clear.

The relationship between wasting and stunting has also been a cross cutting topic throughout this research with higher incidence of concurrent wasting and stunting noted in males [34]. Concurrent wasting and stunting is associated with a high risk of mortality [35, 88] and should therefore be treated as a high priority group [19]. Wasting treatment programmes should ensure they are able to identify all children at high risk of mortality, including those who are both wasted and stunted [19, 91]. The evidence that wasted children go on to experience further episodes of wasting [92] also highlights the importance of links to prevention programming as well as the need for future research into optimised treatments that will both support linear growth and help to prevent future deficits.

Our findings show that boys with severe wasting (WH/LZ score <-3) had a lower mean daily weight gain than girls (mean adjusted difference 0.68 g/kg/day, 95%CI 0.28-1.07, p<0.001), as did boys with concurrent wasting and stunting (mean difference 0.69g/kg/day 95%CI 0.29-1.09, p=<0.001). These differences are likely explained by differences between girls and boys in lean and fat mass from birth onwards which shape sex differences in weight gain [93, 94] Future research should focus on whether this weight gain is sufficient and can be sustained through long term follow up studies involving measures of body composition. Likewise, research should explore whether there are sex differences in relapse following wasting treatment.

Finally, some of the limitations around selection bias, survivor bias, loss to follow up and the higher rates of defaulting and transfers observed in our research highlight the importance of programme evaluation and follow up after wasting treatment. Without this, both the design of treatment programmes and the interpretation of programme outcomes are compromised.

9.4 Future research recommendations

Table 3 outlines a summary of research questions identified in this chapter using an adapted version of the Child Health and Nutrition Research Initiative (CHNRI) framework for systematic listing of research ideas in health research. The CHNRI method started as an initiative of the Global Forum for Health Research in Geneva, Switzerland. Its aim was to develop a method that could assist priority setting in health research investments, and is now widely used by international organisations for setting health research priorities [95]. The framework aims to providing a solution to addressing large numbers of possible research questions through listing them by research instruments (description, delivery, development, and discovery). This results in a logical framework of research priority categories and includes different dimensions of research needs to ensure comprehensive coverage. The framework has been used in a number of research priority identification exercises within

the nutrition sector to support practitioners and future research implementation [96, 97].

Table 4 Future research questions

CHNRI category	**Research Avenue**
Description	How do social, economic, and feeding and care practices impact the epidemiology of sex and age differences in undernutrition? • Why are girls more vulnerable in some contexts? • Is heightened vulnerability in girls specific to certain countries/regions? • Which variables might account for these differences, and which have the strongest influence? • How do gender ideals impact the sex ratio in undernutrition?
	Are standardised MUAC cut off points suitable for identifying the most at-risk older children? • Analysis of mortality outcomes for boys and girls using MUAC in different settings alongside exploration of lean and fat mass gain/loss • What are the programme implications of a move towards WAZ and MUAC for girls and boys?
	Do WHO standards account for sex differences as children move away from the healthy reference population? • Is there a “normal” level of difference outside of our control? • How does body composition differ in girls and boys with anthropometric deficits (including fat mass and fat free mass)?
	Are there sex differences in relapse following wasting treatment? • If differences occur, what is the epidemiology of differences - are there age-specific and/or geographical differences?
	Are sex differences less pronounced in wasting and underweight than in stunting and concurrent wasting and stunting? • If so, what are the reasons for this?
	Are there sex differences in complicated cases of severe wasting? • Do differences appear similar to uncomplicated cases? • If differences occur, what is the epidemiology of differences - are there age-specific and/or geographical differences?

Delivery	Why do girls have a higher risk of mortality associated with anthropometric deficits compared with boys in some contexts (as seen in Nepal in our mortality review)? • Are they true differences? • Do confounding factors such as gender or social and care practices influence this? • What is the cause of increased mortality associated with anthropometric deficits in girls in some contexts
	Why do girls have a lower chance of recovery from wasting treatment in some contexts? • Are there true differences or do confounding factors influence outcomes in difference contexts?
Development	Would easy-to-use look up charts for girls and boys such as the individual sex MOYO chart reduce errors in the identification of undernutrition? • Research on the feasibility and acceptability of difference chart types at scale
Discovery	Why do girls appear to benefit more from supplementation as a means of prevention? • Which mechanisms account for the differences in response between girls and boys to supplementary interventions? • Is there a need for clinical trials on adapted MMN supplements and interventions for PLW? • Is there a need to target preventative interventions by season or population sub-groups defined by sex, social indicators or maternal characteristics?
	Can targeting maternal nutrition impact and reduce sex differences associated with poor nutrition? • What interventions to support better birth outcomes will have the most impact in reaching both male and female infants?
	Are novel treatments required that can address the different needs of boys and girls in both the prevention and management of undernutrition? • What actions could be taken to prevent early wasting and stunting in both girls and boys that will address the increased vulnerability in males in conditions of deprivation? • Are there long-term differences between girls and boys following episodes of undernutrition?

	• Is the lower weight gain seen in boys problematic, do treatments need to be optimised to promote gains in lean mass or promote linear growth?
	How do sex differences in undernutrition manifest in older children and adolescents?

9.5 Conclusion

We have demonstrated that overall, the risk of undernutrition in the form of wasting, stunting and underweight is higher among boys than girls, particularly in children under two. There are however important variations by age, region and context which affect the magnitude and direction of sex differences.

Sex differences vary according to the type of undernutrition. The biggest differences can be seen in stunting and in concurrent wasting and stunting. Overall sex differences are small in comparison with other causes of undernutrition but are exacerbated and more pronounced in more severe forms of undernutrition and in conditions of deprivation and more fragile contexts. A complex interaction of social, environmental, physiological, and genetic factors likely underlies these differences throughout the life cycle and highlights the importance of addressing the determinants of undernutrition.

Despite the differences in risk, we have demonstrated that the risk of mortality associated with anthropometric deficits does not differ by sex or age emphasising the importance of ensuring all wasted children can access effective treatment. Younger children who are stunted or underweight have a heighted risk of mortality suggesting that where resources are limited, nutrition stakeholders may be justified in targeting these age groups.

We observed very few differences in wasting treatment outcomes between sex and age groups suggesting that at present there is no need to change current program inclusion requirements or treatment protocols based on sex or age. Future research should determine if the differences in recovery outcomes observed for girls in some parts of the analysis are true differences or specific to each country, and if the results remain the same after further consideration of health and social care indicators.

Appendix 1: Supplementary materials for paper 1

Systematic review search strategy

Medline 24/6/18 (search V3.0)

1. undernutrition.mp. (5708)
2. malnutrition.mp. (39279)
3. malnutrition/ or exp fetal nutrition disorders/ or exp refeeding syndrome/ or exp severe acute malnutrition/ or exp kwashiorkor/ or exp starvation/ or exp wasting syndrome/ (25202)
4. (severe adj2 malnutrition).mp. (2131)
5. stunting.mp. (3456)
6. exp Growth Disorders/ (30538)
7. chronic malnutrition.mp. (519)
8. stunt*.mp. (6655)
9. MUAC.mp. (407)
10. mid upper arm circumference.mp. (771)
11. exp Nutritional Status/ (38539)
12. marasmus.mp. or Protein-Energy Malnutrition/ (7366)
13. famine.mp. (1726)
14. exp Starvation/ (9562)
15. (failure adj2 thrive).mp. (5307)
16. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 (123406)
17. limit 16 to ("all infant (birth to 23 months)" or "newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)") (35919)
18. (boy* or girl* or male* or female* or gender or sex).ti,ab. (177252)
19. 17 and 18 (6631)

Embase – 26/6/18 (search version 1.1)

1. undernutrition.mp. (8602)
2. malnutrition.mp. (80528)
3. fetal malnutrition/ or malnutrition/ or protein calorie malnutrition/ (62268)
4. (severe adj2 malnutrition).mp. (3655)
5. stunting.mp. (6247)
6. stunting/ or stunting syndrome/ (3015)
7. chronic malnutrition.mp. (929)
8. stunt*.mp. (10385)
9. MUAC.mp. (841)
10. mid upper arm circumference.mp. (1271)
11. nutritional status.mp. (70927
12. nutritional status/ (59492)
13. kwashiorkor/ or marasmus/ or protein calorie malnutrition/ (10572)
14. nutritional disorder/ (14398)
15. famine.mp. or hunger/ (13269)
16. starvation/ or food deprivation/ (28652)
17. failure to thrive.mp. (11731)
18. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 (202365)
19. (boy* or girl* or male* or female* or gender or sex).ti,ab. (3099115)

20. 18 and 19 (36855)
21. limit 20 to (infant or child or preschool child <1 to 6 years>) (10755)

Global health - 26/6/18

1. undernutrition.mp. (7615)
2. exp undernutrition/ (5946)
3. malnutrition.mp. (37019)
4. exp malnutrition/ (26253)
5. (severe adj2 malnutrition).mp. (2148)
6. stunting.mp. (3541)
7. chronic malnutrition.mp. (605)
8. stunt*.mp. (5173)
9. MUAC.mp. (529)
10. Mid upper arm circumference.mp. (888)
11. nutritional status.mp. (32147)
12. famine.mp. (2775)
13. exp famine/ (2140)
14. failure to thrive/ (190)
15. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 (69407)
16. (boy* or girl* or male* or female* or gender or sex).ti,ab. (495655)
17. exp infants/ (125291)
18. (Infant* or infancy or Newborn* or Baby* or Babies or Neonat* or Preterm* or Prematur* or Postmatur*).mp. (200992)
19. child.mp. (86254)
20. (Child* or Preschool* or Toddler*).mp. (391992)
21. pediatrics.mp. (5669)
22. (Paediatric* or Peadiatric*).mp. (20373)
23. 17 or 18 or 19 or 20 or 21 or 22 (511719)
24. 15 and 16 and 23 (8316)

Cochrane library

#1	undernutrition:ti,ab,kw (Word variations have been searched)	300
#2	malnutrition:ti,ab,kw (Word variations have been searched)	2983
#3	stunting:ti,ab,kw (Word variations have been searched)	493
#4	"growth disorders":ti,ab,kw (Word variations have been searched)	762
#5	"nutritional status":ti,ab,kw (Word variations have been searched)	4701
#6	MUAC:ti,ab,kw (Word variations have been searched)	90
#7	"Mid upper arm circumference":ti,ab,kw (Word variations have been searched)	159
#8	marasmus:ti,ab,kw (Word variations have been searched)	25
#9	kwashiorkor:ti,ab,kw (Word variations have been searched)	84
#10	famine:ti,ab,kw (Word variations have been searched)	13
#11	starvation:ti,ab,kw (Word variations have been searched)	204
#12	failure to thrive:ti,ab,kw (Word variations have been searched)	149

Popline
Additional grey literature via ENN database

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	20,21
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	20,21
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	20
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	29
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	31
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	33
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	34

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Appendix 2: Supplementary materials for paper 3

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
United Kingdom
Switchboard: +44 (0)20 7636 8636

www.lshtm.ac.uk

Observational / Interventions Research Ethics Committee

Ms Susan Fuller
LSHTM

3 March 2021

Dear Ms Susan Fuller

Study Title: Evaluation of age, sex and anthropometric case definitions in children 6-59 months and associated risk of mortality: A secondary data analysis

LSHTM Ethics Ref: 22958

Thank you for your application for the above research project which has now been considered by the Observational Committee via Chair's Action.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved is as follows:

Document Type	File Name	Date	Version
Other	Research_Ethics_online_training_certificate_ST		
Investigator CV	Susan_Thurstans CV 2019	22/09/2019	1
Investigator CV	CV Briend 2019	27/10/2019	1
Protocol / Proposal	Extended-Mortality analysis-SOW to SWG (002)	13/12/2020	1
Local Approval	Author permissions (MMCA)-contacts removed	01/02/2021	1
Investigator CV	MarkMyattCV	07/02/2021	1
Investigator CV	CV + Pubs_Marko Kerac_final	07/02/2021	1
Local Approval	ENN Support Letter_ST	21/02/2021	1

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study.

At the end of the study, the CI or delegate must notify the committee using the End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk.

Further information is available at: www.lshtm.ac.uk/ethics.

Yours sincerely,

Professor Jimmy Whitworth
Chair

ethics@lshtm.ac.uk

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4-5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*4-5*
Bias	9	Describe any efforts to address potential sources of bias	5-6
Study size	10	Explain how the study size was arrived at	4-5

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4-5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4-6
		(*b*) Describe any methods used to examine subgroups and interactions	4-6
		(*c*) Explain how missing data were addressed	4-5
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7 and figure 1
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	7 and figure 1
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*8*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*NA*
		Cross-sectional study—Report numbers of outcome events or summary measures	*NA*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-9 and results tables/figures
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7-9

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7-9
Discussion			
Key results	18	Summarise key results with reference to study objectives	10-11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11-12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	See funding statement

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Appendix 3: Supplementary materials for paper 4

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
United Kingdom
Switchboard: +44 (0)20 7636 8636

www.lshtm.ac.uk

Observational / Interventions Research Ethics Committee

Ms Susan Fuller
LSHTM

15 December 2021

Dear Ms Susan Fuller

Study Title: Secondary analysis of sex differences in treatment outcomes following treatment for severe malnutrition

LSHTM Ethics Ref: 26401

Thank you for your application for the above research project which has now been considered by the Observational Committee via Chair's Action.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved is as follows:

Document Type	File Name	Date	Version
Local Approval	ComPAS stage 1 ETHICS final	13/12/2016	1
Other	Research_Ethics_online_training_certificate_ST	07/11/2021	1
Protocol / Proposal	Data management plan_sex diferences treatment analysis	07/11/2021	1
Investigator CV	Susan Thurstans CV Nov 21	07/11/2021	1
Investigator CV	CV - Marko Kerac_final2	07/11/2021	1
Other	Research_Ethics_online_training_certificate_KERAC	07/11/2021	1
Protocol / Proposal	Sex Diffs treatment analysis concept paper	08/11/2021	1

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study.

At the end of the study, the CI or delegate must notify the committee using the End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk.

Further information is available at: www.lshtm.ac.uk/ethics.

Yours sincerely,

Professor Jimmy Whitworth
Chair

ethics@lshtm.ac.uk

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2
Objectives	3	State specific objectives, including any prespecified hypotheses	2
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-5
Bias	9	Describe any efforts to address potential sources of bias	5-6
Study size	10	Explain how the study size was arrived at	

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5-6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	5
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	5
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7 and figure 1
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	7 and figure 1
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*7*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*NA*
		Cross-sectional study—Report numbers of outcome events or summary measures	*NA*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-9 and tables
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7-9

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7-9
Discussion			
Key results	18	Summarise key results with reference to study objectives	10-11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11-12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	See funding statement

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Supplementary table 1a. Association between recovery and age and sex within subgroups of TFP and SFP by individual country.

	TFP					SFP				
Country	No	OR (95% CI)	p value	Adjusted OR (95% CI)*	p value	No	OR (95% CI)	p value	Adjusted OR (95% CI)*	p value
Kenya										
Male	150/184	REF		REF		359/542	REF		REF	
Female	173/219	0.88 (0.53-1.44)	0.602	0.66 (0.39-1.13)	0.130	397/631	0.86 (0.68-1.10)	0.236	0.81 (0.64-1.05)	0.109
6-23	229/304	REF		REF		413/624	REF		REF	
24-59	95/99	7.78 (2.77-21.87)	<0.001	10.03 (3.45-29.15)	<0.001	343/549	0.85 (0.67-1.08)	0.186	0.91 (0.70-1.18)	0.476
Chad										
Male	227/270	REF		REF		521/619	REF		REF	
Female	285/360	0.72 (0.48-1.09)	0.119	0.61 (0.39-0.95)	0.030	637/741	1.15 (0.85-1.55)	0.354	0.69 (0.47-1.00)	0.053
6-23	401/491	REF		REF		916/1082	REF		REF	
24-59	111/139	0.89 (0.55-1.43)	0.629	1.00 (0.61-1.64)	0.997	242/278	1.22 (0.83-1.79)	0.318	1.61 (1.07-2.42)	0.022
Yemen										
Male	88/122	REF		REF		190/345	REF		REF	
Female	112/182	0.62 (0.38-1.01)	0.057	0.47 (0.27-0.81)	0.006	229/397	1.11 (0.83-1.49)	0.475	1.38 (1.00-1.91)	0.052
6-23	117/181	REF		REF		203/361	REF		REF	
24-59	83/123	1.14 (0.70-1.84)	0.609	1.15 (0.70-1.92)	0.573	216/381	1.02 (0.76-1.36)	0.899	0.90 (0.66-1.22)	0.498
South Sudan										
Male	766/1217	REF		REF		No SFP programme				
Female	722/1100	1.12 (0.95-1.33)	0.177	0.96 (0.81-1.15)	0.703					
6-23	1051/1623	REF		REF						
24-59	437/694	0.93 (0.77-1.11)	0.411	0.90 (0.74-1.11)	0.325					

This table represents results from 5 sets of logistic regression models; ORs represent the likelihood of recovery compared with all other outcomes for each country

*adjusted for sex, age, HAZ at baseline and WHZ at baseline.

Supplementary table 1b. Association between recovery and age and sex within subgroups of children who are wasted and stunted (WaSt) or have WAZ <-3 by individual country.

	WaSt					WAZ <-3				
Country	No	OR (95% CI)	p value	Adjusted OR (95% CI)*	p value	No	OR (95% CI)	p value	Adjusted OR (95% CI)*	p value
Kenya										
Male	102/150	REF		REF		177/258	REF		REF	
Female	68/114	0.70 (0.42-1.56)	0.161	0.65 (0.38-1.09)	0.103	140/212	0.89 (0.60-1.31)	0.555	0.83 (0.56-1.25)	0.375
6-23	89/113	REF		REF		158/231	REF		REF	
24-59	81/131	0.80 (0.48-1.33)	0.389	0.79 (0.47-1.34)	0.390	159/239	0.92 (0.62-1.35)	0.665	0.99 (0.67-1.48)	0.375
Chad										
Male	521/628	REF		REF		548/668	REF		REF	
Female	398/498	0.82 (0.60-1.11)	0.191	0.72 (-0.52-0.98)	0.036	492/595	1.05 (0.78-1.40)	0.761	0.90 (0.66-1.22)	0.486
6-23	677/831	REF		REF		771/937	REF		REF	
24-59	242/295	1.04 (0.74-1.47)	0.829	1.19 (0.84-1.70)	0.330	269/326	1.02 (0.73-1.42)	0.925	1.15 (0.82-1.62)	0.413
Yemen										
Male	121/201	REF		REF		139/215	REF		REF	
Female	77/133	0.91 (0.58-1.42)	0.675	0.90 (0.57-1.42)	0.660	95/165	0.87 (0.56-1.33)	0.508	0.83 (0.54-1.29)	0.415
6-23	81/150	REF		REF		115/180	REF		REF	
24-59	117/184	1.49 (0.96-2.31)	0.077	1.55 (0.99-2.43)	0.054	119/190	0.95 (0.62-1.45)	0.802	0.96 (0.62-1.49)	0.867
South Sudan										
Male	329/538	REF		REF		561/940	REF		REF	
Female	268/415	1.16 (0.89-1.51)	0.279	1.01 (0.76-1.33)	0.956	491/769	1.10 (0.98-1.45)	0.078	1.06 (0.86-1.30)	0.600
6-23	324/516	REF		REF		691/1119	REF		REF	
24-59	273/437	0.99 (0.76-1.28)	0.919	0.95 (0.71-1.25)	0.704	361/590	0.98 (0.80-1.20)	0.819	0.87 (0.69-1.09)	0.223

This table represents results from 5 sets of logistic regression models; ORs represent the likelihood of recovery compared with all other outcomes for each country

*adjusted for sex, age, HAZ at baseline and WHZ at baseline,

Supplementary table 2. Multinomial analysis to assess the association between treatment outcomes and sex within TFP.

	Crude			Adjusted		
	RR (95%CI) Female vs male (reference)	Standard Error	P value	RR (95%CI) Female vs male (reference)	Standard Error	P value
Death	REF			REF		
Recovered	4.21 (0.47-3769)	4.71	0.199	2.46 (0.27-22.84)	2.80	0.428
Default	3.80 (0.42-34.20)	4.26	0.233	2.73 (0.29-25.37)	3.11	0.377
Transfer	4.71 (0.52-42.60)	5.29	0.168	3.46 (0.37-32.39)	3.95	0.276
Non-response	4.31 (0.46-40.22)	4.91	0.200	3.46 (0.36-33.34)	4.00	0.282
Recovered	REF					
Death	0.24 (0.03-2.13)	0.27	0.199	0.41 (0.04-3.76)	0.46	0.428
Default	0.90 (0.77-1.07)	0.08	0.231	1.11 (0.93-1.32)	0.10	0.245
Transfer	1.12 (0.88-1.42)	0.14	0.352	1.41 (1.10-1.80)	0.18	0.007
Non-response	1.02 (0.66-1.59)	0.23	0.917	1.41 (0.89-2.22)	0.33	0.145
Default	REF					
Recovered	1.11 (0.94-1.30)	0.09	0.231	0.90 (0.76-1.07)	0.08	0.245
Death	0.26 (0.03-2.36)	0.29	0.233	0.37 (0.04-3.40)	0.42	0.377
Transfer	1.24 (0.95-1.62)	0.17	0.117	1.27 (0.96-1.67)	0.18	0.091
Non-response	1.13 (0.71-1.79)	0.27	0.597	1.27 (0.79-2.03)	0.31	0.325

Table shows the crude and adjusted odds of females reaching each outcome over the baseline outcome compared with males in TFP.

Appendix 4: Contributions of the candidate to research presented in this thesis.

Table 5 contributions of the candidate to research presented in this thesis.

Thesis component	Activities performed	Responsible	Additional contributors
Background and rationale	Conceptualisation and writing	Susan Thurstans	
	Review	Susan Thurstans	Marko Kerac and Rebecca Sear
Research, objectives and structure	Conceptualisation and writing	Susan Thurstans	
	Review	Susan Thurstans	Marko Kerac and Rebecca Sear
Boys are more likely to be undernourished than girls: a systematic review and meta-analysis of sex differences in undernutrition	Conceptualisation	Susan Thurstans	
	Literature search, screening, data extraction	Susan Thurstans	
	Data Analysis	Susan Thurstans	Charles Opondo
	Drafting of manuscript	Susan Thurstans	Charles Opondo
	Review of draft, review of peer review feedback and approval of final manuscript	Susan Thurstans	Charles Opondo, Andrew Seal, Jonathan Wells, Tanya Khara, Carmel Dolan, André Briend, Mark Myatt, Michel Garenne, Rebecca Sear, Marko Kerac
Understanding Sex Differences in Childhood Undernutrition: A Narrative Review	Conceptualisation	Susan Thurstans	Rebecca Sear and Marko Kerac
	Analysis of data for figure	Susan Thurstans, Charles Opondo	
	Drafting of manuscript	Susan Thurstans	
	Review of draft, review of peer review feedback and approval of final manuscript	Susan Thurstans	Charles Opondo, Andrew Seal, Jonathan Wells, Tanya Khara, Carmel Dolan, André Briend, Mark Myatt, Michel Garenne, Andrew Mertens, Rebecca Sear, Marko Kerac
Anthropometric deficits and the associated risk of death by age and sex in children aged 6–59 months: A meta-analysis	Conceptualisation of research	Susan Thurstans, Tanya Khara, Mark Myatt and Andre Briend	Stephanie Wrottesley, Bridget Fenn
	Study design	Susan Thurstans, Martha Mwangome, André Briend, Tanya Khara, Stephanie Wrottesley and Bridget Fenn	

	Data contribution	Michel Garenne, Christine McDonald, Robert Black, Keith West, and Sunita Taneja	
	Data Analysis and interpretation	Stephanie Wrottesley, Bridget Fenn, Susan Thurstans	Tanya Khara, Mark Myatt and Andre Briend
	Drafting of manuscript	Susan Thurstans	Tanya Khara, Mark Myatt and Andre Briend, Stephanie Wrottesley, Bridget Fenn
	Review of draft, review of peer review feedback and approval of final manuscript	Susan Thurstans	Stephanie Wrottesley, Bridget Fenn, Tanya Khara, Paluku Bahwere, James Berkley, Robert Black, Erin Boyd, Michel Garenne, Sheila Isanaka, Natasha Lelijveld, Christine McDonald, Andrew Mertens, Martha Mwangome, Kieran S. O'Brien, Heather Stobaugh, Sunita Taneja, Keith West, Saul Guerrero, Marko Kerac, André Briend, Mark Myatt
Treatment paper	Conceptualisation	Susan Thurstans	
	Data contribution	Jeanette Bailey, Heather Stobaugh, Fabrizio Loddo	
	Data Analysis and interpretation	Susan Thurstans	Charles Opondo
	Review of draft, review of peer review feedback and approval of final manuscript		Susan Thurstans, Charles Opondo, Jeanette Bailey, Heather Stobaugh, Fabrizio Loddo, Stephanie V Wrottesley, Andy Seal, Mark Myatt, André Briend, Michel Garenne, Andrew Mertens, Jonathan wells, Rebecca Sear, Marko Kerac
Discussion	Conceptualisation and writing	Susan Thurstans	
	Review	Susan Thurstans	Marko Kerac and Rebecca Sear
Research priorities	Conceptualisation and writing	Susan Thurstans	
	Review	Susan Thurstans	Marko Kerac and Rebecca Sear
The relationship between wasting and stunting in young children: A systematic review	Conceptualisation	Susan Thurstans, Carmel Dolan, Tanya Khara	
	Search strategy design	Susan Thurstans	Tanya Khara, Carmel Dolan, Kate Sadler, Bernardette Cichon, Sheila Isanaka, Dominique Roberfroid, Heather Stobaugh, Patrick Webb
	Paper selection	Susan Thurstans, Natalie Sessions	Tanya Khara

	Drafting of manuscript	Susan Thurstans	Natalie Sessions, Tanya Khara
	Review of draft, review of peer review feedback and approval of final manuscript	Susan Thurstans, Natalie Sessions, Tanya Khara	Carmel Dolan, Kate Sadler, Bernardette Cichon, Sheila Isanaka, Dominique Roberfroid, Heather Stobaugh, Patrick Webb
Changing sex differences in undernutrition of African children: findings from Demographic and Health Surveys	Conceptualisation and writing	Michel Garenne	
	Analysis of data	Michel Garenne	
	Drafting of manuscript	Michel Garenne	
	Review of draft, review of peer review feedback and approval of final manuscript	Michel Garenne	Susan Thurstans, André Briend, Carmel Dolan, Tanya Khara, Mark Myatt, Andrew Seal, Jonathan Wells
Perceptions of male female differences in malnutrition and implications for field assessment of anthropometry: A qualitative study	Conceptualisation and writing	Muzna Mughal	Susan Thurstans
	Analysis of data	Muzna Mughal	
	Drafting of manuscript	Muzna Mughal	Susan Thurstans
	Review of project	Muzna Mughal	Susan Thurstans

Appendix 5: Changing sex differences in undernutrition of African children: findings from Demographic and Health Surveys

Scope of chapter

This appendix presents a complimentary research paper entitled “Changing sex differences in undernutrition of African children: findings from Demographic and Health Surveys”. The paper describes an analysis of 128 DHS surveys from across Africa exploring sex differences in the prevalence of wasting, stunting, underweight and concurrent wasting and stunting, and the relationship with age and mortality. This research was led by Michel Garenne with contributions from myself throughout the process.

The findings demonstrate a higher susceptibility to wasting, stunting and underweight in boys compared with girls, and shows that sex ratios of prevalence vary by age and type of undernutrition. Sex ratios of prevalence were found to increase with declining level of mortality for stunting, underweight and concurrent wasting and stunting, but remained stable for wasting. The paper was published in the Journal of Biosocial Science 2021.

List of figures

List of tables

Table 3: The effect of maternal multiple micronutrient supplements on low birthweight, preterm birth, small-for-gestational-age birth, and large-for-gestational-age birth, stratified by potential effect modifiers

Citation

Garenne M, Thurstans S, Briend A, Dolan C, Khara T, Myatt M, Seal A, and Wells JC. Changing sex differences in undernutrition of African children: findings from Demographic and Health Surveys. Journal of Biosocial Science. https://doi.org/10.1017/S0021932021000468

Research paper

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT

T: +44 (0)20 7299 4646
F: +44 (0)20 7299 4656
www.lshtm.ac.uk

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	1802701	**Title**	Mrs
First Name(s)	Susan		
Surname/Family Name	Thurstans		
Thesis Title	Sex differences in risk and outcomes from severe malnutrition: implications for management		
Primary Supervisor	Dr Marko Kerac		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	Journal of Biosocial Science		
When was the work published?	July 2021		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	**No**	Was the work subject to academic peer review?	**Yes**

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	**Submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	This paper was the result of discussion following paper 1 and paper 2 of my research. Michel Garenne designed the study, conducted the statistical analysis and wrote the first draft. Myself and other authors contributed significantly through discussions, comments and supporting references during the writing process. All authors agreed with the final version.

SECTION E

Student Signature	[redacted]
Date	

Supervisor Signature	
Date	

Journal of Biosocial Science (2021), page 1 of 11
doi:10.1017/S0021932021000468

CAMBRIDGE UNIVERSITY PRESS

RESEARCH ARTICLE

Changing sex differences in undernutrition of African children: findings from Demographic and Health Surveys

Michel Garenne[1,2,3]*, Susan Thurstans[4], André Briend[5,6], Carmel Dolan[7], Tanya Khara[8], Mark Myatt[9], Andrew Seal[10] and Jonathan C. Wells[10]

[1]Institut de Recherche pour le Développement (IRD), UMI Résiliences, Bondy, France, [2]MRC/Wits Rural Public Health and Health Transitions Research Unit, School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa, [3]Senior Fellow, FERDI, Université d'Auvergne, Clermont-Ferrand, France, [4]Department of Population Health, London School of Hygiene and Tropical Medicine, London, UK, [5]School of Medicine, Centre for Child Health Research, Tampere University, Tampere, Finland, [6]Department of Nutrition, Exercise and Sports, University of Copenhagen, Copenhagen, Denmark, [7]Nutrition for Development (N4D), London, UK, [8]Emergency Nutrition Network, Oxford, UK, [9]Brixton Health, Llwyngwril, Gwynedd, Wales, UK and [10]Population, Policy and Practice Research and Teaching Department, UCL Great Ormond Street, Institute for Child Health, London, UK
***Corresponding author.** Email: Michel.Garenne@ird.fr

(Received 3 February 2021; revised 13 July 2021; accepted 13 July 2021)

Abstract

The study investigates sex differences in the prevalence of undernutrition in sub-Saharan Africa. Undernutrition was defined by *Z*-scores using the CDC-2000 growth charts. Some 128 Demographic and Health Surveys (DHS) were analysed, totalling 700,114 children under-five. The results revealed a higher susceptibility of boys to undernutrition. Male-to-female ratios of prevalence averaged 1.18 for stunting (height-for-age *Z*-score <−2.0); 1.01 for wasting (weight-for-height *Z*-score <−2.0); 1.05 for underweight (weight-for-age *Z*-score <−2.0); and 1.29 for concurrent wasting and stunting (weight-for-height and height-for-age *Z*-scores <−2.0). Sex ratios of prevalence varied with age for stunting and concurrent wasting and stunting, with higher values for children age 0–23 months and lower values for children age 24–59 months. Sex ratios of prevalence tended to increase with declining level of mortality for stunting, underweight and concurrent wasting and stunting, but remained stable for wasting. Comparisons were made with other anthropometric reference sets (NCHS-1977 and WHO-2006), and the results were found to differ somewhat from those obtained with CDC-2000. Possible rationales for these patterns are discussed.

Keywords: Undernutrition; Sex differences; Sub-Saharan Africa

Introduction

Sex differences in health status are complex and evolve with the health transition, i.e. with declining mortality. For instance, in France women tend to live longer than men, and the difference between female and male life expectancy increased from +1.5 years in 1820–1849 to +8.2 years in 1980–1989, to decline in recent years to +6.0 years in 2015–2019 (INSEE, 2020). Sex differences in mortality differ by age and by causes of death, and these differences evolve with the health transition (Stolnitz, 1956; Preston, 1976). These observations also apply to morbidity and mortality of children under-five (age 0–59 months): sex differences in mortality vary with age, with level of mortality in the population and with pathology or causes of death (Preston, 1976; Garenne & Lafon, 1998; Garenne, 2003). The excess male mortality in the neonatal and post-neonatal period is universal, in both developed and developing countries, and is usually more pronounced

than excess male mortality at age 1–4 years (Preston, 1976; Wells, 2000; Garenne, 2003). Sex differences in under-five mortality remain small compared with socioeconomic differentials. In model life tables for developing countries, the sex ratio of under-five death rates averaged 1.08 at moderate level of mortality (122 per 1000 for males, 113 per 1000 for females) (United Nations, 1982). In African Demographic and Health Surveys (DHS) surveys, the sex ratio of under-five mortality averaged 1.11 (136 per 1000 for males, 122 per 1000 for females) (DHS, 2020).

Sex differences are also found in undernutrition of children in low- and middle-income countries, which could be expected because there is a positive correlation between prevalence of undernutrition and child mortality at country level, and because undernutrition is a risk factor for child mortality at the individual level (Pelletier, 1994; Garenne *et al.*, 2000, 2006, 2018). Most studies conducted in developing countries show a higher prevalence of undernutrition among boys than among girls, especially for stunting, with the exception of the Indian subcontinent (Wamani *et al.*, 2007; Schoenbuchner *et al.*, 2019). In a recent meta-analysis of studies of children under-five across the world, stunting was more prevalent among boys in 32/38 studies (84%), wasting in 17/20 studies (85%) and underweight in 18/23 studies (78%) (Thurstans *et al.*, 2020). In published data from African DHS surveys, the prevalence of undernutrition was almost always higher for boys than for girls: 134/137 surveys for stunting, 115/136 surveys for wasting and 119/136 surveys for underweight (DHS, 2020).

The aim of this study was to analyse the evidence of sex differences in undernutrition of children in sub-Saharan Africa. Undernutrition was defined by anthropometric deficits in weight, height or both, as commonly done in population-based surveys (other definitions of undernutrition are used in clinical studies). This continent hosts populations with higher levels of undernutrition and higher levels of child mortality, although with major improvements in the past 50 years. This study focused on different manifestations of undernutrition (wasting, stunting, underweight), on age patterns and on relationships with levels of mortality. An earlier analysis of a smaller data set found only small sex differences in the proportion of children underweight (Garenne, 2003). The present article builds on previous work by considering the effect of declining under-five mortality, and by addressing the possibility of concurrent stunting and wasting – a dual deficit largely ignored until recently (Khara *et al.*, 2018; Myatt *et al.*, 2018).

Methods

This study was based on all DHS surveys conducted in sub-Saharan Africa with information on child anthropometry available in early 2020, covering the period 1986–2017. The DHS surveys are based on large, representative, stratified samples of national populations. Anthropometric assessment of under-five children is done by well-trained fieldworkers and with state of the art equipment. All details of the survey methods can be found in the country reports. All calculations were done by using the sampling weights provided by the DHS programme. Individual data were retrieved from the DHS website, and pooled together. This sample included 128 surveys from 36 countries, and 700,114 children under-five – a very large sample allowing for multiple comparisons. The sample covered a wide variety of situations in terms of prevalence of undernutrition. According to DHS publications, based on the WHO/MGRS-2006 standard, the range of prevalence of undernutrition was wide in Africa: from 16.5% to 60.4% for stunting; from 1.6% to 26.9% for wasting; and from 5.4% to 44.2% for underweight (DHS, 2020). The sex ratios of prevalence of undernutrition (ratio of male-to-female prevalence) were always higher than 1 or equal to 1 across surveys. The sex ratio of prevalence averaged 1.13 for stunting, 1.17 for wasting and 1.15 for underweight, showing overall a higher susceptibility of boys. In the same sample, there was also a wide range of under-five mortality levels, ranging from 50 to 318 deaths per 1000 in the five years

preceding the survey. The sex ratio of under-five mortality was of similar magnitude, and on average equal to 1.13 (DHS, 2020).

The method of analysis for this study was a straightforward statistical analysis of the prevalence of undernutrition by sex among children under-five. This study utilized classic definitions of undernutrition, according to Waterlow's classification (Waterlow, 1972; Waterlow *et al.,* 1977): 'wasting' as weight-for-height *Z*-score: WHZ<−2.0; 'stunting' as height-for-age *Z*-score: HAZ<−2.0; 'underweight' as weight-for-age *Z*-score: WAZ<−2.0; 'concurrent wasting and stunting' as WH*Z* & HAZ <−2.0. The anthropometric norms utilized for this study were the CDC-2000 growth charts (CDC, 2000; Kuczmarski *et al.,* 2000, 2002; Ogden *et al.,* 2002). This reference set was selected because it was found to be more consistent in defining wasting and stunting than other reference sets, as will be seen in this study. Also, the difference between boys' and girls' anthropometry (weight and height) was more pronounced (average difference of 0.550 kg for weight and 1.41 cm for height), and was stable with age between 12 and 59 months, as is the case in real life. The DHS surveys use other reference sets, in particular the DHS/NCHS-1976 reference set and the WHO/MGRS-2006 standard (Hamill *et al.,* 1979; World Health Organization, 2006). These other reference sets were used for comparisons, as they produce different sex differences. Sex differences in the prevalence of undernutrition were computed as the ratio of prevalence of malnutrition for males to that for females (labelled 'sex ratio of prevalence'). They were analysed as a function of the level of mortality, measured by the under-five mortality rate, labelled '$q(5)$', and by 6-months age groups. The level of mortality was that published in the DHS final reports and refers to the five years before survey, which reflects the mortality situation of cohorts aged 0–4 years at the time of the anthropometric assessment. Statistical testing of differences in sex ratios was done using classic statistical tests for risk ratios. The relationship of sex differences with level of mortality was tested with a linear-logistic regression model.

Results

The sample included a total of 700,114 children under five years from 128 surveys of 36 African countries. All surveys were based on representative samples of national populations at various points in time, ranging from 1986 to 2017. Selected countries had an average of 3.5 surveys, ranging from 1 to 9, the highest being Senegal, which has been conducting 'continuous DHS surveys' every year since 2013. Survey results were consistent and showed an excess male susceptibility to stunting and concurrent wasting and stunting (sex ratio of prevalence >1), and hardly any significant difference in wasting prevalence between boys and girls (Table 1).

Sex differences by type of undernutrition

For the sample as a whole, boys were more susceptible to undernutrition than girls. The sex ratio of prevalence (male/female) of stunting was 1.182 (95% CI = 1.172–1.192, $p<10^{-6}$), that of wasting was 1.012 (95% CI = 1.001–1.025, $p = 0.041$), that of underweight was 1.050 (95% CI = 1.041–1.059, $p<10^{-6}$) and that of concurrent wasting and stunting was 1.286 (95% CI = 1.258–1.316, $p<10^{-6}$). Seen in a broad perspective, differences between boys and girls were rather small: hardly significant for wasting (+1%), very small for underweight (+5%), small for stunting (+18%) and moderate for concurrent wasting and stunting (+29%). When studied by survey, the results were quite homogeneous: stunting was always more prevalent among boys (128 surveys), and the sex ratio was significantly higher than 1.0 in 105 surveys; the sex ratio of wasting was higher than 1.0 in 60 surveys, lower than 1.0 in the other 68 surveys but significantly different from 1.0 in only two surveys, which could be attributed to random fluctuations; the sex ratio of underweight was higher than 1.0 in 94 surveys, lower than 1.0 in 34 surveys, significantly higher than 1.0 in 23 surveys and never significantly lower than 1.0; the sex ratio of concurrent wasting and stunting was higher than 1.0 in 112 surveys, lower than 1.0 in 12 surveys, significantly higher than 1.0 in 52 surveys

Table 1. Sex ratio of undernutrition prevalence for African countries

Country	No. of surveys	No. of children	Sex ratio of prevalence (M/F)			
			Stunting	Wasting	Underweight	Wasting+ Stunting
Angola	1	7692	1.199	1.142	1.037	1.657
Benin	4	33,594	1.166	1.076	1.171	1.428
Burkina Faso	4	24,236	1.178	0.998	1.040	1.276
Burundi	3	11,957	1.194	0.985	1.016	1.318
Cameroon	4	21,411	1.192	1.052	1.004	1.392
Central African Rep.	1	2346	1.160	0.977	1.090	1.046
Chad	3	21,233	1.121	1.025	1.049	1.209
Comoros	2	3848	1.158	0.956	1.063	0.949
Congo, Dem. Rep.	2	12,978	1.196	1.143	1.106	1.500
Congo, Rep.	2	8983	1.284	0.945	1.070	1.690
Cote d'Ivoire	3	8838	1.178	1.076	1.043	1.418
Ethiopia	4	33,869	1.126	1.038	1.034	1.256
Gabon	2	7750	1.238	0.975	1.035	1.364
Gambia	1	3630	1.169	1.008	1.030	1.396
Ghana	6	15,587	1.257	0.890	1.013	1.150
Guinea	3	10,902	1.196	1.021	1.002	1.386
Kenya	5	41,000	1.260	0.976	1.104	1.328
Lesotho	3	6083	1.294	0.888	1.035	1.073
Liberia	2	9355	1.195	1.012	1.051	1.325
Madagascar	3	11,769	1.207	1.077	1.086	1.415
Malawi	5	32,698	1.184	0.942	1.047	1.217
Mali	5	33,967	1.131	0.997	1.038	1.210
Mozambique	3	22,189	1.185	0.946	1.047	1.234
Namibia	4	14,607	1.225	0.950	1.052	1.098
Niger	4	18,017	1.160	0.971	1.004	1.220
Nigeria	5	61,800	1.145	1.018	1.056	1.326
Rwanda	5	23,029	1.180	1.024	1.019	1.162
Sao Tome & Principe	1	1790	1.019	0.975	1.072	1.610
Senegal	9	51,730	1.225	1.000	1.027	1.329
Sierra Leone	2	8240	1.150	1.065	1.105	1.370
Swaziland	1	2866	1.381	1.298	1.077	0.788
Tanzania	6	39,871	1.189	1.020	1.027	1.182
Togo	3	8882	1.222	0.906	0.984	1.132
Uganda	6	24,669	1.240	1.009	1.047	1.439
Zambia	5	35,121	1.167	1.003	1.050	1.280
Zimbabwe	6	23,577	1.261	0.996	1.004	1.145

Table 2. Sex ratio of undernutrition prevalence by selected characteristics, African DHS surveys (pooled sample of children aged 0–59 months; CDC-2000 reference set)

	No. of children	Sex ratio of undernutrition			
		Stunting	Wasting	Underweight	Wasting & Stunting
Total	700,114	1.182*	1.012	1.050*	1.286*
Age group					
0–5	75,760	1.320*	1.002	1.190*	1.668*
6–17	161,017	1.311*	1.051*	1.094*	1.515*
18–35	211,713	1.127*	1.000	0.979*	1.178*
36–59	251,624	1.167*	0.989	1.091*	1.120*
Level of mortality					
High (>150)	269,137	1.156*	0.989	1.040*	1.266*
Medium (100–149)	209,002	1.187*	1.000	1.059*	1.279*
Low (<100)	221,975	1.208*	1.051	1.054*	1.324*

Sex ratio=prevalence among boys/prevalence among girls; testing sex ratio <>1: *$p<0.05$.

and never significantly lower than 1.0. When analysed by country, the sex ratio was always higher than 1.0 for stunting, underweight and concurrent wasting and stunting; for wasting it was higher than 1.0 in eighteen countries and lower than 1.0 in eighteen countries, none of these differences being statistically significant (Table 2).

Age pattern

As found in all studies, the prevalence of undernutrition varied with age, and this also applied to sex differences. The sex ratio of prevalence tended to decline with age in three out of four types of undernutrition. For stunting it declined from 1.320 at age 0–5 months to 1.167 at age 36–59 months; for wasting there was no significant change; for underweight the sex ratio of prevalence declined from 1.190 to 1.091; and the largest decline was found for concurrent wasting and stunting, ranging from 1.669 at age 0–5 months to 1.120 at age 36–59 months (Table 2). When plotted by 6-month age groups, the patterns were found to be quite regular and stable. The most striking pattern was that of concurrent wasting and stunting, the sex ratio of which declined markedly from 0–5 months to 24–29 months, then stabilized at lower levels. The decline in the sex ratio of stunting with age was also noticeable, and followed a similar pattern stabilizing at older ages. In comparison, differences in sex ratios of wasting and underweight by age were small (Figure 1).

Relationship with level of mortality

As is the case for the sex ratio of under-five mortality, the sex ratio of undernutrition prevalence tended to increase when the mortality level was declining, revealing an increasing advantage for girls when the health situation improved. The sex ratio for stunting increased from 1.156 to 1.208 when the mortality level went from high values ($q(5)>150$ per 1000) to low values ($q(5)<100$ per 1000). Likewise, the sex ratio for concurrent wasting and stunting increased from 1.266 to 1.324, that of underweight from 1.040 to 1.054 and that of wasting from 0.989 to 1.051. A linear regression on the sex ratio was run on the level of under-five mortality. In three cases (stunting, underweight, concurrent wasting and stunting) trends were statistically significant at $p<0.001$, while there was no significant difference for wasting. The magnitude of changes in the sex ratios of prevalence from high levels of mortality (300 per 1000) to low levels (50 per 1000) were striking:

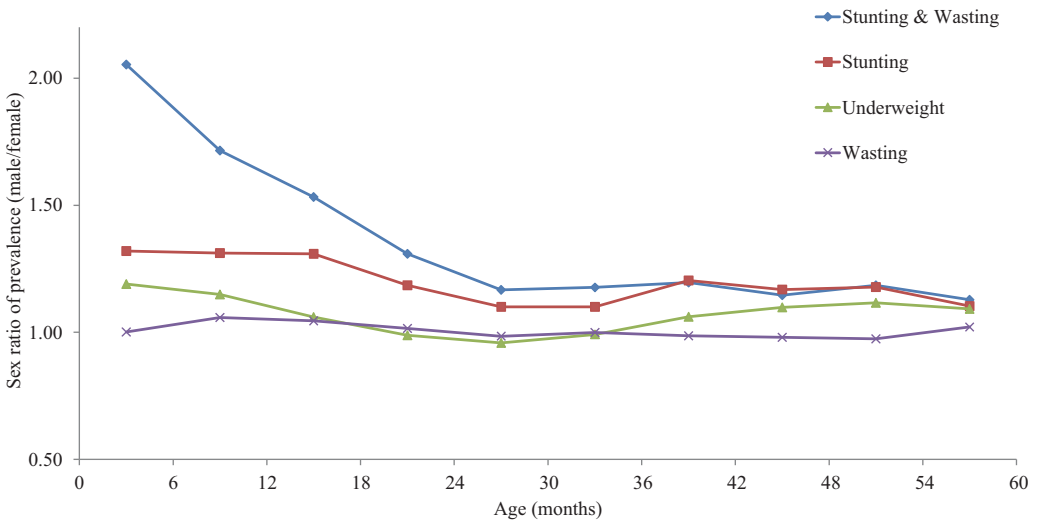


Figure 1. Sex differences in undernutrition by age for children under-five, African DHS surveys, CDC-2000 reference set.

+10.5% for concurrent wasting and stunting (from 1.193 to 1.318), +10.5% for stunting (from 1.114 to 1.231), +4.6% for underweight (from 1.012 to 1.059) but none for wasting, which averaged 1.0 (Table 3).

Effect of the anthropometric reference set

Comparison of sex differences in prevalence of undernutrition between the three anthropometric reference sets could be done on a sub-sample of 340,552 children available in the DHS files with both NCHS-1977 and WHO-2006 – about half of the original sample. Firstly, there were large differences in prevalence of undernutrition according to the reference set – a difference widely noticed earlier (Eckhardt & Adair, 2002; De Onis *et al.*, 2007). In the sub-sample, the prevalence of stunting for both sexes ranged from 26.1% with CDC-2000, 29.5% with NCHS-1977 and 34.5% with WHO-2006. The prevalence of wasting ranged from 15.3% with CDC-2000, 7.7% with NCHS-1977 and 8.6% with WHO-2006. The prevalence of underweight ranged from 27.9% with CDC-2000, 23.2% with NCHS-1977 and 18.8% with WHO-2006. Lastly, the prevalence of concurrent wasting and stunting ranged from 3.8% with CDC-2000, 2.1% with NCHS-1977 and 2.7% with WHO-2006. In brief, the WHO-2006 standard expected the children to be taller and lighter than CDC-2000 (Table 4).

The sex ratios of prevalence of undernutrition were also affected by the reference set. The sex ratio of stunting prevalence was 1.208 with CDC-2000, 1.096 with NCHS-1977 and 1.155 with WHO-2006. The sex ratio of wasting prevalence was 1.000 with CDC-2000, 1.152 with NCHS-1977 and 1.211 with WHO-2006. The sex ratio of underweight prevalence was 1.050 with CDC-2000, 1.061 with NCHS-1977 and 1.163 with WHO-2006. Lastly, the sex ratio of concurrent wasting and stunting prevalence was 1.308 with CDC-2000, 1.428 with NCHS-1977 and 1.652 with WHO-2006. Therefore, the appreciation of sex differences in undernutrition was seriously affected by the choice of the reference set. In particular, using WHO-2006 indicated that boys were more susceptible to wasting than girls, while using CDC-2000 showed no difference in wasting between boys and girls (Table 4).

Table 3. Relationship between sex ratio of undernutrition prevalence and level of under-five mortality, African DHS surveys, pooled sample (fitted by log-linear regression)

	Sex ratio of undernutrition				
	Stunting	Wasting	Underweight	Wasting & Stunting	Sex ratio of under-five mortality
Regression parameters					
Log-slope	−0.00040	+0.00002	−0.00018	−0.00040	−0.0052
p-value	$<10^{-6}$ *	0.857 ns	$<10^{-6}$ *	$<10^{-6}$ *	$<10^{-6}$ *
Estimates of sex ratios by level of $q(5)$					
300	1.114	1.001	1.012	1.193	1.036
250	1.137	1.001	1.021	1.217	1.063
200	1.160	1.001	1.031	1.241	1.091
150	1.183	1.001	1.040	1.266	1.119
100	1.207	1.001	1.049	1.292	1.148
50	1.231	1.001	1.059	1.318	1.178

Testing slope $<>0$; *$p < 0.05$; ns, not significant; $q(5)$ = under-five mortality per 1000.

Table 4. Prevalence and sex ratio of undernutrition according to anthropometric reference set, African DHS surveys (pooled sample, $N = 3{,}400{,}552$ children aged 0–59 months)

Anthropometric reference set	Stunting HAZ<−2.0	Wasting WHZ<−2.0	Underweight WAZ<−2.0	Wasting & Stunting HAZ, WHZ<−2.0
Prevalence				
CDC-2000	26.1%	15.3%	27.9%	3.8%
DHS/NCHS-1977	29.5%	7.7%	23.2%	2.1%
WHO/MGRS-2006	34.5%	8.6%	18.8%	2.7%
Sex ratio				
CDC-2000	1.208	1.000	1.050	1.308
DHS/NCHS-1977	1.096	1.152	1.061	1.428
WHO/MGRS-2006	1.155	1.211	1.163	1.652

Discussion

This study from Africa confirmed the higher susceptibility of boys to undernutrition. The results from this study, based on representative samples of African child populations, were consistent with those of a recent meta-analysis of smaller surveys all over the world: similar values of the sex ratios and similar differences between stunting and wasting (Thurstans *et al.*, 2020). In particular, in this large sample, there was no evidence of a higher prevalence of undernutrition among girls. When it occurred in a particular country or in a survey, the difference could be explained by random fluctuations (Garenne, 2003).

Altogether, sex differences in the prevalence of undernutrition appeared small compared with other differentials, such as socioeconomic differentials. In the sample of African DHS, the differentials in underweight prevalence between lowest and highest wealth quintile averaged 2.8-fold,

and occasionally exceeded 4.0-fold (9% of surveys) – that is 20 to 40 times larger than sex differences (DHS, 2020).

Sex differences varied by type of malnutrition, and this was found whatever the reference set used. The largest differentials were found in concurrent wasting and stunting, followed by differentials in stunting. Sex differences in concurrent wasting and stunting were more than the sum of sex differences in each component, revealing complex layers of vulnerabilities. The age pattern of stunting and concurrent wasting and stunting, with greatest sex differences found in the early ages, suggests that these conditions could originate, at least in part, in intra-uterine growth restriction. As such, they could be related with prematurity or other intra-uterine pathology, which could be risk factors for stunting later in life, and more severe for boys than for girls.

The pattern observed for wasting showed hardly any difference between boys and girls, except in the 6–17 months age group, where prevalence of wasting was highest. Furthermore, the sex difference in wasting prevalence did not change with declining level of mortality. This could be due to similar metabolic responses to nutrition and infection stress between boys and girls. Being underweight is due to stunting, wasting or a combination of both, so that sex differences in underweight fall in between those of the underlying conditions.

The overall prevalence of undernutrition declined in tandem with decreasing mortality in the population, but the sex differences of undernutrition increased with declining mortality, as has been observed for sex differences in mortality. This latter fact has also been noted in Europe. For instance in Sweden, the sex differences in under-five mortality increased from 7.3% in the 1750s to 32.1% in the 1960s when under-five mortality declined from 327 to 17 per 1000 over the same period of time. Similar trends in sex differences in under-five mortality were observed in France from the 1810s (8.4%) to the 1980s (31.8%), as well as in England & Wales from the 1840s (11.9%) to the 1970s (28.5%) (Human Mortality Database, 2020). This shows that girls tend to benefit more than boys from health improvements, at least to a certain point (trends in sex differences in under-five mortality were reversed after 1980 in England & Wales, France and Sweden).

Sex differences in the prevalence of undernutrition appear complex: they differ with the type of undernutrition, with age and with level of mortality. Theories could be proposed to explain these patterns, separately for stunting and wasting. They refer to differences between boys and girls in energy requirements, body composition, susceptibility to infectious diseases, hormonal systems and intra-uterine development. Stunting is seen here as an adaptation to difficult situations, where the body tries to maintain the balance between weight and height by reserving ponderal growth whilst limiting linear growth. Wasting is seen here as a response to stress, due to infectious diseases, food deficit or both.

With respect to nutritional status, boys and girls differ first in weight. In the sample of African DHS surveys, the average weight difference between boys and girls was 411 g, with only minor variations with age (475 g at 6–17 months, 414 g at 18–35 month, 360 g at 36–59 months). Therefore boys require more energy for maintenance and for growth, since there is no difference in energy requirements between boys and girls when controlling for weight (Butte *et al.,* 2000). As a result, in food-scarce situations, and assuming no sex difference in food allocation, boys seem more likely to become malnourished. Secondly, boys and girls differ in body composition: boys have more muscle (bigger lean mass) and girls have more fat. Muscle has a lower energy content than fat, and has a higher cost of maintenance. In contrast, fat is easier to break down and to be converted for other metabolic purposes. This could explain why girls resist better food shortage (as shown also in famine situations), and therefore sex differences in wasting. This difference could also contribute to smaller sex differences in mortality in high-mortality situations, because low muscle mass (as measured by arm circumference) is a major risk factor for child survival (Briend *et al.* 1989; Garenne *et al.,* 2006).

With respect to infectious diseases, the argument refers to the 'synergistic effect of malnutrition and infection', a concept introduced by Nevin Scrimshaw and colleagues some 50 years ago

(Scrimshaw *et al.,* 1968; Scrimshaw & San-Giovanni, 1997; Scrimshaw, 2003). At the individual level, the more infected a child, the more malnourished the child is likely to become, and the higher the risk of death; and conversely, the more malnourished a child is, the higher the susceptibility to infection and the risk of death. Since boys and girls appear to differ in their susceptibility to infectious diseases (Garenne & Lafon, 1998), one could expect differences in undernutrition, differences in age pattern, as well as changing differentials with progress in the health transition. In particular, in high-mortality populations, diseases known to be more deleterious to girls (measles, whooping cough, tuberculosis, streptococcal infections, etc.) are important causes of morbidity, undernutrition and mortality (Garenne & Lafon, 1998). They tend to disappear with improving disease control, providing a comparative advantage to girls.

Boys and girls also differ in endocrinal systems. Linear growth, determining stunting, is largely determined by hormonal dynamics, which are modulated by food intake, infectious diseases and interferences with the immune system, in particular inflammation (Morgan *et al.,* 2011; Briend *et al.,* 2015; DeBoer *et al.,* 2017; Millward, 2017). As a consequence linear growth may differ between boys and girls, and the balance is likely to change with the control of infectious and parasitic diseases. Although the precise mechanisms remain poorly documented, one could at least hypothesize that differences in hormonal systems could contribute to the sex differences in stunting described here.

Lastly, intrauterine life seems to also play a role. Many studies have shown how intra-uterine development shapes the health of young children, with a strong influence until at least age 24 months (Eriksson *et al.,* 2010; Alur, 2019). Male and female fetuses differ in intra-uterine growth from the first weeks of pregnancy, and they respond differently to the same intrauterine environment (Alur, 2019). Levels of growth hormones (Leptin; Insulin-like Growth Factor-1, or IGF-1; IGF binding protein-3, or IGFBP-3) are higher in females than in males (Alur, 2019). The male fetus has been shown to be at greater risk for a variety of conditions originating in the intrauterine period, and in particular for prematurity and intra-uterine growth retardation (Wells, 2000; Kraemer, 2000). These differences could explain the high sex ratios observed for stunting and concurrent wasting and stunting in early life.

The influence of the anthropometric reference set for assessing sex differences was an unexpected finding of this study. Although the main pattern remained, in particular the universal higher susceptibility of boys to undernutrition, different reference sets could lead to different conclusions, notably concerning wasting. The CDC-2000 growth charts are based on a sample of the American population – a heterogeneous population in terms of ethnic composition and socioeconomic status. In contrast, the WHO/MGRS-2006 sample is more selective: even if it included children from various countries, it selected very healthy and exclusively breastfed children, and tended to exclude many outstanding cases. In a sense, the CDC-2000 growth charts represent more of an average heterogeneous population in a developed country with low mortality, while the WHO/MGRS-2006 standards represent more of an 'ideal type' population in favoured socioeconomic conditions in various parts of the world. In addition, exclusive breastfeeding tends to promote linear growth, and to produce taller and thinner children (Martin *et al.,* 2002). What the best reference set is to be used for comparisons of such nature remains a matter of debate. In the Niakhar, Senegal study, both reference sets were used to screen for children at risk of death, and in this case CDC-2000 performed slightly better than WHO/MGRS-2006 in terms of sensitivity and specificity. Another positive feature of CDC-2000 is that the prevalences of stunting and underweight are usually consistent, while they differ widely with WHO-2006. In fact, when children have a low height-for-age, they are expected to also have a low weight-for-age, unless they are overweight. For instance, in the sub-sample used for the comparison, WHO/MGRS-2006 gave a prevalence of stunting of 34.5% and a prevalence of underweight of only 18.8%, which is hard to reconcile, while CDC-2000 gave more consistent values (26.1% and 27.9% respectively).

In conclusion, sex differences in undernutrition are small in Africa (as elsewhere in the world), and they are not fixed: they vary with age, and with level of mortality. Boys appear to have a higher

susceptibility to undernutrition, which is driven by a range of complex factors evolving over time. In particular, girls seem to benefit more from the health transition than boys, as is the case for general mortality. However, recent trends in Europe show a reversal, with smaller sex differences in under-five mortality and in life expectancy. Whether or not sex differences in Africa will also follow this pattern remains to be determined.

Acknowledgments. This study was supported by Institut Pasteur, Paris, France and IRD, Paris, France, without any external grant. The authors thank the DHS programme and the National Statistical Institutes for providing free access to survey data.

Funding. This research received no specific grant from any funding agency, commercial entity or not-for-profit organization.

Conflicts of Interest. The authors have no conflicts of interest to declare.

Ethical Approval. This research was conducted in accord with prevailing ethical principles. Data used for the study are publicly available in open access.

Author Contributions. The paper was the result of intensive discussion in the group, following work by MG, ST, AB and others on the same issue. MG conducted the statistical analysis and wrote the first draft. All authors contributed significantly through arguments, comments and references during the writing process. All authors agreed with the final version.

References

Alur P (2019) Sex differences in nutrition, growth, and metabolism in preterm infants. *Frontiers in Pediatrics* **7**, 22.

Briend A, Garenne M, Maire B, Fontaine O and Dieng K (1989) Nutritional status, age and survival: the muscle mass hypothesis. *European Journal of Clinical Nutrition* **43**(10), 715–726.

Briend A, Khara K and Dolan C (2015) Wasting and stunting – similarities and differences: policy and programmatic implications. *Food and Nutrition Bulletin* **36**(1), S15–S23.

Butte NF, Wong WW, Hopkinson JM, Heinz CJ, Mehta NR and Smith EO (2000) Energy requirements derived from total energy expenditure and energy deposition during the first 2 y of life. *American Journal of Clinical Nutrition* **72**(6), 1558–1569.

Centers for Disease Control (CDC) (2000) CDC Growth charts for the United States: methods and development. *CDC Series Report 11*, No. 246.

DeBoer MD, Scharf RJ, Leite AM, Férrer A, Havt A, Pinkerton R *et al.* (2017) Systemic inflammation, growth factors, and linear growth in the setting of infection and malnutrition. *Nutrition* **33**, 248–253.

De Onis M, Garza C, Onyango AW and Borghi E (2007) Comparison of the WHO child growth standards and the CDC-2000 growth charts. *Journal of Nutrition* **137**, 144–148.

Demographic and Health Surveys (DHS) (2020) URL: https://www.statcompiler.com/ (accessed 16th January 2020).

Eckhardt CL and Adair LS (2002) Differences in stunting prevalences calculated from two similar growth references may be large and inconsistent in undernourished children. *Annals of Human Biology* **29**(5), 566–578.

Eriksson JG, Kajantie E, Osmond C, Thornburg K and Barker DJ (2010) Boys live dangerously in the womb. *American Journal of Human Biology* **22**(3), 330–355.

Garenne M (2003) Sex differences in health indicators among children in African DHS surveys. *Journal of Biosocial Science* **35**(4), 601–614.

Garenne M and Lafon M (1998) Sexist diseases. *Perspectives in Biology and Medicine* **41**(2), 176–189.

Garenne M, Maire B, Fontaine O and Briend A (2006) Distributions of mortality risk attributable to low nutritional status in Niakhar, Senegal. *Journal of Nutrition* **136**, 2893–2900.

Garenne M, Maire B, Fontaine O, Dieng K and Briend A (2000) Risques de décès associés à différents états nutritionnels chez l'enfant d'âge préscolaire. *Etudes du CEPED* No. 17.

Garenne M, Myatt M, Khara T, Dolan C and Briend A (2018) Concurrent wasting and stunting among under-five children in Niakhar, Senegal. *Maternal and Child Nutrition* **15**(2), e12736.

Hamill PW, Drizd TA, Johnson CL, Reed RB, Rocher AF and Moore WM (1979) Physical growth: National Center for Health Statistics percentiles. *American Journal of Clinical Nutrition* **32**, 607–629.

Human Mortality Database (2020) *Human Mortality Database*. University of California, Berkeley, USA, and Max Planck Institute for Demographic Research, Germany. URL: www.mortality.org or www.humanmortality.de (accessed 1st October 2020).

INSEE (2020) URL: https://www.insee.fr/fr/statistiques/ (accessed 20th January 2020).

Khara T, Mwangome M, Ngari M and Dolan C (2018) Children concurrently wasted and stunted: a meta-analysis of prevalence data of children 6–59 months from 84 countries. *Maternal and Child Nutrition* **14**, e12516

Kraemer S (2000) The fragile male. *British Medical Journal* **321**, 1609–1612.

Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, Flegal KM, Guo SS, Wei R *et al.* (2000) CDC Growth Charts: United States. *Advanced Data* **314**, 1–27.

Kuczmarski RJ, Ogden CL, Guo SS, Grummer-Strawn LM, Flegal KM, Mei Z *et al.* (2002) 2000 CDC Growth Charts for the United States: methods and development. *Vital Health Statistics* **246**, 1–190.

Martin RM, Davey Smith G, Mangtani P, Frankel S and Gunnell D (2002) Association between breast feeding and growth: the Boyd-Orr cohort study. *Archives of Diseases in Childhood: Fetal and Neonatal Edition* **87**, F193–F201.

Millward DJ (2017) Nutrition, infection and stunting: the roles of deficiencies of individual nutrients and foods, and of inflammation, as determinants of reduced linear growth of children. *Nutrition Research Review* **30**(1), 50–72.

Morgan K, Dennis NA, Ruffman T, Bilkey DK and McLennan IS (2011) The stature of boys is inversely correlated to the levels of their Sertoli cell hormones: do the testes restrain the maturation of boys? *PLoS One* **6**(6), e20533.

Myatt M, Khara T, Schoenbuchner S, Pietzsch S, Dolan C, Lelijveld N and Briend A (2018) Children who are both wasted and stunted are also underweight and have a high risk of death: a descriptive epidemiology of multiple anthropometric deficits using data from 51 countries. *Archives of Public Health* **6**(28), 1–11.

Ogden CL, Kuczmarski RJ, Flegal KM, Mei Z, Guo SS, Wei R *et al.* (2002) Centres for Disease Control and Prevention 2000 growth charts for the United States: improvements to the 1977 National Center for Health Statistics version. *Pediatrics* **109**(1), 45–60.

Pelletier DL (1994) The relationship between child anthropometry and mortality in developing countries: implications for policy, programs and future research. *Journal of Nutrition* **124**(10), 2047S–2081S.

Preston SH (1976) *Mortality Patterns in National Populations, with Special Reference to Recorded Causes of Death*. Academic Press, New York.

Schoenbuchner SM, Dolan C, Mwangome M, Hall A, Richard SA, Wells JC *et al.* (2019) The relationship between wasting and stunting: a retrospective cohort analysis of longitudinal data in Gambian children from 1976 to 2016. *American Journal of Clinical Nutrition* **110**(2), 498–507.

Scrimshaw NS (2003) Historical concepts of interactions, synergism and antagonism between nutrition and infection. *Journal of Nutrition* **133**, 316S–321S.

Scrimshaw NS and San-Giovanni JP (1997) Synergism of nutrition, infection, and immunity: an overview. *American Journal of Clinical Nutrition* **66**(2), 464S–477S.

Scrimshaw NS, Taylor CE, Gordon JE, Everett J and World Health Organization (1968) *Interactions of Nutrition and Infection. A Report Prepared in Consultation with Seventeen Specialists in Various Countries*. WHO, Geneva. URL: https://apps.who.int/iris/handle/10665/41782 (accessed 15th January 2020).

Stolnitz G (1956) A century of international mortality trends: II. *Population Studies* **10**(1), 17–42.

Thurstans S, Opondo C, Seal A, Wells JC, Khara T, Dolan C *et al.* (2020) Boys are more likely to be undernourished than girls: a systematic review and meta-analysis of sex differences in undernutrition. *BMJ Global Health* **5**(12), e004030.

United Nations (1982) *Model Life Tables for Developing Countries*. United Nations, New York, Sales No. E.81.XIII.7.

Wamani H, Åstrøm AN, Peterson S, Tumwine JK and Tylleskär T (2007) Boys are more stunted than girls in sub-Saharan Africa: a meta-analysis of 16 demographic and health surveys. *BMC Pediatrics* **7**(17), 10.

Waterlow JC (1972) Classification and definition of protein-calorie malnutrition. *British Medical Journal* **3**, 566–569.

Waterlow JC, Buzina R, Keller W, Lane JM, Nichaman MZ *et al.* (1977). The presentation and use of height and weight data for comparing the nutritional status of groups of children under the age of 10 years. *Bulletin of the World Health Organization* **55**(4), 489–498.

Wells JC (2000) Natural selection and sex differences in morbidity and mortality in early life. *Journal of Theoretical Biology* **202**(1), 65–76.

World Health Organization (2006) *WHO Child Growth Standards: Length/height-for-age, weight-for-age, weight for length/height, and body mass index-for-age. Methods and Development*. WHO, Geneva.

Cite this article: Garenne M, Thurstans S, Briend A, Dolan C, Khara T, Myatt M, Seal A, and Wells JC. Changing sex differences in undernutrition of African children: findings from Demographic and Health Surveys. *Journal of Biosocial Science*. https://doi.org/10.1017/S0021932021000468

Appendix 6: Wasting and Stunting systematic review

Scope of chapter

This appendix presents a complimentary research paper entitled “The relationship between wasting and stunting in young children: A systematic review”. The paper describes a systematic review of evidence for the relationship between wasting and stunting and the implications of this relationship for improving child nutrition, health and survival. This study was led by myself as part of the wider ENN wasting and stunting project. It complements the research in this thesis as a cross cutting area of interest.

The findings show that a significant proportion of wasting and stunting is present at birth, and contributes to further growth failure during subsequent infancy and childhood. There is a causal relationship between the two conditions whereby periods of wasting leave a child more likely to experience stunting and, to a lesser extent, vice versa. Concurrently wasted and stunted children are at increased risk of dying and should be considered a high-risk group for the targeting of treatment. In the targeting of treatment, a combination of weight-for-age Z score and mid-upper-arm circumference might be an effective and low-cost way to identify high risk children, including those who are concurrently wasted and stunted. The paper was published in the Maternal and Child Nutrition Journal in 2021 as an open access article.

List of figures

List of tables

Citation

Thurstans, S., Sessions, N., Dolan, C., Sadler, K., Cichon, B., Isanaka, S., Roberfroid, D., Stobaugh, H., Webb, P., & Khara, T. (2021). The relationship between wasting and stunting in young children: A systematic review. Maternal & Child Nutrition, e13246. ttps://doi.org/10.1111/mcn.13246

Research paper 6

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT

T: +44 (0)20 7299 4646
F: +44 (0)20 7299 4656
www.lshtm.ac.uk

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	1802701	**Title**	Mrs
First Name(s)	Susan		
Surname/Family Name	Thurstans		
Thesis Title	Sex differences in risk and outcomes from severe malnutrition: implications for management		
Primary Supervisor	Dr Marko Kerac		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	Maternal & Child Nutrition		
When was the work published?	June 2021		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	**No**	Was the work subject to academic peer review?	**Yes**

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	**Submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I led the development of the study protocol which was reviewed by Tanya Khara and Carmel Dolan. I conducted the search with a second review by Natalie Sessions. I led the analysis and the write up of the manuscript with regular contributions from all authors. All authors read and approved the final manuscript.

SECTION E

Student Signature	[redacted]
Date	

Supervisor Signature	
Date	

Received: 26 March 2021 | Revised: 26 May 2021 | Accepted: 22 June 2021

DOI: 10.1111/mcn.13246

REVIEW ARTICLE

Maternal & Child Nutrition WILEY

The relationship between wasting and stunting in young children: A systematic review

Susan Thurstans[1,2] | Natalie Sessions[2] | Carmel Dolan[3] | Kate Sadler[2] | Bernardette Cichon[4] | Sheila Isanaka[5,6] | Dominique Roberfroid[7,8] | Heather Stobaugh[9,10] | Patrick Webb[10] | Tanya Khara[2]

[1]Department of Population Health, London School of Hygiene and Tropical Medicine, London, United Kingdom, UK

[2]Emergency Nutrition Network, Oxford, UK

[3]Nutrition for Development, UK

[4]No Wasted Lives/Action Against Hunger, London, UK

[5]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA

[6]Department of Research, Epicentre, Paris, France

[7]Faculty of Medicine, University of Namur, Namur, Belgium

[8]Department of Food Technology, Safety and Health, Ghent University, Ghent, Belgium

[9]Action Against Hunger USA, New York, New York, USA

[10]Friedman School of Nutrition Science and Policy, Tufts University, Boston, Massachusetts, USA

Correspondence
Susan Thurstans, Keppel Street, London School of Hygiene and Tropical Medicine, London, WC1E 7HT, UK.
Email: susan.thurstans@lshtm.ac.uk

Funding information
Irish Aid, Grant/Award Number: HQPU/2020/ENN

Abstract

In 2014, the Emergency Nutrition Network published a report on the relationship between wasting and stunting. We aim to review evidence generated since that review to better understand the implications for improving child nutrition, health and survival. We conducted a systematic review following PRISMA guidelines, registered with PROSPERO. We identified search terms that describe wasting and stunting and the relationship between the two. We included studies related to children under five from low- and middle-income countries that assessed both ponderal growth/wasting and linear growth/stunting and the association between the two. We included 45 studies. The review found the peak incidence of both wasting and stunting is between birth and 3 months. There is a strong association between the two conditions whereby episodes of wasting contribute to stunting and, to a lesser extent, stunting leads to wasting. Children with multiple anthropometric deficits, including concurrent stunting and wasting, have the highest risk of near-term mortality when compared with children with any one deficit alone. Furthermore, evidence suggests that the use of mid-upper-arm circumference combined with weight-for-age *Z* score might effectively identify children at most risk of near-term mortality. Wasting and stunting, driven by common factors, frequently occur in the same child, either simultaneously or at different moments through their life course. Evidence of a process of accumulation of nutritional deficits and increased risk of mortality over a child's life demonstrates the pressing need for integrated policy, financing and programmatic approaches to the prevention and treatment of child malnutrition.

KEYWORDS
child growth, infectious disease, international child health nutrition, malnutrition, stunting, wasting

1 | INTRODUCTION

Undernutrition remains a major public health concern in many countries and an underlying cause of almost half of global child mortality (Black et al., 2013). The long-term impacts of childhood undernutrition are far-reaching, resulting in lower educational achievement, lower economic productivity and an increased risk of noncommunicable disease (Black et al., 2013; Murray et al., 2020; Victora et al., 2008) Current estimates suggest that 149 million children under 5 years are stunted and 49.5 million are wasted (Global Nutrition Report, 2020), while 15.9 million are experiencing both forms of undernutrition concurrently (Global Nutrition Report, 2018).

For many years, wasting and stunting have been viewed as separate conditions. As a result, the two have been largely disconnected within nutrition programmes, at policy and financing levels and in many areas of research without clear evidence supporting this distinction. The reasons for the historical shift from a previously more joined up way of looking at undernutrition (Waterlow, Gomez classification) are unclear, although some aspects of the divide have been entrenched by divergent funding and programmatic approaches in humanitarian and development contexts and the separation of wasting treatment and stunting prevention approaches (Wells, Briend, et al., 2019). In humanitarian contexts, the focus of programming tends to be on wasting treatment and mitigating acute mortality risk, whereas in stable development contexts, the bigger policy and programmatic focus is often on stunting prevention and the mitigation of associated longer-term developmental deficits (SUN, 2016). That said, these divides are not typical of all settings and have started to lessen over recent years with growing attention to wasting treatment in developmental settings within health systems. There has also been more recent attention paid to wasting prevention and to issues of stunting in protracted crises with evidence highlighting that in fragile contexts, multiple forms of malnutrition coexist at high levels (Global Nutrition Report, 2020).

In 2014, the Emergency Nutrition Network (ENN) formed a technical interest group (TIG) of global experts (referred to as the WaSt TIG) to examine the relationship between wasting and stunting and published a technical briefing paper (Khara & Dolan, 2014) on the state of evidence, policy, research and programme implications of this relationship. This review concluded that wasting and stunting often coexist in the same child and that the risk of mortality associated with both wasting and stunting is heightened where they coexist. It also highlighted that there are common causal pathways, evidence pointing towards a direct relationship between wasting and stunting, that seasonality has a marked impact on both wasting and stunting prevalence and that in-utero conditions and fetal growth contribute significantly to stunting and wasting at birth and during infancy. The report highlighted challenges around how wasting and stunting are commonly framed and reported, particularly the limitations of applying anthropometric cut-offs at one point in time that fail to represent the process of wasting and/or stunting that a child may experience.

Since 2014, the WaSt TIG and other researchers have focused on more clearly defining the limitations posed by existing approaches to the framing of wasting and stunting. This process has raised critical research questions, including those around how children experience wasting and stunting throughout their life course and the implications of experiencing both. Our objective was to systematically review evidence generated since the original 2014 review to better understand the relationship between wasting and stunting in terms of both the physiological similarities and associations between the two as well as the implications of this relationship on interventions to improve child health, nutrition and survival. With such knowledge, mitigating different levels of risks through preventive approaches and treatment should be possible and, in so doing, would have global relevance towards the attainment of World Health Assembly (WHA) and Sustainable Development Goals (SDG) targets as they relate to wasting and stunting.

Key messages

- A significant proportion of wasting and stunting is present at birth and can contribute to further growth failure during subsequent infancy and childhood. Improving maternal health and nutrition in pregnancy and early life could have a critical role in the prevention of wasting and stunting.
- Periods of wasting leave a child more likely to experience stunting and, to a lesser extent, vice versa. Common risk factors drive an accumulation of vulnerabilities. This underlines the need for cohesive policies and the implementation of services and activities to prevent both wasting and stunting.
- Concurrently wasted and stunted children have an elevated risk of death and should be considered as a high-risk group in the targeting of treatment.
- A combination of weight-for-age *Z* score and mid-upper-arm circumference may be the most effective way to identify children at highest risk of mortality, including those concurrently wasted and stunted. Further evidence is needed to understand the operational implications.

2 | MATERIALS AND METHODS

We conducted a systematic review following the *Preferred Reporting Items for Systematic reviews and Meta-Analyses* (PRISMA) guidelines (Moher et al., 2009). A review protocol was developed, in coordination with a subworking group (SWG) of experts from the WaSt TIG to define the scope of the review. The protocol was registered with the PROSPERO International prospective register of systematic reviews (CRD42019153330).

2.1 | Search strategy

We identified search terms to describe wasting and stunting and the relationship between the two conditions, including implications for ponderal and linear growth. The search terms are listed in Figure 1. We searched Medline, Embase and global health databases through Ovid, applying limits for studies published after 2012 to allow for any studies that may have been missed in the 2014 review and for the age of the individuals included in studies. We also issued a call for studies known to the WaSt TIG members in May 2020. The final search was conducted in June 2020. Both the search strategy and the eligibility criteria were guided by the Population, Intervention, Comparison, Outcome (PICO) framework in order to delineate the question of focus for the review and to define inclusion and exclusion criteria. The PICO is presented in Table 1.

2.2 | Eligibility criteria

We reviewed studies from low- and middle-income countries (LMICs) where wasting and stunting are most prevalent. As wasting and stunting commonly occur in children under 5 years of age, we applied age limits from 0 to 59 months. We considered studies in the review that assessed both ponderal growth/wasting and linear growth/stunting as well as the association between the two. Included studies focused on prevalence, physiological mechanisms and outcomes related to growth and mortality. We included all types of studies that involved primary research (case control studies, cross-sectional studies and secondary data analyses). We also included reviews if they presented pooled analysis or new insights into the relationship between wasting and stunting. Both peer-reviewed papers and grey literature identified through the search were considered for inclusion.

We excluded studies that assessed wasting and stunting separately and that did not report on either condition in relation to the other. Also excluded were studies that focused on obesity,

TABLE 1 Population, Intervention, Comparison, Outcome

Population	**Children 0–5 years Low- and middle-income countries**
Intervention	Assessment, review or treatment of wasting, stunting, concurrent wasting and stunting
Comparison	No comparison
Outcome	Incidence, prevalence, treatment outcome measures (recovery, mortality, length of stay etc.), morbidity, concurrent wasting and stunting

Medline:

1. Wast*
2. GAM
3. SAM
4. MAM
5. Ponderal growth
6. Acute malnutrition
7. Severe adj1 malnutrition
8. Moderate adj1 Malnutrition
9. Mid Upper Arm Circumference
10. MUAC
11. Chronic malnutrition
12. Linear growth
13. Stunt*
14. Short stature
15. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
16. 11 or 12 or 13 or 14
17. 15 and 16
18. Concurre*
19. Combined
20. Simultaneous
21. Relationship
22. Associat*
23. Double burden
24. 18 or 19 or 20 or 21 or 22 or 23
25. 17 and 24
26. limit 25 to ("all infant (birth to 23 months)" or "newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)")

*used as truncation

FIGURE 1 Search strategy

micronutrients, those that included children over 5 years of age and published abstracts and viewpoints.

In most of the literature reviewed, wasting is defined as low weight-for-length/height (WLZ/WHZ) (<−2 *Z* score of the reference), stunting as low height-for-age (HAZ) (<−2 *Z* score of the reference) and concurrent wasting and stunting as both low WHZ and HAZ at the same time (<−2 *Z* score WHZ and <−2 *Z* score HAZ). However, in literature referring to treatment programmes targeting wasting, standard WHO mid-upper-arm circumference (MUAC) criteria for defining wasting may also be included. We have endeavoured to specify literature for which the latter is the case.

2.3 | Study selection, data extraction and analysis

All records identified during the search were exported into EndNote (EndNote V.X8, Clarivate Analytics) and duplicates removed. Initial screening of titles and abstracts was conducted by ST to identify studies unrelated to the scope of the review. The remaining studies were then independently screened by ST and NS by reading the full texts. Discrepancies were resolved via discussion and, where necessary, a third reviewer (TK) was consulted. A data extraction template was developed in Excel, piloted and reviewed by members of the research team before full extraction took place.

We identified three main themes before extraction: physiological understanding of the similarities in wasting and stunting, the interrelationship between the two conditions and the implications of this relationship and then extracted data along these lines. We extracted data into an Excel spreadsheet including information on authors, titles, dates of publication, sample size, data/information relevant to each theme and any research recommendations and conclusions.

2.4 | Risk of bias assessment

We assessed the quality of included studies using an adapted version of the SIGN checklists (https://www.sign.ac.uk/what-we-do/methodology/checklists/). We selected the SIGN checklists as they provide a checklist of items for case–control and cohort studies, study designs commonly used in the studies selected for this review. Adaptation was necessary due to the varied nature of the studies included. We assessed factors such as clearly defined objectives, study design, definition of participants, exposures and outcomes, statistical methods, addressing of bias and potential confounders and the presentation of results.

3 | RESULTS

3.1 | Study selection

The results of the search process are presented in Figure 2. The database search identified 2486 studies and reports and an additional 12 studies came from WaSt TIG members. After removing duplicates, 983 studies and reports remained, of which 867 were excluded following initial screening. One hundred and sixteen full text studies and reports were assessed for eligibility of which 71 were excluded. The reasons for exclusion are given in Figure 2. We included a total of 45 studies and reports in our final review.

3.2 | Study characteristics and risk of bias

We present the characteristics of each included study or report in Table 2. We included a total of 39 peer reviewed studies, one manual chapter, three preprint publications and two published reports (both appearing in ENN's Field Exchange 'peer-to-peer' publication, https://www.ennonline.net/fex). These included 21 cross sectional and 18 longitudinal studies. In total, 14 countries were covered in studies and reports conducted in single countries while 18 studies covered multiple countries—the largest analysis covering 84 countries (Khara et al., 2018). The risk of bias assessment is presented in Table 3. Overall, we assessed the studies and reports selected to be of 'acceptable' quality according to the adapted SIGN criteria, but one study was excluded on the basis of quality (Carroll et al., 2012).

3.3 | Interconnected physiological processes

We reviewed studies that considered the physiological processes underlying the potential interaction between wasting and stunting, either as the primary objective or within the discussion. While little was identified in the way of epidemiological research in this area, published narrative reviews provided some discussion of the possible physiological mechanisms.

Infectious disease has long been recognised as both a cause and consequence of undernutrition. Infectious disease can result in both wasting and stunting through decreased or altered nutritional intake, impaired intestinal absorption and increased metabolism from fever, immune response and environmental enteropathy (Kosek and Mal-Ed Network Investigators, 2017; Nandy & Svedberg, 2012) resulting in a higher risk of mortality (Harding et al., 2018b). Conversely, undernourished children are more vulnerable to infectious disease due to the impairment of their immune system. Children identified as concurrently wasted and stunted have been found to be at increased risk of infectious disease (Harding et al., 2018b; Odei Obeng-Amoako, Karamagi, et al., 2020; Sage, 2017).

The literature describes the association between loss of fat mass and wasting and stunting, although inconsistently so in the case of stunting (Briend, Khara et al., 2015; Fabiansen et al., 2016, 2017; Wells, 2019). Fat plays a role in the maintenance of the immune system, which demands increased energy when stimulated by infection. This suggests that fat depletion acts as an additional mechanism linking wasting and stunting with increased infection and mortality (Briend, Khara et al., 2015). Muscle mass loss also occurs in both

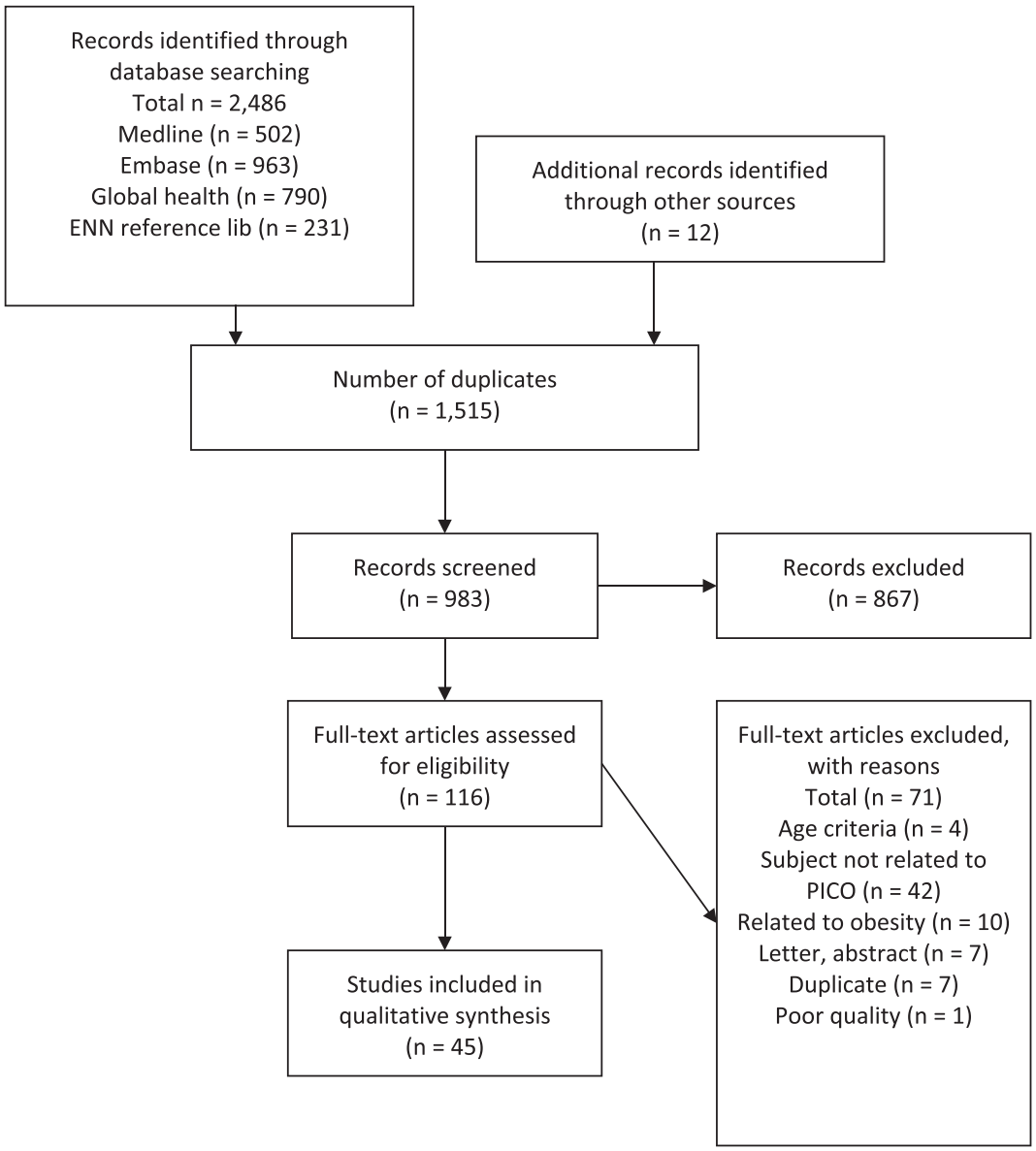


FIGURE 2 PRISMA flow diagram

wasting and stunting, particularly in the case of infection when protein breakdown is increased due to an increased need for amino acids to build the proteins involved in the immune response. As muscle mass is positively associated with age, infants have low levels and are therefore especially vulnerable to the effects of undernutrition and associated mortality (Briend, Khara et al., 2015).

The literature also describes the role of leptin in the relationship between wasting and stunting linked to the above body composition changes above. Leptin is a hormone produced primarily by fat cells and is responsible for the regulation of energy, hunger and metabolism as well as playing a central role in stimulating immune function and linear growth (Wells, Briend, et al., 2019). The levels of leptin produced reflect body fat stores and indeed low levels of leptin are noted alongside the deficits in fat and muscle mass in wasted and stunted children. Furthermore, low levels of leptin in children with undernutrition are predictive of an increased risk of mortality (Briend, Khara et al., 2015) and implicated in slowed linear growth during wasting (Wells, 2019).

Briend, Akomo, et al. (2015) also highlight the coexistence of stunting and high overweight prevalence. They suggest that high fat stores alone are insufficient to support linear growth and that low intake of nutrients such as zinc, sulphur, phosphorous, vitamins D, C and K and copper—nutrients needed for bone growth and lean tissue synthesis—may explain the association between stunting with reduced muscle mass and normal or increased fat reserves. Leptin might also have an effect on bone growth which might explain the reduced linear growth observed in wasted children and the frequent association with stunting (Briend, Khara et al., 2015).

TABLE 2 Study characteristics

No	1st author and year	Study design	Sample size	Country	Age range of sample	Physiology	Relationship	Mortality	Burden
1	Angood (2016)	CHNRI	NA	NA	NA				
2	Benjamin-Chung et al. (2020)	Longitudinal	62,993	Multiple	0–24 months			✓	✓
3	Binns and Myatt (2018)	Longitudinal	163	Malawi	6–59 months				
4	Briend (2012)	Review	NA	NA		✓			
5	Christian et al. (2013)	Cohort	58,317	Multiple	0–59 months			✓	
6	Fabiansen et al. (2017)	RCT	1609	Burkina Faso	6–23 months				
7	Fabiansen (2020)	Cohort	1609	Burkina Faso	6–23 months				
8	Garenne (2020)	Cross-sectional	37,670	Senegal	12–59 months		✓	✓	✓
9	Garenne (2018)	Longitudinal	12,638	Senegal	6–59 months	✓	✓	✓	✓
10	Harding et al. (2018a)	Cross-sectional	62,509	Multiple: South Asia	0–59 months				✓
11	Harding et al. (2018b)	Cross-sectional	252,797	Multiple: South Asia	0–59 months				✓
12	Imam et al. (2020)	Cross-sectional	472	Nigeria	6–59 months				✓
13	Isanaka et al. (2019)	Cohort	1542	Niger	6–59 months		✓		✓
14	Kangas et al. (2020)	RCT	802	Burkina Faso	6–59 months				
15	Kassie and Workie (2019)	Cross-sectional	8768	Ethiopia	0–59 months		✓		
16	Khara (2017)	Cross-sectional	198,005,973	Multiple	6–59 months				✓
17	Kinyoki (2016)	Cross-sectional	73,778	Somalia	6–59 months				✓
18	Kosek and Mal-Ed Network Investigators (2017)	Cohort	1253	Multiple	0–24 months	✓			
19	Lelijveld et al. (2016)	Cohort	320	Malawi			✓		
20	McDonald et al. (2013)	Meta-analysis of cohort studies	53,767	Multiple	0–59 months			✓	✓
21	Mertens, Benjamin-Chung, Colford, Coyle, et al., (2020)	Longitudinal	108,336	Multiple	0–24 months			✓	✓
22	Mertens, Benjamin-Chung, Colford, Hubbard, et al., (2020)	Longitudinal	10,854	Multiple	0–24 months		✓		✓
23	Mutunga (2020)	Cross-sectional	47,481	Multiple	0–59 months				✓
24	Myatt et al. (2019)	Longitudinal	5751	Senegal	0–59 months			✓	
25	Myatt et al. (2018)	Cross-sectional	1,796,991	Multiple	6–59 months		✓	✓	
26	Nandy and Svedberg (2012)	Cross-sectional	45,377	India	0–59 months	✓			
27	Ngari et al. (2019)	Longitudinal	1169	Kenya	2–59 months		✓		
28	Ngwira et al. (2017)	Cross-sectional	4861	Malawi	0–59 months		✓		
29	O'Brien et al. (2020)	Longitudinal	1023	Niger	6–60 months			✓	

TABLE 2 (Continued)

No	1st author and year	Study design	Sample size	Country	Age range of sample	Physiology	Relationship	Mortality	Burden
30	Odei Obeng-Amoako, Karamagi, et al. (2020)	Cross-sectional	32,962	Uganda	6–59 months		✓		✓
31	Odei Obeng-Amoako, Myatt, et al. (2020)	Cohort	788	Uganda			✓	✓	✓
32	Odei Obeng-Amoako, Wamani, et al. (2020)	Cross sectional	33,054	Uganda	6–59 months		✓		✓
33	Pomati and Nandy (2019)	Cross-sectional	28 DHS samples	Multiple	0–59 months			✓	✓
34	Prentice et al. (2013)	Cross-sectional	227	Multiple	0–24 months	✓	✓		
35	Reese-Masterson et al. (2016)	Cross-sectional	227	Kenya	0–24 months				✓
36	Richard, Black, & Checkley (2012)	Longitudinal	1599	Multiple	0–24 months		✓		
37	Roberfroid (2015)	Cross-sectional	14,409	Multiple	6–59 months				
38	Saaka and Galaa (2016)	Cross-sectional	2720	Ghana	0–59 months		✓		✓
39	Sage (2017)	Cross-sectional	6602	Guinea-Bissau	6–59 months				✓
40	Schoenbuchner et al. (2019))	Longitudinal	5160	Gambia	0–24 months		✓		✓
41	Schwinger (2019)	Longitudinal	15,060	Multiple	6–59 months			✓	
42	Shively (2017)	Cross-sectional	11,946	Uganda and Nepal	0–59 months		✓		
43	Stobaugh et al. (2018)	Longitudinal	1487	Malawi	6–62 months		✓		
44	Victora (2015)	Cross-sectional	24,817 girls and 26,378 boys	Multiple	Newborns				✓
45	Wells (2019)	Review	NA	NA	NA	✓	✓		

TABLE 2 Continued

No	Age and sex	Anthropometric indices	Treatment outcomes	Fat accumulation	Research gaps	Key findings	Key conclusions
1					✓	Priority research questions for wasting and stunting identified	Research is needed into wasting and stunting in order to inform global health efforts to address undernutrition
2	✓					The highest incidence of stunting onset occurred from birth to 3 months of age. From 0 to 15 months of age, less than 5% of children per month reversed their stunting status and, among those who did, stunting relapse was common.	Preventive intervention within prenatal and early postnatal phases, coupled with continued delivery of postnatal interventions through the first 1000 days of life, are key to overcoming the early occurrence and low reversal rates of stunting.
3				✓		No incidence of overweight or adiposity.	Children age ≥6 months with a height less than 65 cm will not become overweight or obese following RUTF treatment with MUAC as admission and discharge criteria.
4					✓		

TABLE 2 (Continued)

No	Age and sex	Anthropometric indices	Treatment outcomes	Fat accumulation	Research gaps	Key findings	Key conclusions
						Fat loss and muscle mass loss are associated with both wasting and stunting. Hormones produced by fat play a crucial role in immune function and bone growth which might explain reduced linear growth in the case of low WHZ.	Crucial to prevent both wasting and stunting in order to reduce malnutrition related mortality.
5						LBW was associated with higher odds of wasting, stunting and underweight.	Childhood undernutrition may have its origins in the fetal period, indicating the need for early intervention and targeting of adolescent girls and pregnant women with interventions known to reduce FGR and preterm birth.
6				✓		Compared CSB and LNS and assessed body composition to determine the quality of weight gain with fat free mass tissue accretion as a primary outcome. The findings showed that fat free tissue accretion as well as recovery from MAM were both higher using LNS compared with CSB.	Findings support wider use of LNS in MAM treatment.
7				✓		No difference found in fat accumulation between tall and short children when treated using RUTF.	Short children do not gain excessive fat during supplementation. The use of length as eligibility criteria for treatment should be discontinued and all children ≥6 months with low MUAC should be included in SFPs.
8	✓					Children in Senegal are taller but thinner. Changes in weight and height were most apparent in poorer households. Findings were consistent with reduction in mortality.	Control of stunting likely a result of control of infectious disease. Increase in reduced WHZ requires further investigation.
9	✓	✓			✓	Wasting and stunting are correlated. Concurrent wasting and stunting peaks around 30 months and is higher in boys than girls, but this difference could not be explained by muscle mass or fat mass measured by arm or muscle circumference, triceps or subscalpular skinfold.	Concurrent wasting and stunting is a strong risk factor for mortality.
10						Key determinants of child stunting are also significant determinants of child wasting in Asia.	The co-occurrence of wasting and stunting requires more integrated interventions. That is, programmes aimed at preventing LBW and poor IYCF to avert stunting should be linked more effectively with actions aimed at the management of wasting.
11						LBW strongly associated with wasting and wasting and stunting.	Programmes aimed at preventing LBW and poor IYCF (to reduce stunting) should be linked with actions aimed at the management of wasting.

TABLE 2 (Continued)

No	Age and sex	Anthropometric indices	Treatment outcomes	Fat accumulation	Research gaps	Key findings	Key conclusions
12	✓					Stunting prevalence is high among severely wasted children attending CMAM programmes in North-Western Nigeria.	CMAM programmes should adapt to consider stunting as well as wasting.
13			✓			High burden of stunting in wasting treatment programme. Stunting did not impair response to treatment. There was limited linear growth in this population.	There is a direct relationship whereby inadequate weight is associated with slowed linear growth. Wasting contributes to stunting.
14				✓		Half of weight gained by children during SAM treatment was fat free mass (FFM) and the FFM of treated children at recovery was similar to community controls indicating incomplete FFM recovery during SAM treatment.	There is no evidence from this study of a differential effect of a reduced RUTF dose on the tissue accretion of treated children when compared with standard treatment suggesting that, in a relatively food secure context, a reduction in the RUTF dose can result in similar body composition by recovery.
15						Underweight was associated with both stunting and wasting. There was no association between stunting and wasting. There is no a three way interaction among stunting, wasting and underweight.	Wasting, stunting and underweight should be considered simultaneously to estimate the actual burden of childhood undernutrition.
16	✓					Concurrent wasting and stunting highest in 12–24 months age group and males. Fragile and conflict affected states have higher concurrence than stable countries.	Concurrent wasting and stunting represents a high risk group. Investigations needed to ensure this group is being reached.
17						Determinants of wasting are similar but patterns in correlation are variable.	Wasting, stunting and underweight have common risk factors. Joined up programming is required to address wasting and stunting.
18						Higher burdens of enteropathogens were associated with elevated biomarker concentrations of gut and systemic inflammation and indirectly associated with both reduced linear and ponderal growth.	The strongest evidence for environmental enteropathy was the association between enteropathogens and linear growth mediated through systemic inflammation.
19			✓			More stunting found in case group. Sitting height was similar across groups suggesting preservation of torso growth.	SAM has long term adverse effects on growth and body composition.
20						Hazarad ratio for stunting, wasting and underweight was 12.3.	Children with multiple anthropometric deficits are at increased risk of mortality.
21	✓					Children who experienced early ponderal or linear growth failure were at higher risk of persistent growth failure and were more likely to die by age 24 months.	A focus on pre-conception and pregnancy is key for preventive interventions.

TABLE 2 (Continued)

No	Age and sex	Anthropometric indices	Treatment outcomes	Fat accumulation	Research gaps	Key findings	Key conclusions
22	✓		✓			Wasting incidence is five-fold higher than prevalence estimates suggest. Peak incidence is between 0 and 3 months.	New focus is required to extend preventive interventions for child wasting to pregnant and lactating mothers and children below age 6 months.
23						Concurrent wasting and stunting is prevalent in Southeast Asia.	Both preventive and curative approaches are needed to address wasting in Southeast Asia.
24		✓				MUAC and WAZ detected all near-term deaths associated with anthropometric deficits, including concurrent wasting and stunting.	Therapeutic feeding programmes should consider WAZ and MUAC admission criteria.
25	✓	✓				Children who are wasted and stunted are also underweight. Concurrently wasted and stunted children have a high risk of mortality.	Therapeutic feeding programmes should include concurrent wasting and stunting given the high risk of mortality.
26						The CIAF supports the assessment of the relationship between malnutrition, morbidity and poverty.	Efforts to reduce poverty and increase living standards are needed to support reduction of malnutrition.
27			✓			No significant increase in HAZ at 1 year follow-up after inpatient treatment for complicated SAM, despite MUAC growth and weight gain. Linear growth was associated with less severe wasting and more stunted and with fewer comorbidities at admission.	Intensive nutritional rehabilitation did not resolve stunting.
28						Associations found between wasting and underweight and stunting and underweight but no association found between wasting and stunting.	Wasting, stunting and underweight are valid measures which cannot represent each other.
29		✓				MUAC was the strongest predictor of mortality followed by WAZ.	MUAC is a better predictor of mortality in this study population.
30	✓	✓				All concurrent wasted and stunted children were also underweight. Concurrent wasting and stunting prevalence of 5% raises public health concerns. WaSt was more common among younger children and males, but the majority of WaSt children with low MUAC were female.	Consider the integration of WAZ into therapeutic feeding programmes to detect and treat concurrent wasting and stunting.
31	✓	✓	✓			High number of stunted children in wasting treatment programme.	Existing therapeutic feeding protocols can be used to detect and effectively treat children with concurrent wasting and stunting.
32	✓					Factors associated with concurrent wasting and stunting included male sex, age between 12 and 59 months, acute respiratory infection, diarrhoea, malaria/fever, maternal underweight,	Preventing concurrent wasting and stunting through pragmatic and joint approaches is critical. Future prospective studies should focus

TABLE 2 (Continued)

No	Age and sex	Anthropometric indices	Treatment outcomes	Fat accumulation	Research gaps	Key findings	Key conclusions
						maternal short stature, low MUAC (<23 cm) and mother having ≥4 live-births.	on risk factors in order to inform effective prevention strategies
33		✓				The mortality risk attached to multiple anthropometric deficits is high including children who are wasted and underweight and stunted and underweight.	CIAF identifies children under five with a higher risk of mortality.
34					✓	Infants born with growth deficits will likely continue to have growth deficits as they progress along growth trajectories.	Research is needed to understand causal pathways to growth faltering.
35						A small sub-sample of the population was found to be both wasted and stunted.	The study makes recommendations for programme-specific data and measurement-related improvements to enable more meaningful analysis.
36						Children with wasting only in early life had similar LAZ at 18–24 months than those with no wasting. More recent wasting was associated with lower LAZ.	Wasting is associated with the process of stunting. Prevention of wasting could increase attained stature in children.
37	✓	✓				MUAC <125 mm should not be used as a stand-alone criteria for wasting given its strong association with age, sex and stunting and its low sensitivity to detect slim children.	Further research is needed to better understand the clinical and physiological outcomes of the various anthropometric indicators of malnutrition.
38						Children who were wasted were more at risk of stunting.	WHZ relates to linear growth. Stunting and wasting share common determinants therefore prevention of both wasting and stunting will positively influence linear growth.
39	✓					Associations that were insignificant for wasting and stunting individually were significant for concurrent wasting and stunting. Mosquito nets and lack of diarrhoea in the last two weeks were both protective of concurrent wasting and stunting.	Concurrent wasting and stunting should be a key consideration for nutrition programming in Guinea-Bissau.
40	✓	✓			✓	Being wasted was predictive of stunting, even accounting for current stunting. Boys more likely to be wasted, stunted and underweight than girls, and are more susceptible to seasonally driven growth deficits.	Stunting is in part a biological response to previous wasting highlighting the policy implications of recognising the importance of wasting.
41						Children who have a low WHZ but a MUAC above the cut-off would be omitted from diagnosis and treatment.	In addition to simple tools for case finding, the use of WHZ should be used whenever possible.
42							

(Continues)

TABLE 2 (Continued)

No	Age and sex	Anthropometric indices	Treatment outcomes	Fat accumulation	Research gaps	Key findings	Key conclusions
						Nutritional status was sensitive to rainfall, more so in Uganda than Nepal.	Further research is needed to understand the heterogeneity in results and the role of economic development in promoting child nutrition.
43			✓			Children with poor linear growth after MAM are more likely to experience relapse.	Wasting contributes to stunting.
44						Stunting and wasting are separate anthropometric phenotypes with intrauterine origins. Larger studies in higher risk populations may strengthen the associations between wasting and stunting and will also reinforce the differences.	Newborns should be classified using both wasting and stunting measures.
45				✓		There are different potential pathways which underlie the association with stunting and future body composition including environmental drivers, changes in growth and tissue masses or alterations in metabolic pathways.	Further research is needed in relation to the functional significance of FFM and fat mass for survival, physical capacity and noncommunicable disease risk.

3.4 | The burden, aetiology and timing of wasting and stunting

Cross-sectional population-based surveys are often used to determine prevalence and associated risk factors for wasting and stunting despite being known to be potentially problematic in underestimating the true burden of acute conditions like wasting (Action Against Hunger, 2018; Khara et al., 2018). A recent pooled longitudinal analysis (Mertens, Benjamin-Chung, Colford, Hubbard, et al., 2020) highlights the challenge in the interpretation of cross-sectional data for wasting and demonstrates that these methods fail to measure the onset, recovery and persistence (defined as persistent if ≥50% of WLZ measurements from birth to 24 months fell below −2) of wasting. Data showed that the cumulative incidence of wasting in children under 24 months was 33%, more than five times higher than prevalence which was 6%. This means that the burden of wasting is likely far higher than traditional cross-sectional studies suggest. In the case of stunting, the data suggest that prevalence estimates matched general patterns of cross-sectional studies, gradually increasing with age and therefore are a more accurate estimate of true burden (Benjamin-Chung et al., 2020).

The same analyses provide evidence that challenges a reliance on prevalence estimates to inform interventions. It is often understood that wasting peaks at 12–23 months (Garenne et al., 2019; Schoenbuchner et al., 2019). However, by looking at the incidence of wasting, the study established that peak incidence is between birth and 3 months (Mertens, Benjamin-Chung, Colford, Hubbard, et al., 2020). A similar analysis of stunting (Benjamin-Chung et al., 2020) also offers new insights into the timing of linear growth faltering, typically understood to be highest between 6 and 24 months. Data showed that the incidence of stunting was also highest from birth to 3 months. Although some children went on to experience stunting reversal, they later continued to experience linear growth faltering and more than 20% were stunted again at later measurements. These results emphasise the need for preventive and therapeutic interventions that usually target children from 6 to 59 months to include children under 6 months while also extending inclusion of both prevention and treatment of undernutrition in women of reproductive age, as well as pregnant and lactating women.

As with the 2014 review, studies in this review assessing the aetiology of wasting and stunting and concurrent wasting and stunting demonstrate that many of the driving factors are common (Harding et al., 2018b; Mertens et al., 2020; Saaka & Galaa, 2016; Shively, 2017). Underlying factors such as poor maternal nutrition (Mertens, Benjamin-Chung, Colford, Coyle, et al., 2020), high parity (Mertens et al., 2020), low education levels (Mertens, Benjamin-Chung, Colford, Coyle, et al., 2020; Odei Obeng-Amoako, Karamagi, et al., 2020), low birth weight (LBW) and/or length (Mertens, Benjamin-Chung, Colford, Coyle, et al., 2020) and poor feeding practices (Harding et al., 2018a; Prentice et al., 2013) (Saaka & Galaa, 2016) have all been shown to be associated with both wasting and stunting and concurrent wasting and stunting in cross-sectional analysis. Likewise, poor socio-economic conditions (Mertens,

TABLE 3 Risk of bias assessment

Study	The study addresses an appropriate and clearly focused question	Is the study design clearly described?	Where relevant, are groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	Are eligibility criteria for participants well described (including controls where relevant)?	Are outputs, exposures and potential confounders well described?	Are sources of data and methods of assessment or measurement clearly described?	Are efforts to address potential bias or confounding described?	Is study size clearly stated and an explanation given for study size?
Angood (2016)	●	●	NA	NA	NA	●	NA	NA
Benjamin-Chung (2020)	●	●	●	●	●	●	●	●
Binns and Myatt (2018)	●	●	●	●	●	●	●	●
Briend (2012)	●	NA	NA	NA	NA	NA	NA	NA
Christian et al. (2013)	●	●	●	●	●	●	●	●
Fabiansen et al. (2017)	●	●	●	●	●	●	●	●
Fabiansen (2020)	●	●	●	●	●	●	●	●
Garenne (2020)	●	●	●	●	●	●	●	●
Garenne (2018)	●	●	●	●	●	●	●	●
Harding et al. (2018a)	●	●	●	●	●	●	●	●
Harding et al. (2018b)		●	●	●	●	●	●	●
Imam et al. (2020)	●	●	●	●	●	●	●	●
Isanaka et al. (2019)	●	●	●	●	●	●	●	●
Kangas et al. (2020)	●	●	●	●	●	●	●	●
Kassie and Workie (2019)	●	●	●	●	●	●	●	●
Khara (2017)	●	●	●	●	●	●	●	●
Kinyoki (2016)	●	●	●	●	●	●	●	●
Kosek and Mal-Ed Network Investigators (2017)	●	●	●	●	●	●	●	●
Lelijveld et al. (2016)	●	●	●	●	●	●	●	●

TABLE 3 (Continued)

Study	The study addresses an appropriate and clearly focused question	Is the study design clearly described?	Where relevant, are groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	Are eligibility criteria for participants well described (including controls where relevant)?	Are outputs, exposures and potential confounders well described?	Are sources of data and methods of assessment or measurement clearly described?	Are efforts to address potential bias or confounding described?	Is study size clearly stated and an explanation given for study size?
McDonald et al. (2013)	●	●	●	●	●	●	●	●
Mertens, Benjamin-Chung, Colford, Coyle, et al., (2020)	●	●	●	●	●	●	●	●
Mertens, Benjamin-Chung, Colford, Hubbard, et al., (2020)	●	●	●	●	●	●	●	●
Mutunga (2020)	●	●	●	●	●	●	●	●
Myatt et al. (2019)	●	●	●	●	●	●	●	●
Myatt et al. (2018)	●	●	●	●	●	●	●	●
Nandy and Svedberg (2012)	●	●	NA	NA	NA	NA	NA	NA
Ngari et al. (2019)	●	●	●	●	●	●	●	●
Ngwira et al. (2017)	●	●	●	●	●	●	●	●
O'Brien et al. (2020)	●	●	●	●	●	●	●	●
Odei Obeng-Amoako, Karamagi, et al. (2020a)	●	●	●	●	●	●	●	●
Odei Obeng-Amoako, Myatt, et al. (2020)	●	●	●	●	●	●	●	●

TABLE 3 (Continued)

Study	The study addresses an appropriate and clearly focused question	Is the study design clearly described?	Where relevant, are groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	Are eligibility criteria for participants well described (including controls where relevant)?	Are outputs, exposures and potential confounders well described?	Are sources of data and methods of assessment or measurement clearly described?	Are efforts to address potential bias or confounding described?	Is study size clearly stated and an explanation given for study size?
Odei Obeng-Amoako, Wamani, et al. (2020)	●	●	●	●	●	●	●	●
Pomati and Nandy (2019)	●	●	●	●	●	●	●	●
Prentice et al. (2013)	●	◐	NA	NA	NA	NA	NA	NA
Reese-Masterson et al. (2016)	●	●	●	●	●	●	◦	●
Richard, Black, & Checkley (2012)	NA	NA	NA	NA	NA	NA	NA	NA
Roberfroid (2015)	●	●	●	●	●	●	●	●
Saaka and Galaa (2016)	●	●	●	●	●	●	●	●
Sage (2017)	●	●	●	●	●	●	●	●
Schoenbuchner et al. (2019)	●	●	●	●	●	●	●	●
Schwinger (2019)	●	●	●	●	●	●	●	●
Shively (2017)	●	●	●	●	●	●	●	●
Steenkamp, 2016	●	●	◐	◐	◦	◐	◦	◐
Stobaugh et al. (2018)	●	●	●	●	●	●	●	●
Victora (2015)	●	●	●	●	●	●	●	●
Wells (2019)	●	●	NA	NA	NA	NA	NA	NA

Note: ● = Yes, ◐ = partially, ◦ = no.

TABLE 3 Continued

Study	Is a clear description of statistical methods provided including, where appropriate, how missing data and subgroups were handled and how match of cases and controls was addressed and any sensitivity analysis?	Were the number of participants at each stage of the study (including loss to follow-up) well described?	Were characteristics of the study participants described?	Were outcome indicators clearly reported?	Have estimates (adjusted where relevant) and associated confidence intervals been reported?	Were study limitations recognised?
Angood (2016)	NA	NA	NA	●	NA	●
Benjamin-Chung (2020)	●	●	●	●	●	●
Binns and Myatt (2018)	●	●	●	●	●	●
Briend (2012)	NA	NA	NA	NA	NA	NA
Christian et al. (2013)	●	●	●	●	●	●
Fabiansen et al. (2017)	●	●	●	●	●	●
Fabiansen (2020)	●	●	●	●	●	●
Garenne (2020)	●	●	●	●	●	●
Garenne (2018)	●	●	●	●	●	●
Harding et al. (2018a)	●	●	●	●	●	●
Harding et al. (2018b)	●	●	●	●	●	●
Imam et al. (2020)	●	●	●	●	●	●
Isanaka et al. (2019)	●	●	●	●	●	●
Kangas et al. (2020)	●	●	●	●	●	●
Kassie and Workie (2019)	●	●	●	●	●	●
Khara (2017)	●	●	●	●	●	●
Kinyoki (2016)	●	●	●	●	●	●
Kosek and Mal-Ed Network Investigators (2017)	●	●	●	●	●	●
Lelijveld et al. (2016)	●	●	●	●	●	●
McDonald et al. (2013)	●	●	●	●	●	●
Mertens, Benjamin-Chung, Colford, Coyle, et al., (2020)	●	●	●	●	●	●
Mertens, Benjamin-Chung, Colford, Hubbard, et al., (2020)	●	●	●	●	●	●
Mutunga (2020)	●	●	●	●	●	●
Myatt et al. (2019)	●	●	●	●	●	●
Myatt et al. (2018)	●	●	●	●	●	●

TABLE 3 (Continued)

Study	Is a clear description of statistical methods provided including, where appropriate, how missing data and subgroups were handled and how match of cases and controls was addressed and any sensitivity analysis?	Were the number of participants at each stage of the study (including loss to follow-up) well described?	Were characteristics of the study participants described?	Were outcome indicators clearly reported?	Have estimates (adjusted where relevant) and associated confidence intervals been reported?	Were study limitations recognised?
Nandy and Svedberg (2012)	NA	NA	NA	NA	NA	NA
Ngari et al. (2019)	●	●	●	●	●	●
Ngwira et al. (2017)	●	●	●	●	●	◦
O'Brien et al. (2020)	●	●	●	●	●	●
Odei Obeng-Amoako, Karamagi, et al. (2020a)	●	●	●	●	●	●
Odei Obeng-Amoako, Myatt, et al. (2020)	●	●	●	●	●	●
Odei Obeng-Amoako, Wamani, et al. (2020)	●	●	●	●	●	●
Pomati and Nandy (2019)	●	●	●	●	●	●
Prentice et al. (2013)	NA	NA	NA	NA	NA	NA
Reese-Masterson et al. (2016)	●	●	●	●	●	●
Richard, Black, & Checkley (2012)	NA	NA	NA	NA	NA	NA
Roberfroid (2015)	●	●	●	●	●	●
Saaka and Galaa (2016)	●	●	●	●	●	●
Sage (2017)	●	●	●	●	NA	●
Schoenbuchner et al. (2019)	●	●	●	●	●	◦
Schwinger (2019)	●	●	●	●	●	●
Shively (2017)	●	●	●	●	●	◦
Steenkamp, 2016	◐	◦	◐	●	●	●
Stobaugh et al. (2018)	●	●	●	●	●	●
Victora (2015)	●	●	●	●	●	●
Wells (2019)	NA	NA	NA	NA	NA	NA

Note: ● = Yes, ◐ = partially, ◦ = no.

Benjamin-Chung, Colford, Coyle, et al., 2020) and seasonality (Schoenbuchner et al., 2019) contribute to both conditions.

3.5 | Evidence for the relationship between wasting and stunting

Population-level analyses of the association between wasting and stunting have in the past led to conclusions that the two conditions were unrelated, largely due to the perceived separation in prevalence and distribution patterns across populations. Cross-sectional results have been inconsistent in demonstrating any association between the two, with some single country studies showing low or no association between wasting and stunting (Kassie & Workie, 2019; Ngwira et al., 2017; Reese-Masterson et al., 2016). Population-level datasets mined specifically to explore the pertinent relationships now support a link between wasting and stunting that is more than just chance or random statistical noise. A large cross-sectional study involved analysis of 51 countries and shows the existence of a relationship whereby wasting and stunting were positively and significantly associated with each other in 37 of 51 countries (Myatt et al., 2018). Longitudinal studies in this review are also supportive of a relationship between the two conditions. In Senegal, a two-way dose response relationship was found whereby the proportion of wasted children increases with the degree of stunting and the proportion of stunting increases with the degree of wasting (Garenne et al., 2019). Within treatment programmes for severe acute malnutrition (SAM), evidence of a relationship is also apparent. Several analyses of children admitted into outpatient and/or inpatient feeding programmes indicate children with SAM are often stunted (Isanaka et al., 2019; Ngari et al., 2019; Schoenbuchner et al., 2019) (see Table 2). In Malawi, a strong association was found between poor linear growth and relapse to SAM and to moderate acute malnutrition (MAM) although the exact direction of this relationship was unclear (Stobaugh et al., 2018).

3.6 | Wasting leading to stunting

We identified a number of studies that are supportive of a direct relationship between wasting and stunting whereby episodes of wasting contribute to stunting including one review (Richard, Black, & Checkley, 2012), one cross- sectional (Saaka & Galaa, 2016) and six longitudinal studies (Isanaka et al., 2019; Ngari et al., 2019; Schoenbuchner et al., 2019; Richard, Black, Gilman, et al., 2012; Mertens et al., 2020; Mertens, Benjamin-Chung, Colford, Coyle, et al., 2020). Longitudinal data from The Gambia showed that being wasted was predictive of stunting within the next three-month period by a factor of 3.2 after accounting for current stunting status (Schoenbuchner et al., 2019). Multicountry longitudinal analysis showed that persistent wasting from birth to 6 months (defined as >50% of measurements wasted) was strongly associated with incident stunting at older ages (Mertens, Benjamin-Chung, Colford, Coyle, et al., 2020). Both studies indicate a time lagged effect whereby wasting is followed by stunting.

One hypothesis from these studies suggests that the body's response to weight faltering is to slow or halt linear growth until weight is gained and any infection is treated. In other words, weight (lean and fat mass) can be regained or maintained during nutritional stress at the expense of linear (height/length) growth (Isanaka et al., 2019; Richard, Black, & Checkley, 2012). Analysis from Niger tracking linear growth during wasting treatment suggests that HAZ deteriorates during the period of rapid weight gain that accompanies rehabilitation (Isanaka et al., 2019). Linear growth that was observed during periods of SAM treatment was characterised by children who were less wasted and less stunted (Isanaka et al., 2019; Ngari et al., 2019) and had fewer comorbidities at baseline (Ngari et al., 2019), suggesting that on top of the level of wasting and prior stunting, untreated comorbidities may also hold back linear growth. Population-level data from Senegal supports this suggestion showing trends in linear growth that increased with improving health status (Garenne, 2020).

These studies and data from The Gambia (Schoenbuchner et al., 2019) also suggest that the effect of episodes of wasting on linear growth is modified by age, where wasting appears to be more detrimental to long-term linear growth the later it happens, and recovery of HAZ is more likely if wasting occurs early and not subsequently. For example, a longitudinal study of infants and children 0–24 months in LMIC countries (Richard, Black, Gilman, et al., 2012) found no long-term effect of one period of wasting in the first 6 months of life on length-for-age *Z* score (LAZ) at 18–24 months if no further wasting was experienced after that time, suggesting that one episode of wasting in this age group is not enough to slow/halt linear growth. However, wasting after 6 months of age, and greater variability in WLZ in the first 17 months of life, was associated with lower LAZ at 18–24 months. Seasonal evidence also suggests that wasting is associated with further wasting whereby infants who were wasted in the first wet season of their life were more likely to be wasted in their second wet season, even after controlling for whether they were wasted during the intervening dry season (Schoenbuchner et al., 2019).

3.7 | Stunting leading to wasting

We also identified evidence to support a direct relationship whereby stunting leads to wasting, although the physiological mechanisms are less clear for this direction of the relationship. We identified two longitudinal studies demonstrating a strong and significant effect of stunting on the risk of subsequent wasting (Garenne et al., 2019; Schoenbuchner et al., 2019). The degree of stunting affected the level of risk with more severe stunting more likely to result in wasting.

3.8 | Concurrent wasting and stunting

Some studies conducted since the 2014 review have focused on identifying the burden and implications of concurrent wasting and stunting. We identified studies that explored the prevalence and

TABLE 4 Studies that measured prevalence of concurrence at population level and within SAM treatment programmes

Study (first author/year)	Country	Population	Prevalence findings
Population level data			
Garenne (2018)	Senegal	Children 6–59 m	Wasting 16.3%
			Stunting 24.2%
		12,638 measures	Concurrence 6.2%
Harding et al. (2018a)	6 countries—South Asia	Children 0–59 m	Wasting 15.7%,
			Stunting 40.1%
		n = 62,509	Concurrence 6%
Harding et al. (2018b)	6 countries—South Asia	Children 0–59 m	Wasting 19.4%
			Stunting 38.35%
		n = 252,797	Concurrence 6.11
Khara (2017)	84 countries	Children 0–59 m	Wasting 8.8%
			Stunting 33.0%
		n = 570,930	Concurrence 3.0%
Kinyoki (2016)	Somalia	Children 0–59 m	Wasting 21%
			Stunting 31%
		n = 73,778	Concurrence 9%
Mutanga 2020	6 countries—South East Asia	Children 0–59 m	Wasting 8.9%
			Stunting (not individually presented)
		n = 47,481	Concurrence 1.65%
Odei Obeng-Amoako, Karamagi, et al. (2020)	Uganda	Children 6–59 m	Stunting 33.58
			Wasting 12.03%
		n = 32,962	Concurrence 4.96%
Reese-Masterson et al. (2016)	Kenya	Children 6–23 m	Wasting 8.8%
		227	Stunting 28%
			Concurrence 5%.
Saaka and Galaa (2016)	Ghana	Children 0–59 m	Wasting 4.7%
		n = 2720	Stunting 17.9%
			Concurrence 1.4%.
Sage (2017)	Guinea-Bissau	Children 6–59 m	Wasting 6%
			Stunting 30%
		n = 6602	Concurrence 2.4%
Schoenbuchner et al. (2019)	Gambia	Children 0–23 m	Wasting 18% in boys/12% in girls[a]
		n = 3867	Stunting 39%[a]
		28,403 measures	Concurrence 9% in boys/5% in girls
Victoria, 2015	8 countries	Newborns	Wasting 3.4%
			Stunting 3.8%
		n = 60,206	Concurrence 0.7%
SAM treatment data			
Imam et al. (2020)	Nigeria	472 children in SAM treatment programme	Stunting 82.8%
Ngari (2018)	Kenya	1169 children admitted for SAM treatment	Stunting 69%
Odei Obeng-Amoako, Myatt, et al. (2020)	Uganda	788 children in SAM treatment programme[b]	Stunting 48.7%

[a]Peaks in wasting at 1 year and stunting at 24 months.
[b]MUAC admission criteria in use to define wasting.

distribution of concurrent wasting and stunting at population level or within SAM treatment programmes (results are presented in Table 4). These studies cover a wide geographical area with 17 covering multiple countries. The largest population prevalence study includes analysis of 84 countries and indicates that fragile and conflict affected states (FCAS) appear to be disproportionately affected with higher rates of concurrent wasting and stunting than stable contexts (pooled prevalence 3.6%, 95% CI [3.5, 3.6] in FCAS compared with 2.24%, 95% CI [2.18, 2.30] in stable contexts p value <0.0001), emphasising the increased vulnerability of children growing up in FCAS countries (Khara et al., 2018).

Population-level data show that wasting, stunting and concurrent wasting and stunting are all more prevalent in boys than girls (Khara et al., 2018; Myatt et al., 2018; Odei Obeng-Amoako, Karamagi, et al., 2020; Odei Obeng-Amoako, Myatt, et al., 2020) and that wasting is higher in younger children while stunting is higher in older children. In the case of concurrent wasting and stunting, the peaks seem to appear between 12 and 30 months (Garenne et al., 2019; Imam et al., 2020; Khara et al., 2018; Mertens, Benjamin-Chung, Colford, Coyle, et al., 2020; Myatt et al., 2019; Odei Obeng-Amoako, Myatt, et al., 2020), with younger children and males being most affected (Odei Obeng-Amoako, Wamani, et al., 2020). In Senegal, a change of direction was observed in risk with age whereby males were more likely to be concurrently wasted and stunted below the age of 30 months but less likely to be wasted above 30 months at the same level of stunting (Garenne et al., 2019).

SAM treatment programme data also indicates that concurrent wasting and stunting are more prevalent in boys and younger children (Imam et al., 2020;Isanaka et al., 2019; Odei Obeng-Amoako, Wamani, et al., 2020). Data from an outpatient therapeutic programme (OTP) programme in Uganda showed that, despite higher overall admission in females, there were more males with concurrent wasting and stunting within the admitted group (Odei Obeng-Amoako, Wamani, et al., 2020).

3.9 | Mortality implications of concurrent wasting and stunting

We identified six studies that explored the mortality implications of concurrent wasting and stunting. Overall, studies show that children with concurrent wasting and stunting are at high risk of mortality (Garenne et al., 2019; McDonald et al., 2013; Mertens, Benjamin-Chung, Colford, Coyle, et al., 2020; Myatt et al., 2018; Myatt et al., 2019; Pomati & Nandy, 2019). A meta-analysis of 10 countries (McDonald et al., 2013) showed that children who are wasted, stunted and underweight had a 12-fold elevated risk of mortality compared with those with no deficit. A later analysis of 51 countries demonstrated that all children who are wasted and stunted are also underweight and, therefore, the same elevated mortality estimate is applicable (Myatt et al., 2018). A recent longitudinal analysis of eight cohorts of children showed that all measures of early growth failure were significantly associated with a higher risk of death by age 24 months and those most strongly associated with death were children severely underweight before age 6 months, children with concurrent wasting and stunting and children under 6 months who were persistently wasted (Mertens, Benjamin-Chung, Colford, Coyle, et al., 2020).

3.10 | Wasting treatment outcomes and stunting

As stated above, stunting is highly prevalent among wasted children admitted to therapeutic feeding programmes (TFPs) (Isanaka et al., 2019; Odei Obeng-Amoako, Wamani, et al., 2020), and there is some evidence of the influence of this on treatment response although, due to limited resources, length/height is not always measured upon admission to TFPs and therefore may be underreported. We identified six studies that assessed SAM treatment outcomes for children who are concurrently wasted and stunted with some inconsistencies in results. Data from Niger found the response to SAM treatment was independent of stunting with no difference in weight gain during or after treatment or in mean time to recovery (Isanaka et al., 2019). Conversely, data from Uganda found lower recovery rates in stunted children compared with nonstunted children during SAM treatment (58.0% vs. 65.4%; $p < 0.037$), higher rates of nonresponse (18.7% vs. 9.8%; $p < 0.001$) but greater weight gain (2.2 g/kg/day vs. 1.7 g/kg/day; $p = 0.004$). MUAC gain did not differ between groups (Odei Obeng-Amoako, Wamani, et al., 2020). Similarly, in Malawi, in a study examining children experiencing relapse after treatment for MAM, those who experienced a negative change in HAZ were more likely to experience relapse to MAM or SAM (OR $= 1.72 \pm 0.20$, $p < 0.001$) (Stobaugh et al., 2018).

Given recent concerns that the provision of therapeutic foods might lead to excess fat accretion in stunted children contributing to future overweight, obesity and noncommunicable disease (Hawkes et al., 2020), we reviewed studies which assessed weight gain and body composition following nutritional therapy. The studies suggest that while stunting might affect response to treatment, there is no evidence of an effect of concurrent wasting and stunting on increased fat accumulation with the use of lipid based nutrient supplements (LNS) for either MAM or SAM (Binns & Myatt, 2018; Fabiansen et al., 2017, 2018; Kangas et al., 2020; Wells, Devakumar, et al., 2019).

Finally, we identified one study that explored longer term outcomes (1 to 7 years after treatment) for 378 children after SAM treatment including linear growth (Lelijveld et al., 2016). The data showed some recovery in the height of previously wasted children, but they still demonstrated more severe stunting than controls. Body composition assessment showed smaller calf and MUAC measurements suggesting reduced peripheral mass compared with control, and smaller hip circumference and larger or similar waist circumference suggesting an unhealthy ratio of core to gluteo-femoral fat. In body composition assessment, cases also had lower FFM but similar fat mass compared with community controls after adjustment for age differences.

3.11 | Anthropometric indices and the identification of risk

We found nine studies that assessed the use of different anthropometric indices and the implications of these on caseload and identifying the most vulnerable undernourished children. Many of these studies are rooted in the recent recognition that concurrent wasting and stunting lead to heightened mortality risk (Myatt et al., 2018) and prompt a re-examination of risk and how best to identify it. Longitudinal analysis on data from Senegal found that the combined use of WAZ and MUAC identified all near-term deaths associated with concurrent wasting and stunting and with severe wasting as defined by WHZ < −3 (Garenne et al., 2019). The lowest WAZ threshold that detected all deaths was <−2.8. Data from Niger similarly showed MUAC to be the best predictor of mortality in children 6–59 months followed by WAZ (O'Brien et al., 2020). Analysis of 16 cross-sectional studies found stunting to be associated with WHZ < −2 and MUAC <125 mm but more strongly associated with MUAC <125 mm. The findings from these studies suggest WAZ identifies children with a high risk of mortality and that MUAC and WHZ might not (Odei Obeng-Amoako, Myatt, et al., 2020); therefore, the use of MUAC with the addition of WAZ might effectively identify those children at most risk and in need of some level of treatment.

3.12 | Ongoing research priorities on the relationship between wasting and stunting

We identified one study that focused on the identification of research priorities for concurrent wasting and stunting (Bhutta et al., 2016). This was a Child Health and Nutrition Research Initiative (CHNRI) exercise that identified top-ranked research questions. In addition to this, we also found research recommendations in several studies. In particular, the need was highlighted to better understand the biological processes and causal pathways, for example, the role of gut health/inflammation, body composition and its relation with anthropometric indicators and functional outcomes, the contribution of lean and fat tissue during and after recovery from SAM (Briend, Khara et al., 2015) and the role of environmental factors and patterns of malnutrition (Angood, 2016).

Among the studies reviewed, prevention stood out as one of the key gap areas for further research that examines the interventions needed to halt and prevent the spiralling of vulnerabilities associated with early growth deficits. Studies called for research that focused on identifying interventions to improve maternal nutrition and prevent the risk of being born wasted or stunted or concurrently wasted and stunted, the magnitude of risk between birth and 3 months of age and interventions to mitigate seasonal peaks (Angood, 2016). Studies also highlighted the need for operational research to better understand the programmatic and cost implications of implementing WAZ and MUAC for targeting and caseload and to examine which treatment protocol approaches support the most vulnerable with the highest impact (Angood, 2016). In terms of treatment, some studies called for research to understand if longer treatment time or post-treatment interventions for SAM would allow for fuller recovery (Kangas et al., 2020) and the optimal RUTF formulation to promote linear growth during and after SAM treatment.

4 | DISCUSSION

A significant and still-growing body of evidence supports the existence of a strong relationship between wasting and stunting, which carries important implications for policy and practice. Wasting and stunting, driven by common factors, frequently occur in the same child, either at the same time or through their life course, with important interactions between them. This demonstrates the need for integrated policy and programme considerations and common prevention strategies.

One of the key findings from this review relates to the peak age of wasting and stunting. Research has previously explored the timing of growth faltering (Victora et al., 2010), but evidence reviewed here shows that the peak in incidence of both wasting and stunting is from birth to 3 months with implications for further deterioration in infancy and childhood. This finding offers new insights into how early experiences and underlying factors can lead to the accumulation of nutrition deficits and suggests that a greater focus on the youngest children and what will prevent their wasting and stunting is required. The increased risk of death by age 24 months illustrated following early growth faltering also points towards the need to place prevention of LBW and early growth failure high on the agenda for global health and nutrition stakeholders. To do this, it is widely recognised that innovative prevention programming that combines interventions targeting the health and nutrition status of women of reproductive age and pregnant women is needed (Bhutta et al., 2013; da Silva Lopes et al., 2017). Improvement in some of these early indicators (for example, birth length, maternal weight, birth order, maternal education levels, wealth indicators) has the potential to prevent 20–30% of the incidents of stunting and wasting (Mertens, Benjamin-Chung, Colford, Coyle, et al., 2020).

This review underscores the finding that both wasting and stunting are interconnected processes linked to various deprivations in a child's environment and that of their mothers (both in-utero and during infancy and childhood) and which lead to physiological and development stresses with consequences for body composition and physiological function. Although the evidence is growing and compelling, questions remain around the physiological mechanisms linking wasting and stunting and further research is warranted, particularly to better understand the critical junctures for halting the accumulation of vulnerabilities that are created as these processes interact. Some evidence suggests that, in addition to muscle and fat loss and hormonal imbalances, stunted children show deficits in the form of small organ size (Wells, Devakumar, et al., 2019) with potential deleterious implications for physiological function. Further research is needed to understand the full biological picture in order to intervene more effectively.

We have reviewed evidence that demonstrates that wasting can lead to stunting and, to a lesser extent, stunting can increase the risk of wasting. The former direction is supported by evidence of a mechanism whereby adequate weight and the absence and/or management of underlying morbidities is needed before linear growth can take place (Garenne, 2020; Isanaka et al., 2019; Ngari et al., 2019; Richard, Black, Gilman et al., 2012; Schoenbuchner et al., 2019). Previously published studies have shown similar findings that wasted children only demonstrate height growth once their weight for height is regained (Dewey et al., 2005) and where seasonal conditions are favourable (Maleta et al., 2003). These findings highlight the importance of the integrated medical and nutritional care of children receiving wasting treatment to ensure the effects of wasting on linear growth are minimised. While severe and/or repeated episodes of wasting may contribute to stunting, the higher prevalence of stunting cannot be solely explained by previous wasting. There are many drivers of stunting and many countries where stunting levels are high but wasting prevalence levels are low (GNR, 2020). The importance of wasting as a driver of stunting is therefore likely to vary by context. The evidence that shows stunting leading to wasting provides a new perspective on understanding how wasting and stunting are interrelated although the relationship is weaker. Further research to understand the mechanisms behind this would be informative for identifying programmatic implications.

Children identified as concurrently wasted and stunted have a dual burden of impact on body composition, which might explain the high risk of mortality associated with having both conditions. The cumulative increased risk of death from concurrent wasting and stunting undermines any rationale for different interventions addressing separate forms of undernutrition. Instead, treatment strategies need to shift focus to consider risk of death as paramount to targeting rather than specific categories of anthropometric cut-offs to define wasting while working alongside prevention. Targeting interventions by season or by population subgroups defined by sex, socio-economic status, maternal and child birth characteristics might help to focus preventive interventions to reduce the burden of postnatal growth failure (Mertens, Benjamin-Chung, Colford, Coyle, et al., 2020).

Most of the prevalence studies in this review reported wasting, stunting and concurrent wasting and stunting as point prevalence. We have presented evidence that demonstrates problems in the underestimation of the actual burden of wasting as children can move in and out of periods of this acute condition throughout the year. Wells, Briend, et al. (2019) argue that the reliance on population-level data describing stunting and wasting gives a profoundly misleading representation of the complexity of the causes of undernutrition and unnecessarily narrows programme and policy approaches to separate prevention and treatment of undernutrition rather than combined understanding and approaches. The design and implementation of nutrition programme and policy should therefore consider how incidence might inform more effective targeting of programme resources.

One of the secondary findings from the work identified in this review is higher prevalence of concurrent wasting and stunting in males. Although the concept of higher levels of male undernutrition is not new, the work here has renewed interest in understanding the reasons for these differences. A recent systematic review of sex differences in undernutrition showed that boys are more likely to be wasted, stunted and underweight compared with girls (Thurstans et al., 2020). There are some nuances in sex and age patterns whereby males appear to be more vulnerable in early years, but in some contexts, the risk is inversed as age increases, making girls more vulnerable (Garenne et al., 2019). This may be indicative of the varying influence of sociological factors over biological factors over time. Programme data collection, surveillance systems and national and local survey indicators should not only disaggregate all data by age and sex, but should also be modified to include the calculation of concurrent wasting and stunting (Odei Obeng-Amoako, Myatt, et al., 2020).

The findings regarding response to SAM treatment for children who are both wasted and stunted are inconsistent. Overall, evidence suggests that outcomes are suboptimal for children with concurrent wasting and stunting. Where positive treatment outcomes are reported, this might be reflective of survivor bias. What is clear is that TFPs need to be optimised to identify most at-risk children including those who are concurrently wasted and stunted (Bergeron & Castleman, 2012; Khara & Dolan, 2014). Likewise, the evidence presented above that wasted children often go on to experience further episodes of wasting (Schoenbuchner et al., 2019) and that wasting leads to stunting highlights the importance of strengthening the links between wasting and stunting prevention programmes. Children who have been enrolled in SAM treatment should be targeted to prevent further episodes. While few interventions have been shown to successfully treat stunting, what is not clear from this review is whether treatment of wasting could be adapted to better lay the foundation for linear growth (Briend, Khara, et al. 2015). For example, is the lack of gain in height solely related to the body's focus on weight gain, related to the RUTF formulations in use and lack of micronutrients to support bone growth or to the timeframe of the intervention? In the case of fat accumulation and overweight/obesity risk, findings from this review seem to allay concerns regarding the risk of excess fat accretion in stunted children.

This review highlights findings that support further operational research into the anthropometric identification and assessment of undernutrition. Evidence shows that MUAC and WAZ are the best measures to identify mortality risk (Myatt et al., 2019) including in infants under 6 months of age (Mwangome et al., 2017). The association between young age and low muscle mass also highlights young infants, in particular those born small for gestational age (SGA), as a priority group (Briend, Khara et al., 2015). This age group is often excluded from programming due to the complexities of the identification of undernutrition. In a recent study, the use of MUAC and WAZ were found to identify high-risk infants under 6 months. LBW, MUAC <9 cm and WAZ - < 3 *Z* score at birth were each positively associated with increased risk of mortality during the first year of life (Mwangome et al., 2019). This has important implications in reaching the most vulnerable children in a way that is programmatically practical and potentially less open to measurement error than WHZ.

The findings in this review on the peak timing of wasting and stunting suggest that policy and practice need to address undernutrition in a way that considers the life cycle of undernutrition, from preventative interventions targeted to women of reproductive age through to treatment when undernutrition occurs in the young child. A significant degree of child undernutrition is established before birth (Christian et al., 2013), indicating the need for greater coordination between interventions targeting adolescent girls and mothers and those aiming to prevent child undernutrition (Wells, Briend, et al., 2019). The evidence on the relationship between stunting and wasting suggests that the divide in tackling undernutrition needs to be addressed at all levels including financing arrangements that should promote longer term funding, particularly in protracted crisis contexts, to allow for investments in prevention as well as more immediate life-saving interventions (MQSUN+, 2020).

The strength of the evidence has come a long way since the original review in 2014, and continued robust research on the priorities laid out above will be key to furthering our understanding of the relationship between wasting and stunting. This would serve to better prioritise prevention and treatment-focused interventions in all contexts where undernutrition is a concern.

The strength of this review lies in the systematic approach taken, but we recognise some limitations. Our search strategy might have introduced some bias in the literature that we included. The findings have demonstrated the overlap in wasting and stunting and the utility of measures of underweight in capturing this. As we did not include the term 'underweight' in our search, there is a chance that we missed relevant literature pertaining to underweight only. However, papers would only have been included if they also mentioned wasting and stunting and so should have been identified by the search. We also do not feel that the overall message that a child should be viewed in a more holistic way would be changed. Similarly, our findings demonstrate that, in many instances, children are born wasted and/or stunted and therefore LBW. While we did not include the terms 'low-birthweight' or 'preterm' in our search, we have presented research that highlights the need for prevention through maternal and newborn interventions. Finally, our search may have had reduced sensitivity with the limits we applied related to relationship and association. However, we felt this was necessary to manage the large quantity of literature related to both wasting and stunting given our interest in the relationship between the two.

For all of the above limitations, we feel our request to members of the WaSt TIG SWG to highlight relevant additional literature has contributed to minimising the effects given their expertise and ongoing work in the field of maternal and child health and nutrition. We recognise the limitations of cross-sectional data throughout the text, and this is particularly relevant for assessing causal associations and incidence. In terms of associations, all cross-sectional evidence that we have presented is supported by longitudinal data, providing robust support to the findings. Finally, there might also be a risk of survivor bias in included studies, particularly those related to long-term outcomes of wasting and stunting.

5 | CONCLUSION

The ongoing accumulation of evidence since the 2014 review demonstrates progress in improving the understanding and awareness of the relationship between wasting and stunting. The findings of this review are supportive of a strong relationship between these two manifestations of undernutrition and provide a better understanding of which groups should be considered at risk and therefore prioritised for treatment.

Evidence on the cumulative effects of nutritional deficits, and therefore risk over the life course of a child beginning in-utero, demonstrates the need for a more integrated approach to prevention and treatment strategies in order to interrupt this process. To achieve this, further progress is needed to overcome the divide that has typified undernutrition policy, programme, financing and research initiatives.

ACKNOWLEDGEMENTS

This paper is made possible by funding from Irish Aid (grant number HQPU/2020/ENN). The ideas, opinions and comments therein are entirely the responsibility of its author(s) and do not necessarily represent or reflect Irish Aid policy.

CONFLICTS OF INTEREST

The authors declare that we have no conflict of interest.

CONTRIBUTIONS

ST led in the development of the study protocol which was reviewed by TK and CD. ST conducted the search with a second review by NS. ST led in the analysis and the write up of the manuscript with regular contributions from all authors. All authors have read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

REFERENCES

Angood, C. (2016). Research priorities on the relationship between wasting and stunting. *Field Exchange - Emergency Nutrition Network ENN*, 28–29.

Action Against Hunger (2018). Improving Estimates of Children with Severe Acute Malnutrition. Stakeholders Consultative Meeting Report.

Benjamin-Chung, J., Mertens, A., Colford, J. M., Hubbard, A. E., van der Laan, M. J., Coyle, J., Sofrygin, O., Cai, W., Nguyen, A., Pokpongkiat, N. N., Djajadi, S., Seth, A., Jilek, W. M., Chung, E. O., Dayal, S., Hejazi, N., Malencia, I., Li, H., Hafen, R., … Arnold, B. F. (2020). Early childhood linear growth failure in low- and middle-income countries.

Bergeron, G., & Castleman, T. (2012). Program responses to acute and chronic malnutrition: divergences and convergences. *Advances in Nutrition*, *3*, 242–249.

Bhutta, Z. A., Angood, C., Khara, T., Dolan, C., & Berkley, J. A. (2016). Research priorities on the relationship between wasting and stunting. *PLoS ONE*, *11*, e0153221.

Bhutta, Z. A., Das, J. K., Rizvi, A., Gaffey, M. F., Walker, N., Horton, S., Webb, P., Lartey, A., & Black, R. E. (2013). Evidence-based interventions for improvement of maternal and child nutrition: What can be done and at what cost? *The Lancet*, *382*, 452–477.

Binns, P., & Myatt, M. (2018). Does treatment of short or stunted children aged 6–59 months for severe acute malnutrition using ready to use therapeutic food make them overweight? Data from Malawi. *Archives of Public Health*, *76*, 78.

Black, R. E., Victora, C. G., Walker, S. P., Bhutta, Z. A., Christian, P., de Onis, M., Ezzati, M., Grantham-McGregor, S., Katz, J., Martorell, R., & Uauy, R. (2013). Maternal and child undernutrition and overweight in low-income and middle-income countries. *The Lancet*, *382*, 427–451.

Briend, A., Akomo, P., Bahwere, P., De Pee, S., & Dibari, F. (2015). Developing food supplements for moderately malnourished children: Lessons learned from ready-to-use therapeutic foods. *Food and Nutrition Bulletin*, *36*, S53–S58. https://doi.org/10.1177/15648265150361S109

Briend, A., Khara, T., & Dolan, C. (2015). Wasting and stunting—Similarities and differences: Policy and programmatic implications. *Food and Nutrition Bulletin*, *36*(1_suppl1), S15–S23.

Carroll, C., Booth, A., & Lloyd-Jones, M. (2012). Should we exclude inadequately reported studies from qualitative systematic reviews? An evaluation of sensitivity analyses in two case study reviews. *Qualitative Health Research*, *22*, 1425–1434.

Christian, P., Lee, S. E., Angel, M. D., Adair, L. S., Arifeen, S. E., Ashorn, P., Barros, F. C., Fall, C. H. D., Fawzi, W. W., Hao, W., Hu, G., Humphrey, J. H., Huybregts, L., Joglekar, C. V., Kariuki, S. K., Kolsteren, P., Krishnaveni, G. V., EnQing, L., Martorell, R., … ter Kuile, F. O. (2013). Risk of childhood undernutrition related to small-for-gestational age and preterm birth in low- and middle-income countries. *International Journal of Epidemiology*, *42*, 1340–1355.

da Silva Lopes, K., Ota, E., Shakya, P., Dagvadorj, A., Balogun, O. O., Pena-Rosas, J. P., De-Regil, L. M., & Mori, R. (2017). Effects of nutrition interventions during pregnancy on low birth weight: An overview of systematic reviews. *BMJ Global Health*, *2*, e000389.

Dewey, K., Hawck, M. G., Brown, K. H., Lartey, A., Cohen, R. J., & Peerson, J. M. (2005). Infant weight-for-length is positively associated with subsequent linear growth across four different populations. *Maternal & Child Nutrition*, *1*, 11–20.

Fabiansen, C., Kp, P., Cichon, B., Ritz, C., Briend, A., Kf, M., Friis, H., & Shepherd, S. (2016). Short children with a low midupper arm circumference respond to food supplementation: An observational study from Burkina Faso. *American Journal of Clinical Nutrition*, *103*, 415–421.

Fabiansen, C., Phelan, K. P., Cichon, B., & Yameogo, C. W. (2018). Short malnourished children and fat accumulation with food supplementation. *Pediatrics*, *142*, e20180679. https://doi.org/10.1542/peds.2018-0679

Fabiansen, C., Yaméogo, C. W., Iuel-Brockdorf, A. S., Cichon, B., Rytter, M. J. H., Kurpad, A., Wells, J. C., Ritz, C., Ashorn, P., Filteau, S., Briend, A., Shepherd, S., Christensen, V. B., Michaelsen, K. F., & Friis, H. (2017). Effectiveness of food supplements in increasing fat-free tissue accretion in children with moderate acute malnutrition: A randomised $2 \times 2 \times 3$ factorial trial in Burkina Faso. *PLoS Medicine*, *14*, e1002387. https://doi.org/10.1371/journal.pmed.1002387

Garenne, M. (2020). Taller but thinner: Trends in child anthropometry in Senegal, 1990–2015. *Public Health Nutrition*, *23*(13), 2365–2372.

Garenne, M., Myatt, M., Khara, T., Dolan, C., & Briend, A. (2019). Concurrent wasting and stunting among under-five children in Niakhar, Senegal. *Maternal & Child Nutrition*, *15*, e12736.

Development Initiatives, 2018. 2018 Global Nutrition Report: Shining a light to spur action on nutrition.

Global Nutrition Report 2020: Action on equity to end malnutrition. Bristol, UK: Development Initiatives.

Harding, K. L., Aguayo, V. M., & Webb, P. (2018a). Birthweight and feeding practices are associated with child growth outcomes in South Asia. *Maternal & Child Nutrition*, *14*(Supplement 4), e12650.

Harding, K. L., Aguayo, V. M., & Webb, P. (2018b). Factors associated with wasting among children under five years old in South Asia: Implications for action. *PLoS ONE*, *13*, e0198749.

Hawkes, C., Ruel, M. T., Salm, L., Sinclair, B., & Branca, F. (2020). Double-duty actions: Seizing programme and policy opportunities to address malnutrition in all its forms. *The Lancet*, *395*, 142–155.

Imam, A., Hassan-Hanga, F., Sallahdeen, A., & Farouk, Z. L. (2020). A cross-sectional study of prevalence and risk factors for stunting among under-fives attending acute malnutrition treatment programmes in north-western Nigeria: Should these programmes be adapted to also manage stunting? *International Health*, *13*(3), 262–271.

Isanaka, S., Hitchings, M. D. T., Berthe, F., Briend, A., & Grais, R. F. (2019). Linear growth faltering and the role of weight attainment: Prospective analysis of young children recovering from severe wasting in Niger. *Maternal & Child Nutrition*, *15*, e12817.

Kangas, S. T., Kaestel, P., Salpeteur, C., Nikiema, V., Talley, L., Briend, A., Ritz, C., Friis, H., & Wells, J. C. (2020). Body composition during outpatient treatment of severe acute malnutrition: Results from a randomised trial testing different doses of ready-to-use therapeutic foods. *Clinical Nutrition*, *39*, 3426–3433. https://doi.org/10.1016/j.clnu.2020.02.038

Kassie, G. W., & Workie, D. L. (2019). Exploring the association of anthropometric indicators for under-five children in Ethiopia. *BMC Public Health*, *19*, 764.

Khara, T, & Dolan, C. (2014). Technical Briefing Paper: The relationship between wasting and stunting, policy, programming and research implications.

Khara, T., Mwangome, M., Ngari, M., & Dolan, C. (2018). Children concurrently wasted and stunted: A meta-analysis of prevalence data of children 6–59 months from 84 countries. *Maternal & Child Nutrition*, *14*(2), e12516.

Kosek, M. N., & Mal-Ed Network Investigators. (2017). Causal pathways from enteropathogens to environmental enteropathy: Findings from the MAL-ED Birth Cohort Study. *eBioMedicine*, *18*, 109–117.

Lelijveld, N., Seal, A., Wells, J. C., Kirkby, J., Opondo, C., Chimwezi, E., Bunn, J., Bandsma, R., Heyderman, R. S., Nyirenda, M. J., & Kerac, M. (2016). Chronic disease outcomes after severe acute malnutrition in Malawian children (ChroSAM): A cohort study. *The Lancet Global Health*, *4*, e654–e662.

Maleta, K., Virtanen, S. M., Espo, M., Kulmala, T., & Ashorn, P. (2003). Seasonality of growth and the relationship between weight and height gain in children under three years of age in rural Malawi. *Acta Paediatrica*, *92*, 491–497.

McDonald, C. M., Olofin, I., Flaxman, S., Fawzi, W. W., Spiegelman, D., Caulfield, L. E., Black, R. E., Ezzati, M., & Danaei, G. (2013). The effect of multiple anthropometric deficits on child mortality: Meta-analysis of individual data in 10 prospective studies from developing countries. *American Journal of Clinical Nutrition*, *97*, 896–901.

Mertens, A., Benjamin-Chung, J., Colford, J. M., Coyle, J., van der Laan, M., Hubbard, A. E., Dayal, S., Malenica, I., Hejazi, N., Sofrygin, O., Cai, W., Li, H., Nguyen, A., Pokpongkiat, N. N., Djajadi, S., Seth, A., Chung, E. O., Jilek, W., Subramoney, V., … Arnold, B. F. (2020). Causes and consequences of child growth failure in low- and middle-income countries. *MedRxiv*.

Mertens, A., Benjamin-Chung, J., Colford, J. M., Hubbard, A. E., van der Laan, M., Coyle, J., Sofrygin, O., Cai, W., Jilek, W., Dayal, S., Nguyen, A., Pokpongkiat, N., Djajadi, S., Seth, A., Chung, E. O., Malenica, I., Hejazi, N., Li, H., Hafen, R., … Arnold, B. F. (2020). Child wasting and concurrent stunting in low- and middle-income countries. *MedRxiv*.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & Prisma Group. (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *BMJ*, *339*, b2535.

MQSUN+. (2020). Strengthening the Humanitarian Development Nexus for Nutrition in Protracted Crises.

Murray, C. J. L., Aravkin, A. Y., Zheng, P., Abbafati, C., Abbas, K. M., Abbasi-Kangevari, M., Abd-Allah, F., Abdelalim, A., Abdollahi, M., Abdollahpour, I., & Abegaz, K. H. (2020). Global burden of 87 risk factors in 204 countries and territories, 1990–2019: A systematic analysis for the Global Burden of Disease Study 2019. *The Lancet*, *396*, 1223–1249. https://doi.org/10.1016/S0140-6736(20)30752-2

Mwangome, M., Ngari, M., Bwahere, P., Kabore, P., McGrath, M., Kerac, M., & Berkley, J. A. (2019). Anthropometry at birth and at age of routine vaccination to predict mortality in the first year of life: A birth cohort study in BukinaFaso. *PLoS ONE*, *14*, e0213523.

Mwangome, M., Ngari, M., Fegan, G., Mturi, N., Shebe, M., Bauni, E., & Berkley, J. A. (2017). Diagnostic criteria for severe acute malnutrition among infants aged under 6 mo. *The American Journal of Clinical Nutrition*, *105*, 1415–1423.

Myatt, M., Khara, T., Dolan, C., Garenne, M., & Briend, A. (2019). Improving screening for malnourished children at high risk of death: A study of children aged 6–59 months in rural Senegal. *Public Health Nutrition*, *22*, 862–871.

Myatt, M., Khara, T., Schoenbuchner, S., Pietzsch, S., Dolan, C., Lelijveld, N., & Briend, A. (2018). Children who are both wasted and stunted are also underweight and have a high risk of death: A descriptive epidemiology of multiple anthropometric deficits using data from 51 countries. *Arch Public Health*, *76*, 28.

Nandy, S., & Svedberg, P. (2012). The Composite Index of Anthropometric Failure (CIAF): An alternative indicator for malnutrition in young children. In *Handbook of anthropometry*. New York, NY: Springer.

Ngari, M. M., Iversen, P. O., Thitiri, J., Mwalekwa, L., Timbwa, M., Fegan, G. W., & Berkley, J. A. (2019). Linear growth following complicated severe malnutrition: 1-year follow-up cohort of Kenyan children. *Archives of Disease in Childhood*, *104*, 229–235.

Ngwira, A., Munthali, E. C., & Vwalika, K. D. (2017). Analysis on the association among stunting, wasting and underweight in Malawi: An application of a log-linear model for the three-way table. *Journal of Public Health in Africa*, *8*, 1–4.

O'Brien, K. S., Amza, A., Kadri, B., Nassirou, B., Cotter, S. Y., Stoller, N. E., West, S. K., Bailey, R. L., Porco, T. C., Keenan, J. D., Lietman, T. M., & Oldenburg, C. E. (2020). Comparison of anthropometric indicators to predict mortality in a population-based prospective study of children under 5 years in Niger. *Public Health Nutrition*, *23*, 538–543.

Odei Obeng-Amoako, G. A., Karamagi, C. A. S., Nangendo, J., Okiring, J., Kiirya, Y., Aryeetey, R., Mupere, E., Myatt, M., Briend, A., Kalyango, J. N., & Wamani, H. (2020). Factors associated with concurrent wasting and stunting among children 6–59 months in Karamoja, Uganda. *Maternal & Child Nutrition*, *17*, e13074.

Odei Obeng-Amoako, G. A., Myatt, M., Conkle, J., Muwaga, B. K., Aryeetey, R., Okwi, A. L., Okullo, I., Mupere, E., Wamani, H., Briend, A., Karamagi, C. A., & Kalyango, J. N. (2020). Concurrently wasted and stunted children 6–59 months in Karamoja, Uganda: Prevalence and case detection. *Maternal & Child Nutrition*, *16*, e13000.

Odei Obeng-Amoako, G. A., Wamani, H., Conkle, J., Aryeetey, R., Nangendo, J., Mupere, E., Kalyango, J. N., Myatt, M., Briend, A., & Karamagi, C. A. S. (2020). Concurrently wasted and stunted 6–59 months children admitted to the outpatient therapeutic feeding programme in Karamoja, Uganda: Prevalence, characteristics, treatment outcomes and response. *PLoS ONE*, *15*, e0230480.

Pomati, M., & Nandy, S. (2019). Assessing progress towards SDG2: Trends and patterns of multiple malnutrition in young children under 5 in West and Central Africa. *Child Indicators Research*, *13*, 1847–1873.

Prentice, A. M., Moore, S. E., & Fulford, A. J. (2013). Growth faltering in low-income countries. *World Review of Nutrition and Dietetics*, *106*, 90–99.

Reese-Masterson, A., Maehara, M., & Gathii, M. M. (2016). Stunting and wasting in children under two years old in a semi-nomadic pastoralist population in Kenya. *Field Exchange - Emergency Nutrition Network ENN*, *52*, 11–13.

Richard, S. A., Black, R. E., & Checkley, W. (2012). Revisiting the relationship of weight and height in early childhood. *Advances in Nutrition*, *3*, 250–254.

Richard, S. A., Black, R. E., Gilman, R. H., Guerrant, R. L., Kang, G., Lanata, C. F., Molbak, K., Rasmussen, Z. A., Sack, R. B., Valentiner-Branth, P., Checkley, W., Infection, C., & Network, M. (2012). Wasting is associated with stunting in early childhood. *Journal of Nutrition*, *142*, 1291–1296.

Saaka, M., & Galaa, S. Z. (2016). Relationships between wasting and stunting and their concurrent occurrence in Ghanaian preschool children. *Journal of Nutrition and Metabolism*, *2016*, 4654920.

Sage, A. (2017). Predicting coexistence of wasting and stunting in Guinea-Bissau: A secondary data analysis. *Field Exchange - Emergency Nutrition Network ENN*, *54*, 40–41.

Schoenbuchner, S. M., Dolan, C., Mwangome, M., Hall, A., Richard, S. A., Wells, J. C., Khara, T., Sonko, B., Prentice, A. M., & Moore, S. E. (2019). The relationship between wasting and stunting: a retrospective cohort analysis of longitudinal data in Gambian children from 1976 to 2016. *American Journal of Clinical Nutrition*, *110*, 498–507.

Shively, G. E. (2017). Infrastructure mitigates the sensitivity of child growth to local agriculture and rainfall in Nepal and Uganda. *Proceedings of the National Academy of Sciences of the United States of America*, *114*, 903–908.

Stobaugh, H. C., Rogers, B. L., Rosenberg, I. H., Webb, P., Maleta, K. M., Manary, M. J., & Trehan, I. (2018). Children with poor linear growth are at risk for repeated relapse to wasting after recovery from moderate acute malnutrition. *Journal of Nutrition*, *148*, 974–979.

SUN. (2016). Scaling Up Nutrition. Sun Movement Strategy and Roadmap (2016–2020).

Thurstans, S., Opondo, C., Seal, A., Wells, J. C., & Khara, T. (2020). Boys are more likely to be undernourished than girls: A systematic review and meta- analysis of sex differences in undernutrition. *BMJ Global Health*, *5*, e004030. https://doi.org/10.1136/bmjgh-2020-004030

Victora, C. G., de Onis, M., Hallal, P. C., Blossner, M., & Shrimpton, R. (2010). Worldwide timing of growth faltering: revisiting implications for interventions. *Pediatrics*, *125*, e473–e480.

Victora, C. G., Adair, L., Fall, C., Hallal, P. C., Martorell, R., Richter, L., & Sachdev, H. S. (2008). Maternal and child undernutrition: consequences for adult health and human capital. *The Lancet*, *371*, 340–357.

Wells, J. C. K. (2019). Body composition of children with moderate and severe undernutrition and after treatment: A narrative review. *BMC Medicine*, *17*, 215.

Wells, J. C. K., Briend, A., Boyd, E. M., Berkely, J. A., Hall, A., Isanaka, S., Webb, P., Khara, T., & Dolan, C. (2019). Beyond wasted and stunted—A major shift to fight child undernutrition. *The Lancet Child & Adolescent Health*, *3*, 831–834. https://doi.org/10.1016/S2352-4642(19)30244-5

Wells, J. C. K., Devakumar, D., Manandhar, D. S., Saville, N., Chaube, S. S., Costello, A., & Osrin, D. (2019). Associations of stunting at 2 years with body composition and blood pressure at 8 years of age: Longitudinal cohort analysis from lowland Nepal. *European Journal of Clinical Nutrition*, *73*, 302–310.

How to cite this article: Thurstans, S., Sessions, N., Dolan, C., Sadler, K., Cichon, B., Isanaka, S., Roberfroid, D., Stobaugh, H., Webb, P., & Khara, T. (2021). The relationship between wasting and stunting in young children: A systematic review. *Maternal & Child Nutrition*, e13246. https://doi.org/10.1111/mcn.13246

Appendix 7: Wider PhD Outputs

In addition to the peer reviewed papers included in this thesis, the findings from this PhD have been shared widely to date through various channels.

Podcasts

1. Podcast on sex differences in undernutrition. A podcast was recorded and released on the 30th March 2022 on the ENN website.

The recording is available at the following link:
https://www.ennonline.net/mediahub/podcast/sexdifferencespodcast

"In this podcast, ENN's Tanya Khara discusses with WaSt TIG members Susan Thurstans and Michel Garenne, collaborative work that they have led exploring patterns of sex differences in undernutrition and the early life mechanisms that may underlie them."

2. Podcast on Understanding the relationship between wasting and stunting: A conversation on the findings of our systematic review on this topic.

A podcast was recorded and released on the 19th May 2022 on the ENN website. The recording is available at the following link:
https://www.ennonline.net/mediahub/podcast/wastsystematicreview

"This podcast records a conversation between Tanya Khara (ENN Technical Director and Coordinator of the WaSt TIG) and Susan Thurstans (member of the WaSt TIG and lead author of the systematic review) who discuss some of the key findings of the systematic review which looks at the relationship between wasting and stunting and some of the outstanding questions that remain. Carmel Dolan (member of the WaSt TIG) and Gloria Odei (a researcher who has been influenced by the groups work) also give us their main takeaways from the review and thoughts on what comes next."

Blogs

Boys are more likely to be undernourished than girls: some thoughts on a recently published systematic review by Susan Thurstans

Available at: https://www.ennonline.net/mediahub/blog/sexdifferencesinundernutrition

Targeting wasting treatment and age – are we on the right track? By Tanya Khara and Susan Thurstans on 14 April 2023

Available at: https://www.ennonline.net/mediahub/blog/targeting-wasting-treatment-and-age-are-we-on-the-right-track

Research Summary pieces

Susan Thurstans (2022). Understanding sex differences in childhood malnutrition. Field Exchange 67, April 2022. p58. www.ennonline.net/fex/67/researchsummarysexdifferences [98]

Summer projects supervised

During the course of this research, I was able to work with an MSc student and supervised a summer project evaluating perceptions of male female differences in malnutrition and the implications for field assessment of anthropometry. This was a qualitative study involving key informant interviews. Generally, stakeholders were aware of increased prevalence among males in undernutrition, but it was a surprising trend for many [81].

Citation: Mughal, M. (2020) Perceptions of male female differences in malnutrition and implications for field assessment of anthropometry: A qualitative study. Available at: https://discover.lshtm.ac.uk/discovery/search?query=any,contains,perceptions%20of%20male%20female%20differences%20in%20malnutrition%20and%20implications%20for%20field%20assessment%20of%20anthropometry%20a%20qualitative%20study&tab=Everything&search_scope=MyInstitution&vid=44HYG_INST:44HYG_VU1&offset=0

Presentations and meetings

Research findings were shared at the following:

- LSHTM research degree poster day (see page 202)
- ACF conference 2019 poster presentation (see page 202)
- Speaker presentation: WaSt TiG Group May 2020
- Speaker presentation: Global health Seminar at UCL, March 2022

Boys are more undernourished than girls
A systematic review and meta-analysis

Susan Thurstans (1), Charles Opondo (1), Andrew Seal (2), Jonathan Wells (2), Tanya Khara (3), Rebecca Sear (1), Marko Kerac (1)

(1) London School of Hygiene and Tropical Medicine
(2) University College London
(3) Emergency Nutrition Network

Background

Within neonatal and infant health fields, excess male morbidity and mortality is well recognised and biological mechanisms are well described. How sex differences translate to risk and outcomes in the field of nutrition is understudied, and the practical implications remain to be determined.

Objectives

To review the evidence for sex differences in undernutrition,
To review the recognition and understanding of these differences, review the explanations offered,

Methods

We conducted a systematic review and meta-analysis following PRISMA guidelines. We used search terms that encapsulated undernutrition, sex and gender. Studies were identified by searching Medline, Embase, Global health, Popline and Cochrane databases. The analysis was conducted in two parts, a qualitative systematic review and a meta-analysis of a subset of papers. In the meta-analysis, undernutrition-specific estimates were pooled separately for wasting, stunting and underweight using a random effects model.

Results

The initial search provided 34,270 results. After removing duplicates and screening we included 134 studies in the qualitative synthesis and 46 the meta-analysis.

75 studies reported on measures of undernutrition as an outcome. From this, 63 (84%) reported more undernourished boys than girls, 10 (13%) reported more undernourished girls than boys and 2 (3%) reported no significant difference.

46 of the 75 studies were eligible for inclusion in the meta-analysis as they presented fully disaggregated data.

20 studies were included in the analysis for wasting. Boys were more likely to be undernourished than girls, (OR 1.26, 95% CI- 1.13-1.40, P=<0.001).

39 studies were included in the analysis for stunting. Boys had higher odds of being stunted than girls, (OR 1.31 95% CI-1.24-1.39, P=<0.001).

25 studies were included in the analysis for underweight. Boys had higher odds of being underweight than girls (OR 1.19, 95% CI-1.07-1.32, P=0.001).

When stratified by geographical region (see graphs below) and age, the odds of boys being undernourished remained higher than for girls across most regions, though in South and South East Asia some studies show girls were more likely to be undernourished.

When stratified by age, results also show that boys are at higher risk though the age grouping potentially masks some complexities as detailed analysis of different ages was not possible. Where sex differences are reported, they are not always acknowledged or explored.

We reviewed the discussion sections of studies that identified sex differences to determine if they provided explanations for said differences. 42 (56%) of the studies did discuss the findings, 11 (15%) studies cited articles with similar findings but did not speculate as to the causes of differences and 22 (29%) of the studies provided no discussion on sex differences at all. 5 studies (12%) attributed differences to biological causes, 20 (48%) to social causes and 17 (40%) to a combination of the two.

Discussion

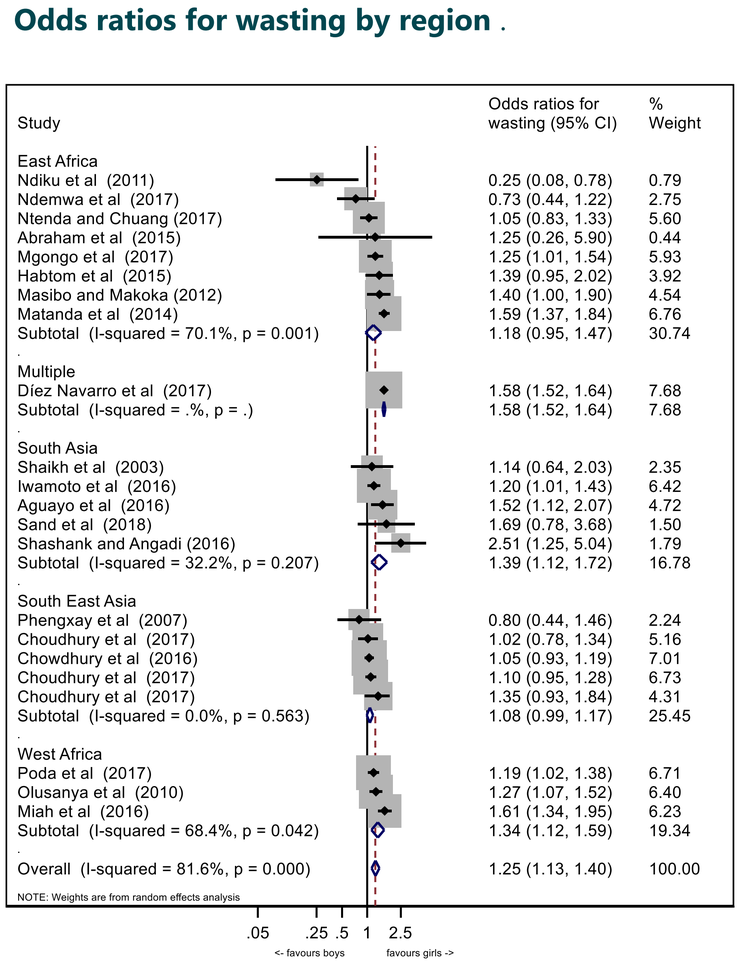
Evidence from this review suggests that the concept of increased vulnerability amongst males is not fully understood in the field of nutrition. The meta-analysis shows overwhelmingly that boys appear to be more at risk of undernutrition than girls.

The results demonstrate geographical variance in sex differences. Overall, with the exception of a South America (single study), there are no regions where girls have a higher risk of undernutrition than boys. Within some regions there are a wide range of odds ratios, particularly in South and South East Asia.

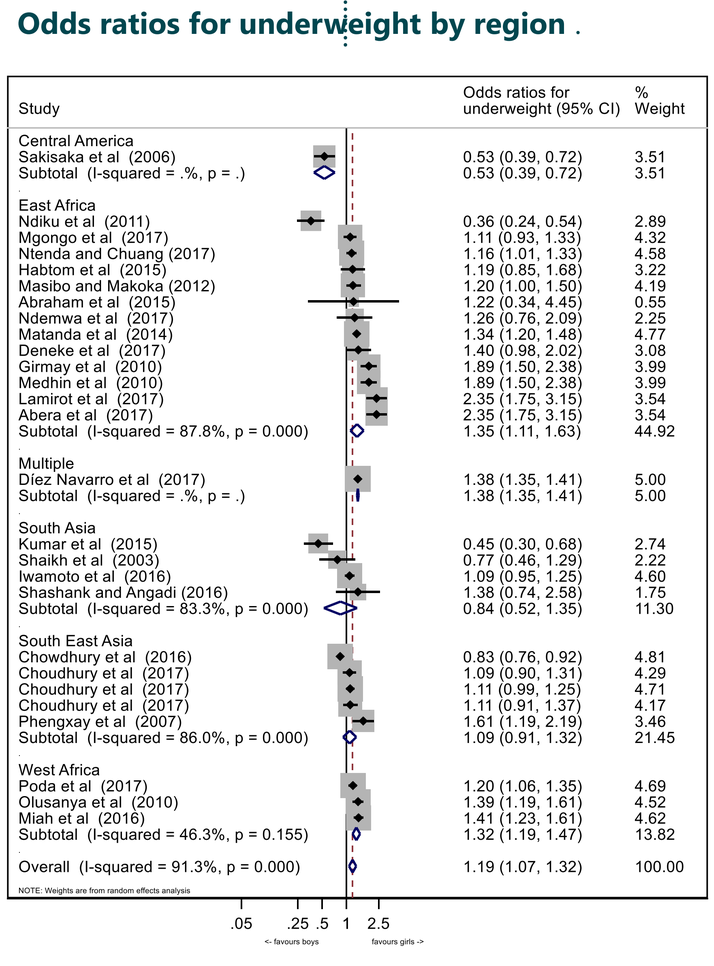
Conclusion

This review suggests that undernutrition is more common among boys, though the extent of these differences vary and can be more pronounced in some contexts than others.

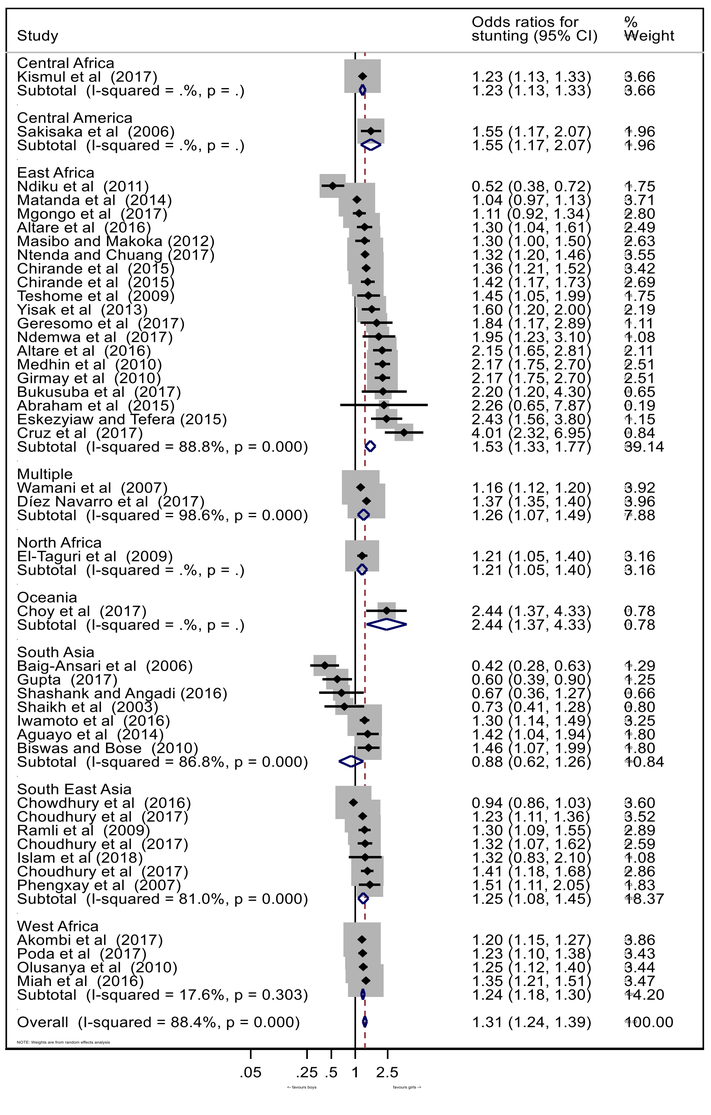
Odds ratios for wasting by region .



Odds ratios for underweight by region .



Odds ratios for stunting by region .



References[6]

1. Group, U.W.W.B., *Levels and trends in child malnutrition. Joint Child Malnutrition Estimates. Key findings of the 2023 edition.* 2023.
2. Isanaka, S., et al., *Improving Estimates of Numbers of Children With Severe Acute Malnutrition Using Cohort and Survey Data.* American Journal of Epidemiology, 2016. **184**(12): p. 861-869.
3. GNR, *Global Nutrition Report The state of global nutrition.* 2021.
4. UNICEF, *Global Action Plan on Child Wasting. A framework for action to accelerate progress in preventing and managing child wasting and the achievement of the Sustainable Development Goals.*
5. ALNAP, *The State of the Humantarian System.* 2022.
6. Akhter, N., et al., *Risk factors for non-communicable diseases related to obesity among first- and second-generation Bangladeshi migrants living in north-east or south-east England.* International Journal of Obesity, 2021. **45**(7): p. 1588-1598.
7. Wells, J.C., et al., *The double burden of malnutrition: aetiological pathways and consequences for health.* The Lancet, 2020. **395**(10217): p. 75-88.
8. Kerac, M., et al., *'Severe malnutrition': thinking deeply, communicating simply.* BMJ Glob Health, 2020. **5**(11).
9. Harding, K.L., V.M. Aguayo, and P. Webb, *Factors associated with wasting among children under five years old in South Asia: Implications for action.* PLoS One, 2018. **13**(7): p. e0198749.
10. Mertens, A., et al., *Causes and consequences of child growth failure in low- and middle-income countries.* 2020.
11. Saaka, M. and S.Z. Galaa, *Relationships between Wasting and Stunting and Their Concurrent Occurrence in Ghanaian Preschool Children.* J Nutr Metab, 2016. **2016**: p. 4654920.
12. Shively, G.E., *Infrastructure mitigates the sensitivity of child growth to local agriculture and rainfall in Nepal and Uganda.* Proc Natl Acad Sci U S A, 2017. **114**(5): p. 903-908.
13. Benjamin-Chung, J., et al., *Early childhood linear growth failure in low- and middle-income countries.* 2020.
14. Prentice, A.M., S.E. Moore, and A.J. Fulford, *Growth faltering in low-income countries.* World Rev Nutr Diet, 2013. **106**: p. 90-9.
15. Martorell, R. and M.F. Young, *Patterns of stunting and wasting: potential explanatory factors.* Adv Nutr, 2012. **3**(2): p. 227-33.
16. Hawkes, C., et al., *Double-duty actions: seizing programme and policy opportunities to address malnutrition in all its forms.* Lancet, 2020. **395**(10218): p. 142-155.
17. Victora, C.G., et al., *Worldwide timing of growth faltering: revisiting implications for interventions.* Pediatrics, 2010. **125**(3): p. e473-80.
18. Mertens, A., et al., *Child wasting and concurrent stunting in low- and middle-income countries.* MedRxiv, 2020.
19. Thurstans, S., et al., *The relationship between wasting and stunting in young children: A systematic review.* Matern Child Nutr, 2021: p. e13246.
20. Black, R.E., et al., *Maternal and child undernutrition: global and regional exposures and health consequences.* The Lancet, 2008. **371**(9608): p. 243-260.

[6] This reference list contains references used in the background, discussion, and recommendations sections. Additional reference lists for the published and submitted papers can be found in the relevant chapters.

21. Swinburn, B.A., et al., *The Global Syndemic of Obesity, Undernutrition, and Climate Change: The Lancet Commission report.* The Lancet, 2019. **393**(10173): p. 791-846.
22. Initiatives, D., *Global Nutrition Report 2018: Shining a light to spur action on nutrition, Development Initiatives.* 2018
23. Olofin, I., et al., *Associations of suboptimal growth with all-cause and cause-specific mortality in children under five years: a pooled analysis of ten prospective studies.* PLoS ONE, 2013. **8**(5): p. e64636.
24. Olofin, I., et al., *Associations of Suboptimal Growth with All-Cause and Cause-Specific Mortality in Children under Five Years: A Pooled Analysis of Ten Prospective Studies.* PLOS ONE, 2013. **8**(5): p. e64636.
25. Dewey, K.G. and K. Begum, *Long-term consequences of stunting in early life.* Matern Child Nutr, 2011. **7 Suppl 3**(Suppl 3): p. 5-18.
26. Victora, C.G., et al., *Maternal and child undernutrition: consequences for adult health and human capital.* The Lancet, 2008. **371**(9609): p. 340-357.
27. Mengling, C., et al., *Exposure to the 1959-1961 Chinese Famine and Risk of Non-Communicable Diseases in Later Life: a Life Course Perspective.* medRxiv, 2022: p. 2022.12.22.22283863.
28. Mbabazi, J., et al., *Effect of milk protein and whey permeate in large quantity lipid-based nutrient supplement on linear growth and body composition among stunted children: A randomized 2 x 2 factorial trial in Uganda.* PLoS Med, 2023. **20**(5): p. e1004227.
29. Amir, K., et al., *Neurodevelopmental, cognitive, behavioural and mental health impairments following childhood malnutrition: a systematic review.* BMJ Global Health, 2022. **7**(7): p. e009330.
30. Lelijveld, N., et al., *Long-term outcomes for children with disability and severe acute malnutrition in Malawi.* BMJ Glob Health, 2020. **5**(10).
31. Grey, K., et al., *Severe malnutrition or famine exposure in childhood and cardiometabolic non-communicable disease later in life: a systematic review.* BMJ Glob Health, 2021. **6**(3).
32. Wells, J.C.K., et al., *Beyond wasted and stunted—a major shift to fight child undernutrition.* The Lancet Child & Adolescent Health, 2019. **3**(11): p. 831-834.
33. de Onis, M., et al., *Prevalence thresholds for wasting, overweight and stunting in children under 5 years.* Public Health Nutr, 2019. **22**(1): p. 175-179.
34. Khara, T., et al., *Children concurrently wasted and stunted: A meta-analysis of prevalence data of children 6-59 months from 84 countries.* Matern Child Nutr, 2018. **14**(2): p. e12516.
35. Myatt, M., et al., *Children who are both wasted and stunted are also underweight and have a high risk of death: a descriptive epidemiology of multiple anthropometric deficits using data from 51 countries.* Arch Public Health, 2018. **76**: p. 28.
36. Wells, J.C., *Natural selection and sex differences in morbidity and mortality in early life.* J Theor Biol, 2000. **202**(1): p. 65-76.
37. Garenne, M. and M. Lafon, *Sexist diseases.* Perspect Biol Med, 1998. **41**(2): p. 176-89.
38. Garenne, M., *Sex differences in health indicators among children in African DHS surveys.* Journal of Biosocial Science, 2003. **35**(4): p. 601-614.
39. Townsel, C.D., et al., *Gender Differences in Respiratory Morbidity and Mortality of Preterm Neonates.* Front Pediatr, 2017. **5**: p. 6.
40. WHO, *Addressing sex and gender in epidemic-prone infectious diseases.* 2007.
41. Kraemer, S., *The fragile male.* Bmj, 2000. **321**(7276): p. 1609-12.
42. Lozano, R., et al., *Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010.* Lancet, 2012. **380**(9859): p. 2095-128.
43. Di Renzo, G.C., et al., *Does fetal sex affect pregnancy outcome?* Gender Medicine, 2007. **4**(1): p. 19-30.

44. Broere-Brown, Z.A., et al., *Fetal sex and maternal pregnancy outcomes: a systematic review and meta-analysis.* Biology of Sex Differences, 2020. **11**(1): p. 26.
45. Hawkes, S. and K. Buse, *Gender and global health: evidence, policy, and inconvenient truths.* The Lancet, 2013. **381**(9879): p. 1783-1787.
46. Zarulli, V., et al., *Women live longer than men even during severe famines and epidemics.* Proceedings of the National Academy of Sciences, 2018. **115**(4): p. E832-E840.
47. Heidari, S., et al., *Sex and Gender Equity in Research: rationale for the SAGER guidelines and recommended use.* Research Integrity and Peer Review, 2016. **1**(1): p. 2.
48. Forum, W.E., *Global Gender Gap Report* 2023.
49. Gribble, K.D., et al., *Effective Communication About Pregnancy, Birth, Lactation, Breastfeeding and Newborn Care: The Importance of Sexed Language.* Front Glob Womens Health, 2022. **3**: p. 818856.
50. WHO, *Assessment of differences in linear growth among populations in the WHO Multicentre Growth Reference Study.* Acta Paediatr Suppl, 2006. **450**: p. 56-65.
51. Kerac, M., et al., *Improved assessment of child nutritional status using target weights and a novel, low-cost, weight-for-height slide chart.* Trop Doct, 2009. **39**(1): p. 23-6.
52. Sikorski, C., et al., *Preliminary evaluation of the Moyo chart-a novel, low-cost, weight-for-height slide chart for the improved assessment of nutritional status in children.* Trans R Soc Trop Med Hyg, 2010. **104**(11): p. 743-5.
53. IASC, *Inter-Agency Standing Commitee. The Gender Handbook for Humantarian Action* 2018.
54. UNICEF, *Undernourished and Overlooked: A Global Nutrition Crisis in Adolescent Girls and Women. UNICEF Child Nutrition Report Series, 2022. UNICEF, New York, 2023.* 2023.
55. Wamani, H., et al., *Boys are more stunted than girls in sub-Saharan Africa: a meta-analysis of 16 demographic and health surveys.* BMC Pediatrics, 2007. **7**: p. 17.
56. Khara, T., et al., *Anthropometric criteria for best-identifying children at high risk of mortality: a pooled analysis of twelve cohorts.* Public Health Nutrition, 2023. **26**(4): p. 803-819.
57. Chase, R.P., et al., *Acute malnutrition recovery energy requirements based on mid-upper arm circumference: Secondary analysis of feeding program data from 5 countries, Combined Protocol for Acute Malnutrition Study (ComPAS) Stage 1.* PLoS One, 2020. **15**(6): p. e0230452.
58. Bailey, J., et al., *A simplified, combined protocol versus standard treatment for acute malnutrition in children 6-59 months (ComPAS trial): A cluster-randomized controlled non-inferiority trial in Kenya and South Sudan.* PLoS Med, 2020. **17**(7): p. e1003192.
59. Garenne, M., et al., *Changing sex differences in undernutrition of African children: findings from Demographic and Health Surveys.* Journal of Biosocial Science, 2021: p. 1-11.
60. Odei Obeng-Amoako, G.A., et al., *Factors associated with concurrent wasting and stunting among children 6-59 months in Karamoja, Uganda.* Matern Child Nutr, 2020: p. e13074.
61. UN, *United Nations Department of Economic and Social Affairs. Sex Differentials in Childhood Mortality* 2011.
62. Marino, M., et al., *Nutrition and human health from a sex-gender perspective.* Mol Aspects Med, 2011. **32**(1): p. 1-70.
63. Pedersen, J.F., *Ultrasound evidence of sexual difference in fetal size in first trimester.* British medical journal, 1980. **281**(6250): p. 1253-1253.
64. Eriksson, J.G., et al., *Boys live dangerously in the womb.* American Journal of Human Biology, 2010. **22**(3): p. 330-5.
65. Mora, J.O., et al., *Sex related effects of nutritional supplementation during pregnancy on fetal growth.* Early Human Development, 1981. **5**(3): p. 243-251.
66. Macaulay, S., et al., *The effects of gestational diabetes mellitus on fetal growth and neonatal birth measures in an African cohort.* Diabet Med, 2018. **35**(10): p. 1425-1433.
67. Wrottesley, S.V., et al., *A maternal "mixed, high sugar" dietary pattern is associated with fetal growth.* Matern Child Nutr, 2020. **16**(2): p. e12912.

68. Prioreschi, A., et al., *Understanding how maternal social and biological factors are related to fetal growth in an urban South African cohort.* J Dev Orig Health Dis, 2021. **12**(1): p. 79-87.
69. Alkema, L., et al., *National, regional, and global sex ratios of infant, child, and under-5 mortality and identification of countries with outlying ratios: a systematic assessment.* Lancet Glob Health, 2014. **2**(9): p. e521-e530.
70. Costa, J.C., C. Blumenberg, and C. Victora, *Growth patterns by sex and age among under-5 children from 87 low-income and middle-income countries.* BMJ Global Health, 2021. **6**(11): p. e007152.
71. Neelam, I., et al., *Girls' hidden penalty: analysis of gender inequality in child mortality with data from 195 countries.* BMJ Global Health, 2018. **3**(5): p. e001028.
72. Pelletier, D.L., *The relationship between child anthropometry and mortality in developing countries: implications for policy, programs and future research.* J Nutr, 1994. **124**(10 Suppl): p. 2047s-2081s.
73. UNICEF, *Nutrition, for Every Child: UNICEF Nutrition Strategy 2020–2030. UNICEF.* 2020.
74. UNICEF, *UNICEF Child Alert. Severe Wasting. An overlooked child survival emergency.* 2022.
75. Karlsson, O., et al., *Child wasting before and after age two years: A cross-sectional study of 94 countries.* eClinicalMedicine, 2022. **46**.
76. Mwangome, M., et al., *Anthropometry at birth and at age of routine vaccination to predict mortality in the first year of life: A birth cohort study in BukinaFaso.* PLoS One, 2019. **14**(3): p. e0213523.
77. Kerac, M. and M. McGrath, *Management of acute malnutrition in infants under 6 months of age* The biology of the first 1000 days 2018: p. 207-220.
78. Hofmeyr, G.J., et al., *Evidence-based antenatal interventions to reduce the incidence of small vulnerable newborns and their associated poor outcomes.* The Lancet, 2023.
79. Dewey, K.G., et al., *Characteristics that modify the effect of small-quantity lipid-based nutrient supplementation on child growth: an individual participant data meta-analysis of randomized controlled trials.* Am J Clin Nutr, 2021. **114**(Suppl 1): p. 15s-42s.
80. Smith, E.R., et al., *Modifiers of the effect of maternal multiple micronutrient supplementation on stillbirth, birth outcomes, and infant mortality: a meta-analysis of individual patient data from 17 randomised trials in low-income and middle-income countries.* Lancet Glob Health, 2017. **5**(11): p. e1090-e1100.
81. Mughal, M., *Perceptions of male female differences in malnutrition and implications for field assessment of anthropometry: A qualitative study.* 2020.
82. Janna, R.S., L.K. Sabra, and M. Rosemary, *Stop 'controlling' for sex and gender in global health research.* BMJ Global Health, 2021. **6**(4): p. e005714.
83. Butte, N.F., et al., *Energy requirements derived from total energy expenditure and energy deposition during the first 2 y of life.* Am J Clin Nutr, 2000. **72**(6): p. 1558-69.
84. Lampl, M., et al., *Sex differences in fetal growth responses to maternal height and weight.* Am J Hum Biol, 2010. **22**(4): p. 431-43.
85. Rasmussen, J., et al., *Mid-upper-arm-circumference and mid-upper-arm circumference z-score: the best predictor of mortality?* European Journal of Clinical Nutrition, 2012. **66**(9): p. 998-1003.
86. Blackwell, N., et al., *Mothers Understand And Can do it (MUAC): a comparison of mothers and community health workers determining mid-upper arm circumference in 103 children aged from 6 months to 5 years.* Arch Public Health, 2015. **73**(1): p. 26.
87. McDonald, C., et al., *Changes in plasma citrulline concentration among young Malian children with moderate acute malnutrition following a 12-week dietary intervention.* FASEB Journal. Conference: Experimental Biology, 2013. **27**(Meeting Abstracts).
88. Myatt, M., et al., *Improving screening for malnourished children at high risk of death: a study of children aged 6-59 months in rural Senegal.* Public Health Nutr, 2019. **22**(5): p. 862-871.

89. Briend, A., et al., *Prognostic value of different anthropometric indices over different measurement intervals to predict mortality in 6–59-month-old children.* Public Health Nutrition, 2023: p. 1-12.
90. Odei Obeng-Amoako, G.A., et al., *How do children with severe underweight and wasting respond to treatment? A pooled secondary data analysis to inform future intervention studies.* Matern Child Nutr, 2023. **19**(1): p. e13434.
91. Bergeron, G. and T. Castleman, *Program responses to acute and chronic malnutrition: divergences and convergences.* Adv Nutr, 2012. **3**(2): p. 242-9.
92. Schoenbuchner, S.M., et al., *The relationship between wasting and stunting: a retrospective cohort analysis of longitudinal data in Gambian children from 1976 to 2016.* Am J Clin Nutr, 2019. **110**(2): p. 498-507.
93. Rodríguez, G., et al., *Gender differences in newborn subcutaneous fat distribution.* Eur J Pediatr, 2004. **163**(8): p. 457-61.
94. Andersen, G.S., et al., *Body composition from birth to 6 mo of age in Ethiopian infants: reference data obtained by air-displacement plethysmography.* Am J Clin Nutr, 2013. **98**(4): p. 885-94.
95. Rudan, I., *Setting health research priorities using the CHNRI method: IV. Key conceptual advances.* J Glob Health, 2016. **6**(1): p. 010501.
96. Angood, C., et al., *Treatment of child wasting: results of a child health and nutrition research initiative (CHNRI) prioritisation exercise [version 1; peer review: 2 approved with reservations].* F1000Research, 2021. **10**(126).
97. Angood, C., et al., *Research Priorities to Improve the Management of Acute Malnutrition in Infants Aged Less Than Six Months (MAMI).* PLOS Medicine, 2015. **12**(4): p. e1001812.
98. Thurstans, S., *Understanding sex differences in childhood malnutrition.* Field Exchange 67, 2022. **67**: p. 58.