CHRISSIE MADALITSO THAKWALAKWA

Effect of Lipid Based Nutrient Supplementation on Growth and Intake of Breast Milk, Energy and Nutrients in Rural Malawian Children

ACADEMIC DISSERTATION
To be presented, with the permission of
the Board of the School of Medicine of the University of Tampere,
for public discussion in the Small Auditorium of Building B,
School of Medicine of the University of Tampere,
Medisiinarinkatu 3, Tampere, on June 11th, 2015, at 12 o'clock.

UNIVERSITY OF TAMPERE

CHRISSIE MADALITSO THAKWALAKWA

Effect of Lipid Based Nutrient Supplementation on Growth and Intake of Breast Milk, Energy and Nutrients in Rural Malawian Children

Acta Universitatis Tamperensis 2070
Tampere University Press
Tampere 2015

UNIVERSITY OF TAMPERE

ACADEMIC DISSERTATION
University of Tampere, School of Medicine
Finland

Supervised by
Professor Per Ashorn
University of Tampere
Finland
Professor Ken Maleta
University of Malawi
Finland

Reviewed by
Docent Harri Niinikoski
University of Turku
Finland
Professor Aila Rissanen
University of Helsinki
Finland

The originality of this thesis has been checked using the Turnitin OriginalityCheck service in accordance with the quality management system of the University of Tampere.

Cover design by
Mikko Reinikka

Distributor:
verkkokauppa@juvenesprint.fi
https://verkkokauppa.juvenes.fi

Acta Universitatis Tamperensis 2070
ISBN 978-951-44-9841-1 (print)
ISSN-L 1455-1616
ISSN 1455-1616

Acta Electronica Universitatis Tamperensis 1563
ISBN 978-951-44-9842-8 (pdf)
ISSN 1456-954X
http://tampub.uta.fi

Suomen Yliopistopaino Oy – Juvenes Print
Tampere 2015

ABSTRACT

Children require nutritionally adequate foods for optimal growth and development. In developing countries, most of the complementary foods offered to children are inadequate in quality and quantity leading to the development of undernutrition. Child undernutrition is associated with morbidity and mortality and as such poses a major public health problem.

Supplementary feeding is one of the effective ways of meeting the nutrient gap left by the poor complementary food. Even though supplementary feeding of children with high energy density food results in higher weight gain, it has also been shown to displace breast milk and the regular diet. Therefore, there is need to identify an effective supplementary food that improves weight and provides adequate energy and micronutrients with minimal risk of displacing breast milk and the regular diet. As such, this present research work was conducted in two trials and two studies namely the efficacy trial, effectiveness trial, breast milk study and dietary intake study. All these are referred to as studies in this thesis. These studies took place at 7 health facilities in Mangochi district in Malawi, South East Africa.

The efficacy study (I) was conducted in a controlled setting to determine whether supplementation of moderately underweight children with lipid based nutrient supplements (LNS) or corn-soy blend (CSB) improves weight gain. Total of 192 underweight children aged 6-15 months received for 12 weeks a daily portion of 43 g LNS or 71 g CSB, which provided 220kcal and 284kcal, respectively, or no supplementation (control). These supplements were provided at the participants' homes weekly for 12 weeks. The primary outcome was weight change. At the end of the 12-week supplementation period, the LNS but not CSB group gained more weight compared to the control group. Higher weight gains were observed among the most undernourished participants.

The effectiveness study (II) was carried out to determine if supplementation of moderately underweight children with CSB or LNS through the National Health Service could improve weight gain. The participants' guardians collected the

supplements from the health facility every four weeks for 12 weeks. A total of 299, 6-15 month-old children received on average 43g LNS or 71g CSB daily, providing 220kcal and 284kcal, respectively, or no supplement (control) for 12 weeks. Main outcome was weight gain. Compared to no supplementation, a modest gain in weight was associated with LNS supplementation and not CSB supplementation.

The breast milk study (III) was conducted to test the hypothesis that provision of LNS to Malawian infants would not decrease their breast milk intake more than a provision of CSB. A total of 44 mother-infant pairs took part. The infants received a daily ration of 25 g LNS, 50 g LNS, or 72 g CSB that provided 127 kcal, 256 kcal and 282 kcal respectively. The primary outcome was the difference in the quantity of breast milk intake after one month of complementary feeding. After one month of complementary feeding, breast milk intake in all the three groups reduced significantly but were comparable in all groups. The results suggested that complementary feeding of Malawian infants with LNS and CSB have similar effects on breast milk intake.

The dietary intake study (IV) assessed the effect of supplementation of CSB or LNS on energy and nutrient intake from the regular complementary foods to moderately underweight children. A structured interactive 24-hour recall method was used to collect data on intake of the regular complementary foods from 188 children aged between 8 and 18 months and participating in study I. Intakes were estimated and compared between the unsupplemented (control) group and the intervention groups (CSB and LNS). In this trial, LNS supplementation was associated with significantly higher energy and protein intakes. CSB supplementation was associated with higher but not significantly increased intakes of energy and proteins. Both CSB and LNS led to higher intakes of micronutrients (calcium, iron, zinc, and Vitamin C).

In conclusion, these studies show that LNS supplementation to children improves weight gain and leads to higher intakes of energy and nutrient from the regular complementary foods than CSB supplementation. A similar effect on intake of breast milk is observed with supplementation of either LNS or CSB

LIST OF ORIGINAL PUBLICATIONS

The thesis is based on the original articles as below which are referred to in the thesis by the roman numerals.

I. Thakwalakwa Chrissie, Ashorn Per, Phuka John, Cheung Yin Bun, Briend Andre´, Puumalainen Taneli, Maleta Kenneth (2010). A Lipid-based nutrient supplement but not corn-soy blend modestly increases weight gain among 6- to 18-month-old moderately underweight children in Rural Malawi. *J Nutr:* 140 (11):2008–2013.

II. Thakwalakwa C M, Ashorn P, Jawati M, Phuka J C, Cheung Y B and Maleta K M. (2012). An effectiveness trial showed lipid-based nutrient supplementation but not corn-soy blend offered a modest benefit in weight gain among 6-18 month-old underweight children in rural Malawi. *Public health nutrition*: 15: 1755-1762.

III. Galpin Lauren, Thakwalakwa Chrissie, Phuka John, Ashorn Per, Maleta Ken, Wong William W, and Manary Mark J. (2007). Breast milk intake is not reduced more by the introduction of energy dense complementary food than by typical infant porridge. *J. Nutr:* 137: 1828–1833.

IV. Thakwalakwa, Chrissie. M., Ashorn, P., Phuka, John. C., Cheung, Yin. Bun, Briend, Andre and Maleta, Kenneth. M. (2014). Impact of lipid-based nutrient supplements and corn–soy blend on energy and nutrient intake among moderately underweight 8–18-month-old children participating in a clinical trial. *Maternal & Child Nutrition*. doi:10.1111/mcn.12105

LIST OF FIGURES AND TABLES

FIGURES

Fig 1: Overall study design of the present studies 31
Fig 2: Follow up of participants in studies I, III and IV 39
Fig 3: Follow up of participants in study II 39
Fig 4: Participant flow for study I 47

TABLES

Table 1: Physical body signs and the associated nutritional deficiencies 10
Table 2: Comparisons of the four studies 34
Table 3: Nutritional composition of a daily dose of LNS and CSB used in studies I, II and IV 36
Table 4: Nutritional composition of a daily dose of LNS and CSB used in study III 37
Table 5: Baseline characteristics of participants in study I 48
Table 6: Quantitative outcomes among participants; stratified analysis based on weight-for-age Z score at enrollment: Based on WHO growth reference 50
Table 7: Baseline characteristics of participants in study II 51
Table 8: Prevalence of undernutrition at enrollment and at the end of the intervention amongst the children supplemented with LNS, CSB or no supplements (control). 52
Table 9: Baseline characteristics of participants in study III 54
Table 10: Breast milk intake before and after one month of complementary feeding 55
Table 11: Baseline characteristics of participants in study IV 56

ABBREVIATIONS AND ACRONYMS

AE	Adverse event
AIDS	Acquired immune deficiency syndrome
ANOVA	Analysis of variance
CDC	Centres for Disease control
CSB	Corn soy blend
CTC	Community-based therapeutic care
DSMB	Data safety and monitoring board
EBF	Exclusive breast feeding
EFA	Essential fatty acids
FAO	Food and Agriculture Organisation
FBF	Fortified Blended Flours
FFQ	Food frequency questionnaire
HAZ	Height for age z score
HIV	Human immune-deficiency virus
ICH-GCP	International Conference of Harmonization-Good Clinical Practice
LAZ	Length for age z score
LNS	Lipid-based nutrient supplement
MAM	Moderate Acute Malnutrition
MDG	Millennium Development Goals
MDHS	Malawi demographic and health survey
MGRSG	Multicentre Growth Reference Study Group
MNP	Micro Nutrient Powder
MUAC	Mid Upper Arm Circumference
NCHS	National Centres for Health Statistics
NGO	Non-governmental organization
NNPSP	National Nutrition Policy and Strategic Plan
ORS	Oral rehydration salts
PAHO	Pan American Health Organisation
RCT	Randomized controlled trial

RNI	Recommended Nutrient Intake
RR	Relative risk
RUF	Ready to use Food
RUSF	Ready to use supplementary food
RUTF	Ready to use therapeutic food
SAE	Serious adverse event
SAM	Severe Acute Malnutrition
SD	Standard Deviation
UNICEF	United Nations International Children's Emergency Fund
WAZ	Weight for age z score
WFP	World Food Programme
WHO	World Health Organization
WHZ	Weight for height z score
WLZ	Weight for length z score

Table of Contents

1 INTRODUCTION 1

2 LITERATURE REVIEW 4

2.1 Scope of the Literature Review 4

2.2 Concepts and definitions in child malnutrition 5

2.2.1 Malnutrition 5

2.2.2 Undernutrition 5

2.2.3 Micronutrient deficiency 5

2.3 Measures of nutritional status 6

2.3.1 Anthropometric measurements 7

2.3.2 Biochemical/ Laboratory assessments 9

2.3.3 Clinical indicators 9

2.3.4 Dietary assessments 11

2.3.5 Interpretation of dietary data 14

2.3.6 Breast milk intake assessments 15

2.4 Prevalence and trends of child undernutrition 16

2.5 Determinants of optimal child nutrition, growth and development 17

2.6 Risk factors for undernutrition and growth faltering 17

2.7 Consequences of undernutrition 18

2.8 Management strategies for optimal nutrition, growth and development..... 18

2.8.1 Disease prevention and management..... 19

2.8.2 Child growth monitoring and promotion..... 20

2.8.3 Maternal education..... 20

2.8.4 Nutrition education..... 21

2.8.5 Dietary Supplementation during pregnancy..... 21

2.8.6 Promotion of breast feeding and exclusive breast feeding..... 22

2.8.7 Promotion of complementary feeding..... 23

2.8.8 Fortification of staple food and specific foods..... 25

2.8.9 Dietary Supplementation for children..... 26

3 AIMS..... 28

4 METHODS..... 29

4.1 Approach to the present studies..... 29

4.2 Study area and participants..... 32

4.2.1 Study area..... 32

4.2.2 Study participants..... 33

4.3 Nutritional interventions..... 34

4.4 Data collection..... 37

4.4.1 Enrollment and follow-up..... 37

4.4.2 Anthropometric measurements 40

4.4.3 Measurement of dietary intake 40

4.4.4 Measuring energy and nutrient intake 41

4.4.5 Measurement of breast milk intake 42

4.4.6 Laboratory measurements 43

4.4.7 Monitoring child survival and morbidity 43

4.5 Statistical approach 44

4.5.1 Sample size 44

4.5.2 Data management and analysis 44

4.6 Ethics 45

5 RESULTS 46

5.1 Efficacy of LNS/CSB supplementation to moderately underweight children on growth (I) 46

5.2 Effectiveness of LNS/CSB supplementation of moderately underweight children on growth (II) 50

5.3 Effect of LNS/CSB supplementation to healthy infants on breast milk intake (III) 53

5.4 Effect of LNS and CSB supplementation on energy and nutrient intake (IV) 55

6 DISCUSSION 57

6.1 Strengths and weaknesses of this research 57

6.2 Promotion of growth 59

6.3 Promotion of intake of breast milk, energy and nutrients 61

6.4 Prevention from morbidity 63

7 CONCLUSIONS 64

8 PUBLIC HEALTH IMPLICATIONS AND TOPICS FOR FUTURE RESEARCH 65

9 ACKNOWLEDGEMENTS 67

10 REFERENCES 69

11 APPENDICES 89

12 ORIGINAL PUBLICATIONS 91

1 INTRODUCTION

Provision of adequate and good quality nutrition during infancy and early childhood is essential for optimum growth and development. Poor nutrition increases the risk of morbidity and leads to the development of undernutrition (Black et al., 2008). Globally about 165 million children younger than 5 years are stunted, 101 million are underweight and 52 million are wasted (UNICEF, 2012; Black et al., 2013). Undernutrition is strongly associated with mortality and the association increases with declining anthropometrical status (Schroeder and Habitch 1995; Caulfield et al., 2004; Olofin et al., 2013). Overall, undernutrition is implicated in about 3.1 million deaths or 45% of all underfive children's deaths every year (Black et al., 2013). The risk of death due to mild, moderate and severe undernutrition is twice, five and seven times, respectively, greater than normal. However, with the high prevalence of mild and moderate undernutrition in children worldwide, majority of child deaths, (about 55%) as a result of undernutrition are attributable to mild and moderate rather than severe undernutrition (Caulfield et al., 2004; Pelletier et al., 1993; Pelletier et al., 1994). As such, finding interventions that address mild and moderate malnutrition would help to reduce child deaths due to undernutrition.

The period between conception and the first two years after birth, when most undernutrition occurs, is considered the most critical period for ensuring adequate growth and development. From birth, the infants are exclusively breast fed and starting from when the children are six months of age, complementary foods should be provided in addition to breast milk to meet their nutritional needs. This is a time when problems start especially in most resource-poor countries where most of the locally-produced complementary foods are inadequate in quality as well as quantity due to limited accessibility of nutrient-rich foods, such as animal source foods or fortified, processed complementary foods as well as inadequate supply of foods (Dewey and Vitta, 2013). To compensate for the shortfalls from these complementary foods, the infants and young children could be provided with nutrition-specific interventions. These nutrition- specific interventions include dietary supplementation of children and micronutrient supplementation or fortification as some examples (Black et al., 2013). Two of the most commonly used

supplementary food items are fortified lipid-based spreads and fortified blended foods (Manary and Sandige 2008).

Fortified lipid-based spreads, with varying energy and nutrient concentrations, are referred to as lipid-based nutrient supplements (LNS). Different forms of LNS include ready-to-use supplements, both therapeutic (ready-to-use therapeutic food (RUTF) (Briend et al., 1999; Briend, 2001) and supplementary (ready-to-use supplementary food (RUSF). RUTF has proved effective in the management of severe acute malnutrition in children (Manary and Sandige, 2008;Collins, 2001; Diop et al., 2003; Manary et al., 2004; Sandige et al., 2004; Ciliberto et al., 2005; Ndekha et al., 2005; Patel et al., 2005; Linneman et al., 2007). The good results with RUTF led to the successful use of LNS in the form of RUSF as a complementary as well as supplementary food for the moderately undernourished children or those at risk of developing undernutrition (Briend, 2001, Kuusipalo et al., 2006; Adu-Afarwuah et al., 2007; Dewey and Adu-Afarwuah, 2008; Phuka et al., 2008; Phuka et al., 2009; Matilsky et al., 2009; Nackers et al., 2010). LNS has proven acceptable to its beneficiaries (Adu-Afarwuah et al., 2010; Hess et al., 2011; Phuka et al., 2011).

Fortified blended flour (FBF) is widely used in supplementary and complementary feeding programs (Dewey and Adu-Afarwuah, 2008; Dijkhuisen, 2000; Navarro-Colorado, 2007; de Pee and Bloem, 2009) and has several advantages as it can be locally produced and procured, and is well accepted by most beneficiaries in developing countries (de Pee and Bloem, 2009). In Malawi, porridge made from corn-soy blend (CSB) is used as a complementary as well as supplementary food for moderately undernourished children. However, scientific literature shows that with CSB supplementation, recovery rates from undernutrition are below 75% in both controlled research trials and operational emergency settings (Matilsky et al., 2009; Navarro-Colorado, 2007). There are concerns that this may be so because FBF has poor energy and micronutrient content and that there is a possibility that the ration may be shared with other family members or neighbours (Wood and Sibanda-Mulder, 2011) thereby contributing less towards recovery from undernutrition.

Previous studies in Malawi and other developing countries showed an increase in weight gain among moderately wasted and underweight children with LNS supplementation but not with CSB supplementation (Patel et al., 2005; Kuusipalo et al., 2006; Nackers et al., 2010; LaGrone et al., 2012; Ackatia-Armah et

al., 2012). Later, another trial in Malawi documented similar weight and length gains among moderately underweight children supplemented with either LNS or an isoenergetic CSB for 12 weeks (Phuka et al., 2009). This trial, however, did not include an unsupplemented group and it was conducted during the time when plenty of food was available. As such, it was not possible to determine how either of the interventions would have compared to no external food supplements or how they would influence growth before the harvest, i.e. during the lean season of the year. Other efficacy studies from Malawi, Ghana and South Africa suggested a modest growth promoting effect after CSB supplementation (Kuusipalo et al., 2006; Lartey et al., 1999; Oelofse et al., 2003). As such, we expected the CSB to have some growth promotion effect. The present studies were conducted in both more controlled and less controlled settings to determine if the growth promoting effect of LNS and CSB could be similar if the supplementation was conducted in either controlled settings or through the public health channels.

Although provision of high energy density supplements to children has been shown to lead to weight gain (Brown et al., 1995) it has also been shown to lead to displacement of breast milk and other complementary foods (Bajaj et al., 2005; Islam et al., 2006). In these studies, the energy density was increased by adding oil and making the gruel thick. The problem with this approach is that it is difficult for the children to eat thick porridge and also that edible oil is too expensive for most families in the developing countries. As such, there is a need to identify appropriate complementary food or food supplements that will promote growth but will not displace breast milk intake or intake of the regular complementary foods. The present studies were therefore conducted to determine whether LNS and CSB supplementation to children in more controlled and less controlled settings has any effect on growth. The other aim of the present studies was to determine intake of energy and nutrients from the regular complementary foods and intake of breast milk with LNS and CSB supplementation.

2 LITERATURE REVIEW

2.1 Scope of the Literature Review

This chapter describes the forms, severity, causes and consequences of malnutrition and common measurements of nutritional status. The chapter also provides an overview of the prevalence and trends of undernutrition, determinants of optimal nutrition, growth and development and consequences of undernutrition. A review of evidence of the efficacy and effectiveness of different intervention strategies for optimum nutrition, growth and development is also presented in this chapter. The final section provides the justification for conducting the present studies.

The literature review involved a targeted search of systematic reviews, peer-reviewed journal articles, meta-analyses and randomised control trials (RCTs) from electronic journals and online databases (e.g PubMed, the Cochrane library). A search was also conducted for data and reports from the World Bank, UNICEF, WHO, FAO and other relevant reports or position papers by governmental and non-governmental organisations and international bodies. The search mainly covers a period from 1970 to 2014. However some background data older than the stated period was also reviewed but the main emphasis was put on the most recent data, that is, data between 2000 and 2014.

2.2 Concepts and definitions in child malnutrition

2.2.1 Malnutrition

Malnutrition is defined as a state which results from a deficiency or excess of one or more essential nutrients (Blossner and de Onis, 2005). It may be due to undernutrition which arises from unbalanced or insufficient diet, or by medical conditions such as infections that affect the digestion of food or absorption of nutrients from food (Scrimshaw et al., 1968). It may also be due to overnutrition (excess of one or more essential nutrients) (Blossner and de Onis 2005). The present studies mainly focus on undernutrition.

2.2.2 Undernutrition

Undernutrition is the inadequate intake and use of energy and nutrients to maintain normal body functions and daily activities including growth, fighting infections, working and learning (UNICEF, 2006). It is a condition that may be caused by consumption of poor quality food combined with interaction with infections. Undernutrition encompasses wasting, stunting, underweight and micronutrient deficiencies (deficiencies of essential vitamins and minerals) (Black et al., 2008, Black et al., 2013).

2.2.3 Micronutrient deficiency

This is defined as a lack of essential vitamins and minerals required in small amounts by the body for proper growth and development. It increases the general risk of infectious illness and of dying from diseases like malaria, diarrhoea, pneumonia and measles (WHO, 2002b). Globally, over 2 billion people in the world are estimated to be suffering from micronutrient deficiencies (WHO/WFP/SCN/UNICEF, 2007). The majority of them reside in low income

countries (Caulfield et al., 2006). Vitamin A deficiency affects about 190 million pre-school age children mostly in Africa and South-East Asia (WHO, 2011). It causes blindness and poses a higher mortality risk of infectious diseases like measles, diarrhea, and malaria (Scrimshaw et al., 1968). Iron deficiency anemia affects about 47 percent of children less than five years. It has been shown to cause neurological impairment and a reduction in immune function (WHO, 2008). Zinc deficiency affects up to 79 percent of children less than five years and it retards growth and increases susceptibility to infection (Black and Sazawal, 2001).

2.3 Measures of nutritional status

An individual's nutritional status results from many interrelated factors. It is influenced by an individual's food intake which include quantity and quality of food and also by physical health. Assessment of nutritional status can help to identify individuals or population groups at risk of becoming malnourished, identify malnourished individuals or population groups, to develop healthcare programs that meet the needs as defined by the assessment and to assess the effectiveness of nutritional programs and interventions.

Child's nutritional status or health is in most cases assessed through the following methods: anthropometric measurements (measurements of growth and body composition), biochemical analysis (analysis of the biochemical content of blood and urine to determine a deficiency such as iron deficiency anemia or Vitamin A deficiency); clinical indicators analysis (examination of external physical signs of nutrient deficiencies such as goiter for iodine deficiency or night-blindness in the case of Vitamin A deficiency*);* and through assessment of the diet and breast milk intake (de Onis, 2000). These methods are discussed below with a focus on description of each method, its strengths and limitations.

2.3.1 Anthropometric measurements

Anthropometric measurements are relatively non-invasive methods that assess the size or body composition of an individual. These include measurements of the height or recumbent length for children under two years, weight, head circumference, mid-upper-arm circumference (MUAC), skinfold thickness etc. The strengths of using this method are that it is objective with high specificity and sensitivity, the readings are numerical and gradable on standard growth charts, the readings are reproducible, it is not expensive and needs minimal training, it measures many variables of nutritional significance (height, weight, MUAC, head circumference, skinfold thickness etc). Its limitations include inter-observer errors in measurement, limited nutritional diagnosis, possible problems with reference standards (local versus international standards) and there may be arbirtrary statistical cut off levels for what is considered as abnormal values (Habitch, 1974). Nutrition indices, which are formed by combining various body measurements and assessments, are used to assess the child's nutritional status. Three of the most commonly used nutrition indices are weight-for-age, weight-for-height and height-for-age (de Onis et al., 2006, WHO, 2006).

Weight-for-age is a measure of both short- and long-term effects of undernutrition (WHO, 2006). It is mostly used to assess child's nutritional status and routinely collected in growth promotion programs. A child is regarded as moderately underweight when the weight-for-age is below -2 SD and as severe underweight when the weight-for-age is below -3SD (WHO, 1995; UN Millenium Project, 2005; UNICEF, 2009).

Weight-for-height measures acute or short-term nutritional deficiency (Cogill, 2003).Wasting, a term applied when weight-for-height is below – 2SD of the reference population (WHO, 2004), is a sensitive indicator often used for short-term program intervention such as providing nutritional supplementation in emergencies. Wasting can be calculated even when the age of the child is not known. Therefore, it is a very useful undernutrition indicator when the exact age is not known (for example in complex emergencies like famines).

Height-for-age measures linear growth. Low height-for-age or stunting depicts chronic or long-term effects of inadequate nutrition or poor health status (WHO, 1968; Gibson, 2005). A stunted child is one whose height-for-age is below

– 2SD for the reference population. A child is considered severely stunted if the height-for-age is under – 3 SD.

To determine growth faltering in a child requires comparison with a reference child of the same age and sex. The justification for use of a reference population is based on the finding that children who are properly nourished grow similarly no matter where they live (Habitch, 1974; Martorell and Habitch, 1986). A proportion of a population may be considered undernourished depending on the growth standard or growth reference that has been used. A growth reference is usually developed based on data collected from a representative sample of a population. It shows the pattern of growth of the reference population, which may not be an optimal growth pattern. A growth reference simply describes 'what is' in the sense that it describes the growth pattern of a defined population without specifying any health outcomes associated with it. A growth standard, on the other hand, describes 'what should be' in that it defines a recommended pattern of growth and specifies health outcomes associated with the pattern. It represents an ideal population growth and suggests a growth pattern to be achieved by all children (WHO MGRSG, 2006). The differences between the individual/group measurements with the reference population are expressed as a z-score, percent of median or percentile (Cogill, 2003; Allen and Gillespie, 2001).

A z-score, also known as standard deviation (SD) scores describes how far and in what direction (positive/negative) the weight of a child is from the median value of a child with similar age / height in the reference population (WHO, 1995). According to the cut-off point for undernutrition recommended by WHO, children are regarded as undernourished if they fall below minus 2 SD (<-2 z-score) and as severely undernourished if they fall below minus 3 SD (< -3z-Score).

The percent of the median is the ratio of the child's weight to the median weight of a child with similar height in the reference data and is expressed as a percentage. It is commonly used in screening and follow up of children feeding programmes such as community-based therapeutic care (CTC). Children who fall between 70 and 80 percent of the median are classified as having moderate acute malnutrition. Those who fall below 70% of the median are classified as having severe acute malnutrition (WHO, 1995).

A percentile is the position of an individual in a given reference distribution (WHO, 1995). The examples of percentiles include the 1st 3rd, 5th, 15th, 50th (median), 85th, 95th, 97th, 99th (WHO, 1995). The percentiles can be used to represent z scores as follows: the 50th percentile represents a z-score of 0, the 15th and 85th percentiles represent z-scores of -1 and +1 respectively, the 3rd and 97th percentiles represent z-scores of -2 and +2 respectively and the 1st and 99th represent z-scores of -3 and +3 respectively.

2.3.2 Biochemical/ Laboratory assessments

Biochemical or laboratory assessments indicate the level of nutrition by examining an individual's blood and/ or urine (for example, measurements of serum retinol, serum iron, and urinary iodine). The strengths of this method are that it is accurate, precise and reproducible. It could be used to validate data from dietary methods (e.g comparing salt intake with 24-hour urinary excretion). It could be used to detect early changes in body metabolism and nutrition before the visible clinical signs appear. The limitations are that it requires more time. It is also costly and as such may not be applied on large scale and needs trained personnel.

2.3.3 Clinical indicators

Clinical indicators are the simplest and most practical methods in ascertaining nutritional status of a group of individuals. It examines the physical representation of malnutrition and deficiency of vitamins and micronutrients (Berti et al., 2003) with special attention to some body parts to establish the nutritional diagnosis as shown in Table 1. The advantages are that it is fast and easy to carry out, cheap and non-invasive. The disadvantage is that they cannot detect early cases.

Table 1. Physical body signs and the associated nutritional deficiencies

Physical sign	Deficiency
Hair	
Spare and thin	Protein, Zinc and Biotin
Easy to pull out	Protein
Corkscrew coiled hair	Vitamin A and C
Mouth	
Bleeding and spongy gums	Vitamins C, A, K, Folic acid,Niacin
Sore mouth and tongue	Vitamins B12, 6, C, Niacin, Folic acid, Iron
Leukoplakia (white/gray patches in mouth)	Vitamin A, B12, Bcomplex, Folic acid,Niacin
Angular stomatitis (inflamation of corner/angle of the lip	Vitamins B2, 6, Niacin
Eyes	
Xelopthalmia, night blindness	Vitamin A
Photophobia-blurring conjunctival inflamation	Vitamins B2, A
Nails	
Spooning (upward curving of nails)	Iron
Transverse lines	Protein
Skin	
Pallor	Folic acid, Iron, Vitamin B12,
Flaking dermatitis	Vitamins B2, A, Zinc, Niacin
Pigmentation, desquamation (skin peeling)	Niacin
Bruising, purpora	Vitamins K, C, Folic acid

2.3.4 Dietary assessments

The first stage of any nutritional deficiency can be identified by dietary assessment methods only (Gibson, 2005) although biochemical/laboratory, anthropometric and clinical studies can also be used to assess some aspects of undernutrition. Measurement of dietary intake is complex and the most appropriate measurement method depends on the assessment objectives, the type of data required, availability of resources and the population of interest. Diets may vary due to seasonal effects. As such, a study seeking to detect dietary change after a dietary intervention should be undertaken at similar times of the year.

There are quantitative and qualitative approaches to dietary assessments. **Quantitative approaches** assess current and past intakes and can help inform food and nutrition policy by showing average consumption of foods and nutrients by target groups, frequency of consumption of different foods or food groups, adequacy of diet for different population groups and any diet-disease relationships. Examples of quantitative approaches include: 24-hour recall, the structured interactive 24 hour method, weighed food records, dietary history and food frequency questionnaire techniques.

In the **24-hour recall**, the participant estimates amount of food and drink taken during the previous 24-hours (Gibson, 2005, FAO guidelines). The advantage of using this method is that the researcher is able to estimate nutrient intakes of population groups. It is used widely to compare nutrient intakes with recommended nutrient intakes (RNI). The major limitation of the recall method is that it does not represent the usual intake.

The structured interactive 24-hour recall is a modification of the traditional 24-hour recall and was developed to improve the validity of the 24-hour recall in

measuring intake of nutrients in poor rural areas in Africa (Ferguson et al., 1995). Generally, this technique has three main steps that take place in three consecutive days as follows: Day 1: The participants or participants' guardians are prepared for the technique, that is, the purpose of the technique is explained to them, portion size estimation is rehearsed with them, picture calendars are left with them and they receive instructions on how to mark on the picture calendar during the second day. Day 2: The participant/ guardian marks off all eaten food items on the picture calendar. The picture calendar shows the commonly consumed local foods of the target area and is used to reduce memory lapses. Day 3: The participant is asked to describe all foods and drinks consumed during the previous 24 hour period. This description includes the list of the food items consumed as well as the food preparation methods and any other details about the food. Then the participant is asked to estimate the quantity of food or drink consumed. These data are collected on specially designed questionnaires. Before the interviewer leaves the home, he/she compares the information given orally and information on the picture calendar and discusses possible discrepancies. If a food item appears on the picture calendar but is not among the foods orally mentioned, the research assistant and the participant discuss whether this food item was actually consumed or not. Corrections are made to the data collection form accordingly. If a food item is verbally mentioned but not marked on the picture calendar, the same discussions take place and corrections are made. The picture calendar is also helpful at this point as it helps to reduce the number of additions and omissions of foods.

One major limitation of this method is that it requires a lot of resources in terms of time money and personnel.

The Weighed food records technique is regarded as the most precise method for estimating food and/or nutrient intakes of individuals. In this method, a researcher weighs each ingredient before cooking/ preparation and then, when the meal is served, he/she weighs the portion of the prepared food that is served to the participant. To determine how much was consumed, plate waste, leftovers and food containers are weighed and their values are subtracted from the total weight of the portion that was served. The advantage of this method is that it is accurate since the foods consumed are actually weighed and recorded (Gibson, 2005). The

disadvantages of this method are that it is costly, requires highly motivated subjects and highly literate people.

Dietary history (FAO guidelines; Burke and Stuart, 1983; Burke, 1947) is designed to assess usual individual intake. It consists of a detailed listing of the types of foods and fluids commonly consumed over a defined time period which is often a "typical" week. A trained interviewer probes for the respondent's usual eating pattern for each day of the week. The reference time frame is often the past month or the past several months, or may reflect seasonal differences if the time frame is the past year. The advantages of this method include its ability to detect seasonal changes and obtain data on all nutrients. The methods also correlates well with biochemical measures. However, its major limitation is high respondent burden.

Food-frequency questionnaire (FFQ) (Zulkifli and Yu, 1992; Willet, 1998), also known as "list-based diet history", consists of a structured listing of individual foods or food groups. The participant is asked to estimate how often each food item on the list is consumed. The food item list has specified frequency categories which indicate the number of times the food is usually consumed per day, week, month or year. FFQs are commonly used to rank individuals by intake of selected nutrients (Beaton, 1994; Semphos et al., 1999). FFQs are either self-administered or interviewer-administered. FFQs may be unquantified, semi-quantified or completely quantified (FAO guidelines). The unquantified questionnaire does not specify serving sizes, whereas the semi-quantified tool provides a typical serving size as a reference amount for each food item. A quantified FFQ allows the respondent to indicate any amount of food typically consumed. The strengths of FFQ are that it is cheap, easy to use and more representative. Its limitations are difficulties in estimating serving size, the list needs to be updated to keep pace with the changing dietary habits.

Qualitative approach to dietary assessment involves the examination of people's beliefs, perceptions and behaviours around dietary intake. Initial qualitative data can be gathered rapidly, thus providing information that is up to date. The

approach can also facilitate inquiry into sensitive issues, which are often difficult to investigate through standard survey methods. These qualitative approaches include in-depth interviews, observations and focus group discussions.

In-depth interview is an exploratory dialogue between the researcher and participant, where the participant is seen as teaching the interviewer about their cultural setting. The advantage of using this method in nutrition is that it is useful in identifying actual dietary practices. As such, it can help to determine facilitators and barriers to recommended practices such as in young child feeding.

Observation includes direct and participant observation. Direct participation involves recording of actual behaviour as opposed to reported or recalled behaviour. This method could be useful in describing food behaviours among various population groups while participant observation involves the observer residing in the community of interest for some time observing and participating in local activities. This could help the researcher understand the context and process of activities and may be very useful in examining infant and young child-feeding practices.

Focus-group discussion is a carefully planned discussion designed to obtain perceptions on a defined area of interest in a permissive non-threatening environment. In nutrition, the method is very useful in obtaining information like eating habits from children and from individuals who are not highly literate.

2.3.5 Interpretation of dietary data

Dietary data is interpreted by using either qualitative or quantitative methods. In **qualitative methods**, the researcher can use a food pyramid or a basic food groups method whereby various nutrients are classified into groups (for example, the

Malawian 6 food groups consist of fats, staples, vegetables, fruits, foods from animals and legumes and nuts). Then the researcher determines how much was consumed from each group and compares it with minimum requirements. In **Quantitative methods**, food composition tables are used to determine the amount of energy and other nutrients in each food consumed. The values are then compared with the recommended daily allowance. Evaluation by this method is expensive and time consuming, unless computing facilities are available.

2.3.6 Breast milk intake assessments

Measurement of dietary intake in infants and young children also involves assessment of breast milk intake. Unlike the other dietary assessment methods, breast milk intake assessment is not easy since one cannot directly observe the quantity taken (WHO 2002a). Breast milk intake is measured through the test-weighing, maternal breast milk expression or dose-to-mother deuterium dilution methods. In the **test-weighing method** (Coward et al., 1979; Savenije and Brand, 2006), the infant is weighed with its clothes before and after breast feeding without changing the diaper between the weight measurements. The infant's weight before breast feeding is subtracted from the weight after feeding and the difference represents the amount of milk consumed with the assumption that 1 gram of weight represents 1ml of milk consumed (Scanlon et al., 2002). This method can lead to an overestimation of the test weight since milk is denser than water (Meier, 2001; Lawrence and Lawrence, 2005). The **maternal breast milk expression method** involves pumping breast milk out of the breast. The problem with the test weighing and the maternal breast milk expression methods is that they interfere with the process of breast feeding and are unable to show habitual infant intakes. The **dose-to-mother deuterium dilution method** (Coward et al., 1982) is an improvement over these methods. The mother is given an accurately weighed dose of deuterium oxide which rapidly mixes well with her body water including her milk. Saliva and urine samples are collected from the mother and the baby respectively during the following two weeks. Deuterium in the baby's body will come from maternal milk only. As such, an estimate of breast milk intake by the infant over this period is calculated. The technique also allows the researcher to estimate intake of water from

other sources than breast milk. The strengths of this technique are that it is precise, non-invasive and does not interfere with the normal breastfeeding practices and it does not depend on maternal ability to recall the time she breastfed her infant (Coward et al., 1982; Butte et al., 1988; Haisma et al., 2003). It may be used to evaluate effect of complementary feeding on the intake of breast milk (Cisse et al., 2002; Albernaz et al., 2003; Ettyang et al., 2005; Moore et al., 2007).

2.4 Prevalence and trends of child undernutrition

Globally, about 165 million or 26% of under five year old children are stunted, 101 million or about 16% are underweight and 52 million (8%) are wasted (Black et al., 2013). Of the 165 million stunted children, over 90% are found in Africa and Asia while about 70% of the 58 million wasted children are in Asia, mainly in South-Central Asia. These children are at a high risk of developing severe acute malnutrition or dying (Black et al., 2008; UNICEF-WHO-WORLD BANK, 2012).

In developing countries, undernutrition prevalence dropped from around 23% in 1990 to 15% in 2012. Since 2012, the rate of decline has been constant and the prevalence of undernutrition is estimated to be at 10% by 2015. Although there has been this substantial change, progress has been varying in the different continents. Africa, for example, has experienced an increase in the prevalence while other continents have experienced a decrease (in trend) (Meerman et al., 2012).

In Malawi, the prevalence of undernutrition has not changed much since 1992. At this time, stunting, wasting and underweight were at 49%, 5% and 27% respectively (MDHS, 2004). In 2010, eighteen years later, the rates were 47%, 5% and 13% (MDHS, 2010) showing no change of the trends. Prevalence of underweight and stunting has been documented to be high at one year of age and wasting at about 18 months of age (Maleta et al., 2003). Prevalence of micronutrient malnutrition is also high. A 2009 survey showed an iron deficiency of 48% in children under the age of five while 23% were vitamin A deficient (Malawi country presentation, 2013) The 2010 MDHS survey reported 64% of children 6-59 months

as anemic, 61% mildly and moderately anemic, and 3% severely anemic (MDHS, 2010).

2.5 Determinants of optimal child nutrition, growth and development

The determinants of optimal nutrition, growth and developments can be divided into dietary, behavioral and health factors (Black et al., 2013). As shown by Black and colleagues, these determinants are affected by food security, care giving resources and environmental conditions. These, in turn, are affected by the economic and social conditions, national and global contexts, resources and governance (Black et al., 2013).

2.6 Risk factors for undernutrition and growth faltering

Childhood growth faltering or poor child growth is of public health concern in many poor countries especially in Asia and Sub Saharan Africa (UNICEF, 2013). It is an indicator of undernutrition and other health problems in children below the age of 5 (UNICEF, 2013). Literature suggests that growth faltering starts in utero or soon after birth and it reaches a climax between 12 and 18 months of age and may continue until 40 months before the faltering stops (Maleta et al., 2003; Martorell et al., 1995; Shrimpton et al., 2001; Victora et al., 2008).

Several factors have been associated with growth faltering. These include poor maternal nutrition, inappropriate complementary feeding and infections (Black et al., 2008; Martorell et al., 1994; Singh, 2005). Other factors include environment and heredity (the process by which the features and characteristics are passed from parents to the child before the child is born). These features and characteristics may include skin colour, eye colour, height, body build. Environmental factors include nutrition, physical environment, education, morbidity (Cameron, 1992; Dubois et al., 2007). The growth of the child can be adversely affected if the mother is undernourished, emotionally upset or smokes, drinks, or takes some medicine or

suffers from certain diseases. A malnourished child's growth may be retarded. Proper nutrition is essential for the healthy development of the child. Socio-economic status also influences the development by deciding the kind of nutrition, facilities and opportunities that the child gets (Wong et al., 2014). Apart from improving maternal nutrition and infection control, appropriate complementary feeding to children from the age of 6 months is the most feasible and effective intervention.

2.7 Consequences of undernutrition

Undernutrition leads to immediate as well as long-term consequences. When a child is undernourished before birth, it is very likely that he/she will be born with low birth weight. Low birth weight babies are at a higher risk of morbidity, mortality and with cognitive and mental problems (WHO, 2002b; Black et al., 2003; Black et al., 2008; Victora et al., 2008; Black et al., 2013). Undernourished children including those who are poorly breast fed and those with micronutrient deficiencies have a higher risk of morbidity and mortality due to diarrhoea, measles, pneumonia, malaria and HIV and AIDS (Pelletier et al., 1993, Rice et al., 2000; Habitch, 2008). Children who experience poor growth before the age of two have an increased risk of developing chronic diseases in adulthood if they gain weight rapidly at later stages of childhood (Delisle, 2005).

2.8 Management strategies for optimal nutrition, growth and development

Undernutrition is a global problem with developing countries suffering the most. Several different approaches have been applied to enhance growth and development. These are grouped into (1) nutrition specific interventions and programs; (2) an enabling environment programmes and (3) nutrition sensitive programmes and approaches (Black et al., 2013). Black and colleagues further give examples of the nutrition specific interventions and programs that help boost growth and development. These include adolescent health and preconception nutrition, maternal dietary supplementation, micronutrient supplementation or fortification,

breastfeeding and complementary feeding, dietary supplementation for children, dietary diversification, feeding behaviours and stimulation, treatment of severe acute malnutrition, disease prevention and management and nutrition interventions in emergencies (Black et al., 2013). Amon the nutrition sensitive programmes and approaches that address the underlying determinants of malnutrition, the same lists agriculture and food security, social safety nets, early child development, maternal mental health, women's empowerment, child protection, classroom education, water and sanitation and health and family planning services. The report further gives examples of the different ways that an environment can support interventions and programmes to boost growth and development. These include rigorous evaluation, advocacy strategies, horizontal and vertical coordination, accountability, incentives regulation and legislation, leadership programmes, capacity investments and domestic resource mobilization (Black et al., 2013). Some of the management strategies are reviewed below with attention to their successes and in some cases challenges.

2.8.1 Disease prevention and management

An estimated seven million children die annually with infectious diseases and undernutrition as the leading causes of the deaths (Black et al., 2013; UNICEF, 2012).Undernourished children are more than nine times more likely to die from infectious diseases such as pneumonia, diarrhoea, malaria and measles than well-nourished ones and aproximately 1.3 million children die of diarrhea every year (Black et al., 2010). Those that survive may experience the next diarrhea episode before they fully recover. This contributes to malnutrition, reduced resistance to infections and when prolonged, to impaired growth and development (Ejemot et al., 2008).

Approximately six million child deaths in the world are prevented by vaccines every year (Ehreth, 2003) and there is evidence that vaccines help prevent some of the chronic consequences of undernutrition (Moore et al., 2010; Anekwe and Kumar, 2012; Guerrant et al., 2013). Measles is thought to cause undernutrition while measles vaccination protects against problems such as dysentery, bacterial pneumonia, keratomalacia and malnutrition (Strebel et al., 2004).

Research has shown that integration of health systems with strategies to address undernutrition and national immunisation delivery systems is effective in that more mothers and children receive comprehensive healthcare (Doherty et al., 2010). This results into an improvement in the children's nutritional status.

2.8.2 Child growth monitoring and promotion

Child growth monitoring is the process of comparing growth rate of a child to standard, periodic, frequent anthropometric measurements over a specified time to assess growth faltering as early as possible (Griffiths and Del Rosso, 2007). The first two years of life are a window of opportunity for growth promotion. Monitoring of growth throughout infancy and childhood is essential because faltering can be detected as early as possible and can be acted upon.

Prevention is one of the most cost-effective ways to address undernutrition. This means making sure that all normal birth weight children continue growing within the normal range while those with a low birth weight are helped to get to the optimum growth range. To reduce proportion of children with undernutrition, programs should identify children as they become undernourished, not after they are already undernourished (Hendrata and Rohde, 1998)

2.8.3 Maternal education

Maternal education can be defined as the level of schooling that a mother attains. Research shows a strong and positive link between maternal education and children's health and nutritional outcomes (Handa, 1999; Frost et al., 2005; Kabubo-Mariara et al., 2008; Abuya et al., 2011). Glewwe explains the strong link between the health knowledge and formal education (Glewwe, 1999). The other reason highlighted by Glewwe is that the knowledge the women acquire help them to recognise illnesses

and seek treatment in time. In addition, the mothers acquire reading skills and can read treatment instructions and are able to apply the treatment (Frost et al., 2005; Glewwe, 1999; Desai and Alva, 1998; Cleland and van Ginneken, 1988).

2.8.4 Nutrition education

Nutrition education is the process of promoting healthier eating habits by disseminating knowledge to people on how they can choose good quality foods, prepare and preserve them (FAO, 2008). Nutrition education has been linked to improved complementary feeding practices, dietary intake and growth (Caulfield et al., 1999; Guldan et al., 2000; Perez-Rodrigo and Aracenta, 2003; Blom-Hoffman et al., 2004; Penny et al., 2005, Anderson et al., 2005; Roy et al., 2005; Matvienko, 2007; Dewey and Adu-Afarwuah, 2008; Shi and Zhang, 2011). However, in most resource poor countries where animal-source foods are inadequate or not available, nutrition education alone has not been effective in helping to meet some of the most limiting nutrients like zinc and iron (Walsh et al., 2002; Dewey and Adu-Afarwuah, 2008; Vazir et al., 2012).

2.8.5 Dietary Supplementation during pregnancy

Nutrient requirements increase during pregnancy (Picciano, 2003) and play an important role in determining fetal growth (Victora et al., 2008). It is important to increase one's intake of nutrients during this period to prevent risk of deficiencies. However, it is also important not to consume too much of any nutrient to reduce risk for levels of intake that may be harmful. An undernourished mother is likely to give birth to a low-birth-weight baby (Fishman et al., 2004) who is highly susceptible to premature death and diseases even as an adult. Maternal undernutrition

contributes to about 800,000 neonatal deaths annually (Bhutta et al., 2013). Provision of dietary supplements to the undernourished pregnant women has been shown to reduce the risk of delivering low- birth- weight babies and stillbirths (Bhutta et al., 2008; Ota et al., 2012; Haider and Bhutta 2012) with more pronounced effects in malnourished women (Imdad and Bhutta, 2012).

2.8.6 Promotion of breast feeding and exclusive breast feeding

Breast milk is the main source of nutrition for infants during early infancy and promotion of breast feeding is an important public health measure (Haroon et al., 2013**).** The benefits of breast milk include reduction in acute gastro-intestinal tract infections, respiratory infections and otitis media as well as a lower risk of mortality and allergic diseases (DFID, 2012).

Exclusive breastfeeding (EBF) is defined as giving no other food or drink nor water except breast milk (including milk expressed or from a wet nurse) until 6 months of age but allowing for oral rehydration salts (ORS), drops and syrups (vitamins, minerals and medicines). (WHO infant feeding recommendation) EBF promotes growth, immunity and prevents morbidity in young children (WHO, 2000a; Arifeen et al., 2001; Simondon et al., 2001; Jones et al., 2003; Oddy et al., 2003; Mahgoub et al., 2006; Kalanda et al., 2006; Black et al., 2008; Dewey et al., 2009). A partly breast fed child is more than 14 times likely to die from all causes than an exclusively breastfed infant (Brown et al., 1989; Almeida et al., 1999; Kramer et al., 2001; Kramer et al., 2003; Bahl et al., 2005; Monterossa et al., 2008; Black et al., 2008).

Exclusive breast feeding is recommended for children up to six months of age and complementary feeding thereafter until two years of age with continued breast feeding as long as it suits mother and child (WHO, 2001; WHO, 2003). Breast feeding support has been shown to be effective in increasing the number of women breast feeding (Imdad et al., 2012). As a result, this has a positive effect on child mortality and morbidity

(Bhutta et al., 2008). Evidence also shows that EBF reduces mother to child transmission of HIV, and ends up reducing the risk of undernutrition (Coutsoudis, 2005; Coovadia et al., 2007).

2.8.7 Promotion of complementary feeding

Complementary food is defined as any nutrient containing food or fluid other than breast milk given to a child during a complementary feeding period (WHO/UNICEF, 1998) and complementary feeding is the giving of infants foods or fluids in addition to breast milk or breast milk substitutes (WHO, 2002a). Complementary feeding period is the period when older infants and young children progress from exclusive consumption of breast milk and / or breast milk substitutes onto a normal family diet (WHO/UNICEF, 1998; Brown, 1997; Dewey and Brown, 2003). A proper complementary food is said to be rich in energy and nutrients, contamination free, low in salt or spices, easy to eat and easily accepted by the infant, served in an appropriate amount, easily prepared from family foods, and acquired at an acceptable cost (WHO, 2000b). There are significant associations between complementary feeding practices and height-for-age z scores (Arimond and Ruel, 2004; Marriot et al., 2012).

Complementary feeding that has been introduced at the right time reduces the incidence of undernutrition (Dewey, 2001; Child Health Research, 2002; Bhandari et al., 2004). Children have high demand of nutrients during the first two years of life and if they receive food of poor quality and quantity after 6 months of age, they are more likely to become stunted and wasted (Dewey et al., 1992; Shrimpton et al., 2001). Children of this age also experience a high rate of infectious diseases such as diarrhea that negatively affect their growth and nutritional status (Ejemot et al., 2008; Dewey and Adu-Afarwuah 2008). In resource poor countries, inadequate nutrient intake from complementary foods and high incidence of infections during the

complementary feeding period are the major causes of undernutrition and other adverse health and development outcomes (Dewey and Adu-Afarwuah, 2008; Dewey and Mayers, 2011). Most of the plant-based diets are high in phytates which bind some important minerals like iron and zinc and limit their absorption in the child's body. Some studies have shown that local processing technologies such as roasting, malting, drying, fermentation and grinding can reduce the phytate concentration thereby improving quality of the complementary foods (Ferguson et al., 1993; Mensah and Tomkins, 2003).

The total daily energy requirements for healthy, breast fed children aged 6 to 8 months, 9 to 11 months and 12 to 23 months are approximately 615kcal, 686 kcal and 895 kcal respectively (Dewey and Brown, 2003). The average daily breast milk energy intake for the breastfed children in developing countries is approximately 413 kcal, 379 kcal and 346 kcal at 6-8months, 9-11months and 12-23 months of age, respectively (WHO/UNICEF, 1998). By subtracting the average estimated breast milk energy intake from the total daily energy requirements at each age, one is able to estimate expected energy needs from complementary foods. Therefore, a child on an average breast milk intake in developing countries, needs about 200kcal, 300 kcal and 550 kcal daily from complementary foods at 6 to 8 months of age, 9 to 11 months of age, and at 12 to 23 months of age respectively (WHO/UNICEF, 1998). Since the children have limited gastric capacity (Brown et al., 1995) and are able to consume only a relatively small amount of complementary foods at a time before the age of two years (Brown et al., 1982), their complementary foods need to be nutrient dense (Scrimshaw et al., 1996; PAHO/WHO, 2003).

The guiding principles for complementary feeding of the breast fed child among other things emphasize the importance of offering complementary foods more than once during the day, and of providing a variety of foods to children from six months of age (PAHO/WHO, 2003). The guidelines also state that meat products should be eaten daily or as often as possible since consumption of meat has been shown to improve nutritional status in developing countries (Allen et al., 1992; Marquis et al., 1997; Penny et al., 2005). The challenge with this guideline is that the majority of the poor families cannot afford meat or meat products and mainly rely on the poor quality diets.

In countries like Malawi where food insecurity is prevalent and with a plant based diet, children certainly do not meet their nutrient requirements for optimal growth

and development and the diet requires adding high quality nutritious foods to improve its quality. This is impossible in food insecure households (NNPSP 2007-2011). To help improve quality of the diet, high quality supplementary foods or nutrient fortification of staple foods could be used (PAHO/WHO, 2003).

2.8.8 Fortification of staple food and specific foods

Food fortification is defined as the addition of one or more essential nutrients to a food with the aim of preventing or correcting a deficiency of one or more nutrients in the population or specific population groups (UNICEF/UNU/WHO, 1999; FAO/WHO, 2004).

Foods can be fortified at three different levels: mass or universal, targeted or household level (Bhutta et al., 2013). Mass/ universal fortification is mandatory for industries and aims at producing foods or food products for the general population. For example, in Malawi, there is universal vitamin A fortification of cooking oil and sugar. The problem with this approach is that the products become more expensive so that the targeted population, more especially in rural areas, cannot benefit (Harvey and Dary, 2012). Fortification has been shown to be cost-effective when it is done by medium-large scale industries (WHO, 2006). The targeted fortification is done a specific nutritionally vulnerable group/ population or in emergency situations where there are insufficient intakes of nutrients from the diet or where animal- source foods are rare or limited in the diets (Bhutta et al., 2013). Household fortification involves additions of nutrients directly to the foods that women and children eat. This could be in a form of micronutrient powders or fortified lipid-based spreads like lipid-based nutrient supplements. The process has little effect on taste and does not make the targeted individuals to change their dietary practices (Bhutta et al., 2013). All nutrients that are essential for child's growth need to be provided in required amounts at the same time. A deficiency of any of the essential nutrients results in slow growth rate.

2.8.9 Dietary Supplementation for children

Supplementary feeding of children is defined as the process of providing food to children in addition of their normal diet with an aim of improving their nutritional status or preventing nutritional deterioration (Beaton and Ghassemi, 1982). Provision of high quality supplementary food to individuals is expected to result in better anthropometric status.

Some examples of supplementary foods are fortified blended foods (FBFs) (such as corn-soy blend), micronutrient powders (MNPs) and LNS in the form of ready-to-use foods (RUFs) or ready-to-use therapeutic foods (RUTF). Fortified blended foods are products that are used as a replacement for the traditional porridge. They are usually made from cereals, legumes, and sugar or oil and are fortified with certain micronutrients (Dewey and Vitta, 2013). They are easily accepted by recipients because they normally resemble family foods. However, the products' daily ration usually provides a relatively large amount of energy (e.g., 200 kcal/ day), which may displace breast milk. Secondly, over-reliance on a single food may reduce dietary diversity and limit intake of animal-source foods, fruits, and vegetables (Dewey and Vitta, 2013).

MNPs are products that usually contain only vitamins and minerals for home fortification of traditional infant foods. MNP do not displace breast milk or other foods because they contain little or no energy. As compared to the other options, MNPs are less expensive. The limitations of MNPs are that it is difficult to include all of the essential nutrients in a single serving and they do not increase energy, fat or fatty acid, or protein content of the diet. MNPs are associated with improved haemoglobin concentration and reduced iron deficiency anaemia and retinol deficiency. (Salam et al., 2013). However, MNPs have also been shown to increase the incidence of diarrhea. (Soofi et al., 2013)

LNS contain milk powder, high-quality vegetable oil, peanut paste, sugar and micronutrients (de Pee and Bloem, 2009). LNS in the form of RUTF is the recommended way of treating severe acute malnutrition in children in developing countries (WHO/WFP/UNICEF, 2007). RUTF is designed to achieve rapid nutritional recovery and is provided in large amounts (200-300g/day) temporarily replacing most or other foods apart from breast milk (Dewey and Arimond, 2012). RUTF can be eaten without cooking, can be easily kept where there are no refrigerators and as such, can easily be used in any situation. Additionally, the type I and II micronutrient densities available in RUTF are effective in the management of severe acute malnutrition in children (WHO/WFP/UNICEF, 2007). LNS in the form of RUSF was designed for the prevention of wasting and stunting. They are more concentrated in micronutrients, are given in smaller quantities (20-50g/day) and cost less (Dewey and Arimond, 2012). RUSF has proven beneficial in the management of moderate acute malnutrition (Dewey and Vitta 2013).

Type I nutrients are nutrients that are needed in the body for specific biochemical functions. These nutrients include vitamins, iron, iodine, selenium and calcium. When a child is deficient in a Type 1 nutrient, he/she will show clinical signs or symptoms but his/her growth will not necessarily reduce. Type II nutrients are the growth promoting nutrients. They include proteins, energy, potassium, magnesium, phosphorus, zinc, and sodium (Golden, 1996). A deficiency in any of these nutrients leads to reduced growth (Dewey and Vitta, 2013).

The literature review has shown that out of the many types of interventions for optimal nutrition, growth and development for children aged between 6 and 24 months, a comprehensive food-based intervention that includes both type I and type II nutrients is likely to be successful in promoting healthy growth. With a food based approach, it is possible to improve the quality of macronutrients as well as micronutrients without introducing infections. These qualities are available in LNS. With this background, the present studies were conducted to assess the efficacy and effectiveness of supplementation of LNS and CSB to rural Malawian children on growth and intake of breast milk and intake of energy and nutrients from the regular complementary foods.

3 AIMS

The present studies aimed at assessing, in Malawian children, the effects of supplementation of LNS and CSB on weight and intake of energy and nutrients from the regular complementary foods and intake of breast milk.

The following were the specific objectives:
To analyse whether LNS/CSB supplementation, when provided in controlled conditions, boosts growth among moderately underweight children.

To compare growth among moderately underweight children supplied with LNS, CSB or no supplementation through the public health channels

To test the hypothesis that LNS supplementation does not reduce breast milk intake more than CSB supplementation.

To compare the intake of energy and nutrients from the regular complementary foods among moderately underweight children receiving LNS, CSB or no supplementation for 12 weeks.

4 METHODS

4.1 Approach to the present studies

The aim of the present research was met by using data from two clinical trials (efficacy and effectiveness) and two studies (dietary intake and breast milk intake), which are all referred to as studies in this thesis. The efficacy, effectiveness and dietary intake studies involved underweight children while breast milk intake study involved healthy children. All studies were conducted by the author. Figure I shows the overall design of the studies.

The efficacy study (I), conducted in a controlled setting, aimed at determining whether supplementation with LNS or CSB improves weight gain of moderately underweight young children. The food supplements were delivered weekly for 12 weeks in the participants' homes. A total of 192 underweight children aged between 6 and15 months of age were randomly selected to receive weekly a daily ration of either 43g LNS (220 kcal), 71g CSB (284 kcal) or no supplementation for 12 weeks. Weight gain was the primary outcome. Secondary outcomes included changes in anthropometric indices and incidence of adverse events.

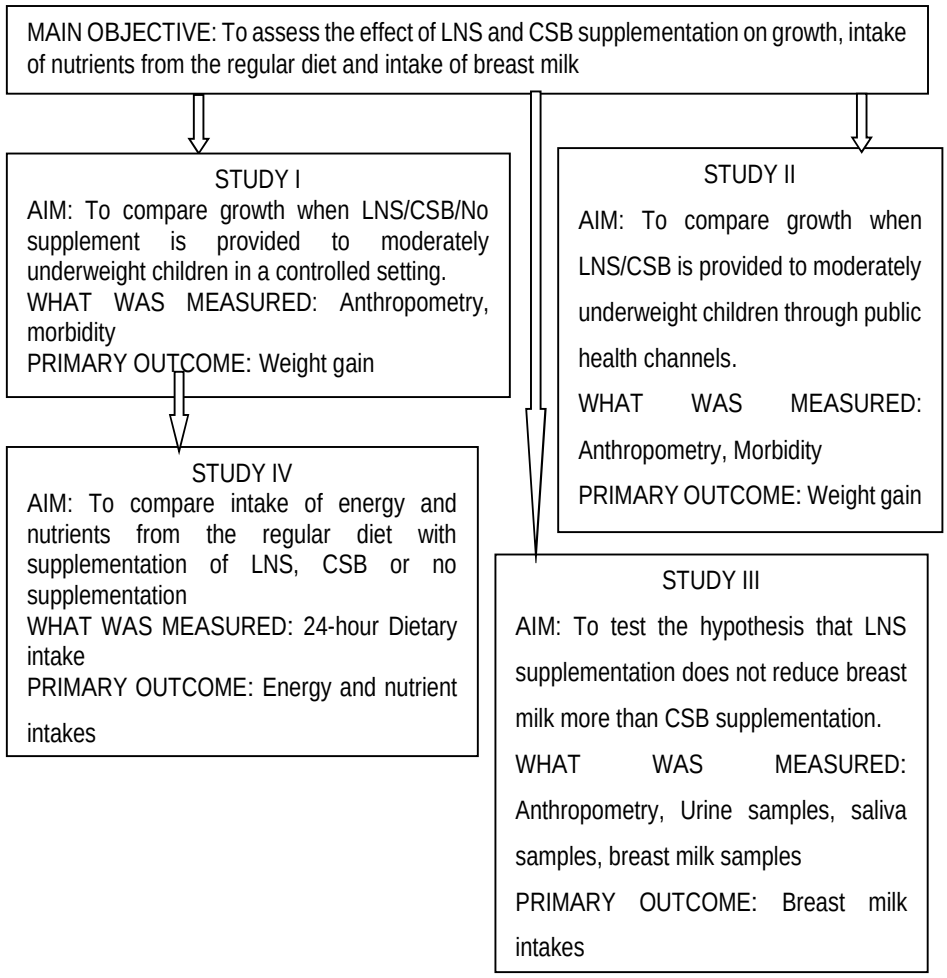
The effectiveness study (II) was carried out through the National Health Service to determine if LNS and/or CSB supplementation when provided to moderately underweight children through the National Health Service improves weight. A total of 299 moderately underweight children were randomly assigned to receive an average daily ration of 43g LNS or 71g CSB, providing 220kcal and 284kcal respectively or no supplement. The participants' guardians collected the food supplements from the health facility every 4 weeks for 12 weeks. The main outcome

was weight gain. Changes in anthropometric indices and incidence of adverse events were the secondary outcomes.

The breast milk intake study (III) was conducted to test the hypothesis that the provision of LNS to Malawian infants would not decrease their breast milk intake more than the provision of CSB. This was part of a clinical trial that aimed at comparing growth and incidence of malnutrition in infants receiving long-term dietary supplementation with LNS or CSB (Phuka et.al, 2008). A total of 44 mother-infant pairs participated in the study. The main outcome was the difference in breast milk intake before the dietary supplementation and after one month of dietary supplementation.

The dietary intake study (IV) assessed the effect of LNS or CSB supplementation on the intake of energy and nutrients from the regular complementary foods among the moderately underweight children participating in the efficacy trial. A total of 188 children aged between 8 and 18 months participated in this study. Estimated energy and nutrient intakes were compared between the unsupplemented group and each of the intervention groups (CSB and LNS).

Figure 1. Overall design of the present studies



4.2 Study area and participants

4.2.1 Study area

The present studies were conducted at seven health facilities (Lungwena, Malindi, Namalaka, Jalasi, Koche, Kukalanga and Katema) in Mangochi District, southern Malawi (Appendix I). Malawi is a small country, about 94,000 square kilometers in south-east Africa. The country experiences three climatic seasons namely: cool season (May to August), hot season (September to November), and rainy season (December to April).

Mangochi is one of the districts in the southern region of Malawi and is estimated to cover about 6,273 square kilometers. About 76% of the inhabitants are of the yao ethnic tribe and approximately 70% of the population are moslems. About 80% of the people live in rural areas and are generally poor. Farming is their main occupation with maize, cassava and beans as the main food crops grown. Fishing is the major source of income followed by tourism.

Lungwena health centre catchment area was chosen as one of the present studies' sites since it has been the College of Medicine's maternal and child health research site for over 20 years. The Namalaka, Malindi, Jalasi, Koche, Kukalanga and Katema health facilities were added as part of the research sites because of their economic and social similarities with Lungwena site, large populations in their catchment areas and because of their easy accessibility.

Lungwena, Jalasi and Kukalanga are public health facilities while Malindi, Katema, Koche and Namalaka are mission-run health facilities where clients pay a small fee to access some services. All of these facilities provide preventive and curative services as well as maternal and child health services. The main referral health facility for complicated cases in the whole district is Mangochi District

Hospital. At community level, health surveillance assistants provide services including growth monitoring and immunisations among other things.

4.2.2 Study participants

Children from the catchment areas of the seven target health facilities were eligible for participation in the present studies. The following were the general inclusion criteria for all studies: an informed consent signed by a guardian, being available during the whole study period, permanent residency in the target health facilities' catchment areas. General exclusion criteria for all studies included severe wasting (WLZ < -3.0 z-scores) or presence of oedema, peanut allergy, any serious allergic reaction to any substance requiring emergency medical care, history of anaphylaxis, severe illness warranting hospital referral and concurrent participation in another clinical trial with intervention to the child. Those who did not meet any of the exclusion criteria were randomly assigned into one of the study's intervention groups. Group allocation was done through simple randomisation from a computer generated list. Table 2 below shows the specific inclusion and exclusion criteria for each of the studies.

Table 2. Comparisons of the four studies

Criteria	I	II	III	1V
Enrollment age, Months	6-15	6-15	5-6	8-18
Number of Subjects	192	299	44	188
Key enrollment criteria	<-2 WAZ	<-2 WAZ	age 5-6 mo	<-2 WAZ
Number of study groups	3	3	3	3
Interventions	CSB/LNS/Control	CSB/LNS/Control	FS/FS/CSB	CSB/LNS/Control
Intervention period, weeks	12	12	4	12
Timing of study	Dec '06-May '07	Nov '07-April '08	Sept- Dec 04	March-May 07

*FS (fortified spread) is the name that was used previously for LNS. Similar ingredients used in the FS and LNS.

4.3 Nutritional interventions

Participants for studies I, II and IV received weekly a daily ration of 71g CSB, 43g LNS or no supplementation for 12 weeks. Table 3 shows the nutritional composition of the daily dose of LNS and CSB.

In study III, participants in the control group received a daily ration of 71g CSB. The first intervention group received 25g/day LNS while 50g/day LNS was given as the second intervention. Table 4 shows the nutritional composition for the daily LNS and CSB dose.

The LNS was produced and packed by Project Peanut Butter, a Malawian NGO, from a mixture of about 26% peanut butter, 25% dried skimmed milk, 20% vegetable oil, 28% icing sugar and about 2% mineral and vitamin mix which was purchased from Nutriset, Malaynay, France. The LNS was packed in opaque, plastic containers, stored at the trial office at a temperature between 20^{o}C and 35^{o}C with a maximum storage time of three months from production to consumption.

The CSB was produced and packed by Rab Processors in Blantyre, Malawi. It was packed in opaque, plastic bags and was stored at the trial office at a temperature between 20^{o}C and 35^{o}C. The maximum storage time from production to consumption was six months.

Table 3. Nutrient composition of a daily dose of LNS and CSB used in I, II and IV (Thakwalakwa et al., 2010; Thakwalakwa et al., 2012; and Thakwalakwa et al., 2014 respectively)

	CSB	LNS
Weight, g	71	43
Energy, kJ	1189	921
Protein, g	10.4	6.0
Carbohydrates, g	NA[1]	11.9
Fat, g	3.1	13.5
Retinol, µg RE	139	400
Folate, µg	43.2	160
Niacin, mg	3.5	6
Pantothenic acid, mg	NA[1]	2
Riboflavin, mg	0.3	0.5
Thiamin, mg	0.13	0.5
Vitamin B-6, mg	0.3	0.5
Vitamin B-12, µg	0.9	0.9
Vit. C, mg	48	30
Vit. D, (cholecalciferol), µg	NA[1]	5
Calcium, mg	72	366
Copper, mg	NA[1]	0.4
Iodine, µg	NA[1]	135
Iron, mg	5.46	8
Magnesium, mg	NA[1]	60
Zinc, mg	3.6	8.4

1 kcal = 4.186kJ; [1] = No information available

Table 4. Nutrient composition of a daily dose of LNS and CSB used in III (Galpin et al., 2007)

	CSB	LNS	LNS
Weight, g	71	50	25
Energy, kJ	1189	1070	535
Protein, g	10.3	7.0	3.5
Carbohydrates, g	NA[1]	13.8	6.6
Fat, g	3.1	16.9	8.5
Retinol, µg RE	139	400	400
Folate, µg	43	160	160
Niacin, mg	3	6	6
Pantothenic acid, mg	NA[1]	2	2
Riboflavin, mg	0.3	0.5	0.5
Thiamin, mg	0.1	0.5	0.5
Vitamin B-6, mg	0.3	0.5	0.5
Vitamin B-12, µg	0.9	0.9	0.9
Vitamin C, mg	48	30	30
Vitamin D (Cholecalciferol), µg	NA[1]	5	5
Calcium, mg	71	366	283
Copper, mg	NA[1]	0.4	0.4
Iodine, µg	NA[1]	135	135
Iron, mg	5	8	8
Magnesium, mg	NA[1]	60	60
Selenium, µg	NA[1]	17	17
Zinc, mg	3.6	8.4	8.4

1 kcal = 4.186 kJ; [1] = No information available

4.4 Data collection

4.4.1 Enrollment and follow-up

For all studies, group allocation was done through simple randomisation from a computer generated list. Based on the list, randomisation codes were placed into opaque envelopes. Each caretaker of the study participant was asked to choose and open one of the envelopes from a pack of reshuffled envelopes.

The participants for studies I, III, and IV were visited weekly in their homes by research assistants for 12 weeks (Figure 2). At the participant's home, the research assistant delivered the study supplements. In addition, they collected information on how the study supplements were used and on morbidity and any adverse event (AE). The following medical problems were regarded as AE: abdominal discomfort, vomiting and/or diarrhea for more than two days; skin rash for two or more days; noisy, wheezy, rapid or difficult breathing; and any other medical conditions that the study physician judged as abnormal or not typical childhood illnesses. The serious adverse events (SAE) included: death; life-threatening condition; in-patient hospitalization or prolonged hospitalization; persistent or significant disability or incapacity; or any other serious medical condition. Participants were advised to report to the clinical officer at the health centre if they had any of these symptoms or problems during the study period. The clinical officer determined if the problem was an AE or SAE and also determined if the AE or SAE was related to the study supplements. An independent data safety and monitoring board (DSMB) also determined if the SAE were related to the study supplements. To check for compliance of the food supplements, empty containers of the supplements were collected back to the study station. Every four weeks, the participants underwent medical and anthropometric examination at the health centre.

Participants of study 1 participated in study IV when they had been in study I for 9 weeks receiving LNS, CSB or no supplements. Study III took place before enrollment and a month after the participants had enrolled into a clinical trial (Phuka et al., 2008). Participants for studies I, III and IV underwent some laboratory tests for malaria and anaemia at the health centre. These tests were done at enrollment and during the last visit except for malaria tests which were done anytime the participant presented with fever at the health centre. The follow up picture of participants in studies I, III and IV is shown in figure 2 below.

Figure 2. Follow up of participants in studies I, III and IV

Week	0	1	2	3	4	5	6	7	8	9	10	11	12
Medical and anthropometric exam	X				X				X				X
Laboratory tests	X												X
Home visits	X	X	X	X	X	X	X	X	X	X	X	X	X
Monitor dietary intake										X			

In study II, the participants came to the health centre every four weeks for a follow up visit. During these visits the following took place: the participant's guardian collected study supplements for the next four weeks; the participants underwent medical and anthropometric examinations and the guardians were inquired about morbidity and any AE. Laboratory tests were conducted at enrollment as well as during the last visits (Fig 3)

Figure 3. Follow up of participants in study II

Week	0	1	2	3	4	5	6	7	8	9	10	11	12
Medical & anthropometric exam	X				X				X				X
Laboratory tests	X												X
Health facility visits	X				X				X				X

4.4.2 Anthropometric measurements

Infants were measured nude to the nearest 10g using a seca 735 electronic infant weighing scale (SECA 735, Chasmors Ltd, London, England). Head circumference and mid upper arm circumference were measured to the nearest 1mm by a non stretchable measuring tape (Lasoo-o-tape, Harlow Printing Ltd, South Shields, Tyne and Wear, England). Length was measured to the nearest 0.1 cm using a length board (infantometer, Child Growth Foundation, London, UK). WAZ, WLZ, LAZ were calculated using Epi Info 3.3.2 software (Centres for Disease Control and Prevention, Atlanta Georgia based on the Centres for Disease Control and prevention 2000 growth reference (Kuczmarski et al., 2002). The studies were planned before the WHO growth standards 2005 reference became available. As such, the CDC 2000 growth standards reference was used. Anthropometric measurements in this research were done in triplicate by either the author, Mpumulo Jawati or John Phuka.

4.4.3 Measurement of dietary intake

A structured interactive 24-hour recall method (Ferguson et al., 1989; Ferguson et al., 1995) was used to collect data on intake of energy and nutrients. The structured interactive 24-hour dietary recall was modified from the original 24-hour recall and has previously been used to assess dietary intake of both children and pregnant women (Ndekha et al., 2000; Maleta et al., 2004). The relative validity of this method has been documented (Ferguson et al., 1989; Thakwalakwa et al., 2012b).

Focus group discussions were conducted with mothers of 6-24 month old children to collect a list of foods and drinks commonly consumed by children of that age group in the area. The data collected from the focus group discussion was used to develop a local food picture calendar that was used during the 24-hour recall. Colour photographs of the common foods for the target group were taken and made into the picture calendar (Appendix II).

The process happened in three days. During the first day, the interviewer visited the participant's home and agreed with the participants to conduct the interactive 24-hour recall interview process. The participant was left with the local food picture calendar (Appendix II) and asked to tick all foods and drinks that would be eaten the following day (Day two). During the second day, the guardian marked on the picture calendar all foods and fluids that the participant consumed. On the third day, the interviewer collected the marked food picture calendar and asked the participant's guardian to describe all the foods and drinks consumed by the participant the previous 24-hour period. This included listing the foods and drinks consumed, quantity taken and all the ingredients included in any of the consumed food or drink. The interviewer compared what was orally reported by the guardian with what was marked on the food calendar and the interviewer discussed with the guardian any differences in the data collected. The guardian was asked to estimate quantity taken using the salted replicas of food and the measuring spoons, cups and plates.

4.4.4 Measuring energy and nutrient intake

To determine the nutrient values of the foods and drinks, the measurement values of the foods or drinks consumed were converted into grams and computed using a computer program installed in Microsoft Excel 7.0 (Microsoft corp, Redmond,WA, USA) (Ndekha et al., 2000). The program has pre-entered data on raw food groups and is linked to a food composition database which has a total of 212 foods coded into 14 food groups. These food groups include starchy staples, legumes, fats and oils, sugars, roots, meats, dairy products, vegetables, beverages, fish, fruits, spices, LNS and CSB. For the food composition database, 118 foods were adapted from the Kenyan food composition table and 64 were from the international Minilist nutrient database (World Food Dietary Assessment System, version 2.0, Office of Technology Licensing, University of California Berkeley). The nutrient composition of the remaining foods were analysed by Malawi Bureau of Standards.

4.4.5 Measurement of breast milk intake

The quantity of breast milk taken by the study participant was estimated by using the dose-to-mother deuterium oxide dilution method (Coward et al., 1982; Haisma et al., 2003). This method is suitable for estimating average daily breast milk intake in community settings.

Anthropometric measurements of the mothers as well as their babies were taken. Infants' weights were taken without clothes on using an electronic infant scale (SECA Model 334) with a precision of 10 g. Mothers were weighed with their light clothes. At enrollment, saliva and urine samples were obtained from mothers and babies respectively. Then 10g of deuterated water was given to mothers. The mothers and their infants were followed on days 1, 3, 4, 13, and 14 after taking the deuterated water. During all the follow-up days, infant urine samples were collected while saliva samples from mothers were only collected on days 1, 4, and 14. Mothers were asked not to take any food or drink 30 minutes before the sample collection. To collect saliva samples, the mothers were given some cotton wool and asked to put in their mouth for about 5 minutes then the saliva was squeezed out of the cotton wool using a plastic syringe. As for urine sample collection, cotton wool balls were placed in infants' disposable diaper then the urine was squeezed out of the cotton wool balls using plastic syringe. Urine and saliva samples were then stored at −20 °C before transporting them to the lab for analysis. After completion of the 2-week period, the infants were randomized to receive 1 of the 3 complementary feeding supplements. The infants received the complementary food supplements for a month before the process of assessing breast milk intake was repeated. This study took place between 15 September and 12 December, 2004.

The isotope ratio mass spectrometry at the Biogeochemical laboratory, Department of Geological Sciences, Indiana University, Bloomington, IN assessed the deuterated water content in the saliva and urine samples.

4.4.6 Laboratory measurements

Blood haemoglobin concentration were measured locally with a Hemo-Cue® – instrument from a finger-prick or heel prick blood sample. Peripheral blood malaria parasitaemia was assessed microscopically from Giemsa -stained thick and thin blood films (one of each).

4.4.7 Monitoring child survival and morbidity

Child survival and morbidity for participants in in studies I, III and IV was queried from the guardians through weekly interviews conducted by a research assistant at their homes using a structured questionnaire about the number of days when the child had symptoms of malaria, diarrhoea, cough or other illnesses. For studies I and II, further morbidity information was obtained at the 4-weekly medical and athropometric visits at the health facility. During all these times, a special form was used to record any illnesses or problems encountered during the study. For all studies, child survival and morbidity assessments were done by a Clinical officer whenever the participant's guardian brought the participant to the clinic because of any disease or any problem encountered during the study.

4.5 Statistical approach

4.5.1 Sample size

For studies I, II, and IV, the sample sizes were calculated from the expected difference in the primary outcome, weight gain, among infants provided with either LNS, CSB or no supplements. This expected difference was assumed to be mean (SD) weight gain of 550 (440) g among the control infants and 800 (440) g among infants receiving either LNS or CSB supplementation (Kuusipalo et al., 2006). This provided the studies with 85% power and 95% confidence.

For study III, based on an assumption that a standard deviation of 10 g/kg body weight/day in breast milk intake would happen before and during the complementation (Sandige et al., 2004), the sample size was 15 per group providing 80% power and 95% CI to test the hypothesis that supplementation with LNS would not decrease breast milk intake more than supplementation with CSB.

4.5.2 Data management and analysis

Data from studies I, II and IV were analysed using Stata 9.0 (Stata Corp, College Station, Texas) based on an intention to treat method. Group means were compared between control and each of the supplemented groups at a single time point using t test and results expressed as absolute differences and their 95% CI. Risk ratio (RR) and risk difference were estimated for comparison of binary end-points between the control and each of the supplemented groups and tested the difference in proportion using Fisher's exact test. To prevent inflated type 1 errors due to multiple comparisons, hypothesis testing began by testing the global null hypothesis of all three groups being identical, using Fisher's exact test (categorical variables) and

ANOVA (quantitative variables). Only if the global null hypothesis was rejected would the pairwise comparisons be interpreted in a confirmatory manner. For all studies, all confirmatory analyses were considered significant if $P< 0.05$. Linear regression modeling was used to determine whether the type of food supplement given was associated with the primary outcome of each study, with adjustment for some baseline factors.

Statistical analyses for study III were conducted using GLM procedure (SAS/STAT software). Mean breast milk intake were compared before and after intervention using ANOVA.

4.6 Ethics

All studies were performed according to International Conference of Harmonization Good Clinical Practice guidelines (ICH-GCP) and the ethical standards of Helsinki Declaration. The protocols were reviewed and approved by the College of Medicine Research and Ethics Committee, University of Malawi and the Ethical Committee of Pirkanmaa Hospital District, Finland. At least one guardian signed or thumb-printed an informed consent form before enrolment of each participant. The study components were registered with the following registration IDs: NCT00131209, NCT00420368, and NCT00420368 at http://www.clinicaltrials.gov/. Each of the four studies had an independent data safety and monitoring board monitoring the incidence of suspected SAE.

5 RESULTS

In this section, the main results of each of the four studies are presented separately. Some published tables and figures are shown and referenced while others are only described and shown in the actual attached publication.

5.1 Efficacy of LNS/CSB supplementation to moderately underweight children on growth (I)

192 children were randomly selected to receive LNS, CSB or no supplement weekly for 12 weeks (Fig 4). At baseline, there were slightly more participants in the LNS and CSB groups than the control group, but the participants characteristics were comparable (Table 5). This study took place between December 2006 and May 2007. A total of 188 participants (98%) completed the 12 week follow up.

Figure 4. Participant flow

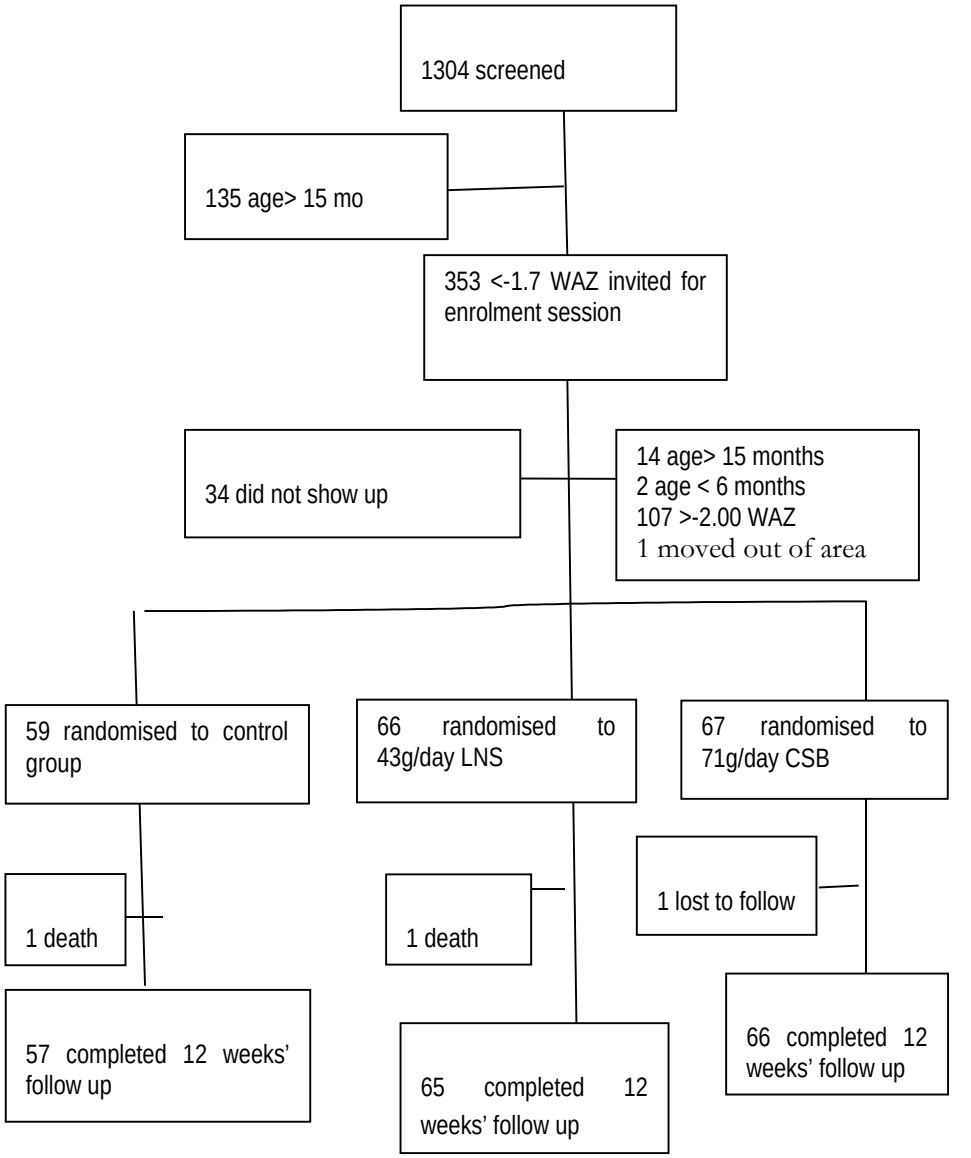


Table 5. Baseline characteristics of participants in study I (Thakwalakwa et al., 2010)

Variable	Control	LNS	CSB
Participants, n (% males)	59 (58)	66 (47)	67 (45)
Age, mo	11.3±2.5	11.3±2.5	11.2±2.7
Weight, kg	7.03±0.74	7.11±0.91	6.89±1.04
Length, cm	66.1±3.2	66.3±4.0	65.6±4.5
MUAC, cm	13.5±0.8	13.5±0.9	13.4±1.1
Head circumference, cm	44.5±1.5	44.1±1.3	43.8±1.8
WAZ	-2.98±0.86	-2.83±0.78	3.06±1.08
WLZ	-0.69±0.78	-0.56±0.73	0.67±0.79
LAZ	-2.80±0.97	-2.67±0.94	2.81±1.13
Hb, g/L	97±14	97±18	95±14

Values are Mean±SD or n (%); WAZ= Weight-for-Age Z-score, WLZ= Weight-for-Length Z-score; LAZ= Length-for-Age Z-score; MUAC=mid-upper-arm circumference; Hb= haemoglobin concentration (g / L)

During the 12-week intervention period, the mean weight gain was 470g, 510g and 610g in the Control, CSB and LNS groups respectively(p=0.109). WAZ changes were -0.32,-0.31 and +0.02 units, respectively (p=0.030). Compared to the control group, infants in the LNS group had on average (95% CI) 140 (0 to 300, p=0.055) grams higher weight gain and 0.33 (-0.02 to 0.65, p=0.039) unit larger increase in WAZ-score. CSB and control groups were comparable in the weight gain. The difference (95% CI) between LNS and control groups was 140 (0 to 290) grams in weight (p=0.049) and 0.35 (0.08 to 0.62) Z-score units in WAZ (p=0.011) when adjusted for baseline weight and age. There were no differences in the observed changes in head circumference, MUAC, and haemoglobin levels in all the three groups.

Stratified analyses were conducted based on baseline WAZ according to CDC 2000 growth standards. Among those whose baseline WAZ at enrollment was below the median, the LNS group had an average weight gain (95% CI) 250 (60 to 430) grams higher compared to the control group (p=0.01). CSB was not associated with higher weight gain in this group (Table 4 in manuscript I). The stratified analyses were conducted again based on the baseline WAZ and according to WHO 2006 growth standards. Those with baseline WAZ below the median and in the LNS

group gained 230g (30 to 440) higher weight (p=0.02) and 0.28 WAZ higher (p=0.02) than the control. Compared to the control group, those below the median and in CSB group had a length gain of 0.7cm (0.0 to 1.4) higher (p=0.04). Among those with WAZ above the median in both analyses, marginal differences were observed between control and either of the intervention groups (all p=>0.05) (Table 6 and Table 4 in manuscript I).

During the study period, 36 participants experienced any AE with 10 of them being SAE. In general, more participants in the LNS group experienced any AE (23%) as compared to CSB (19%) and control (14%) groups. Compared with the control group, children in the LNS group registered more episodes of vomiting (P = 0.02) and skin rash (P = 0.04). All SAE were assessed as unlikely related to the intervention (Table 5 in the published manuscript).

Table 6. Quantitative outcomes among participants; stratified analysis based on weight-for-age Z-score at enrolment: Based on the WHO growth reference (WHO MGRSG, 2006).

	Results by study group				Comparison between LNS and Control		Comparison between CSB and Control	
	Control	LNS	CSB	P-value	Difference (95% CI)	P-value	Difference (95% CI)	P-value
Baseline WAZ below median (<-2.08)								
Mean weight gain (kg)	0.43±0.34	0.66±0.43	0.51±0.39	0.07	0.23(0.03 - 0.44)	0.02	0.08 (-0.10 – 0.26)	0.38
Mean length gain (cm)	3.2±1.4	3.4±1.0	3.9±1.2	0.08	0.2(-0.4 – 0.9)	0.50	0.7 (0.0 – 1.4)	0.04
Mean WAZ change	-0.10±0.44	0.18±0.49	-0.03±0.51	0.08	0.28 (0.04 – 0.53)	0.02	0.07 (-0.17 – 0.31)	0.56
Mean Hb change	-7.1±21	-0.0±19	-4.2±14	0.33	7.1 (-3.4 – 17.5)	0.18	2.9 (-6.0.– 11.8)	0.51
Baseline WAZ above median (>-2.08)								
Mean weight gain (kg)	0.51±0.36	0.58±0.51	0.51±0.32	0.75	0.07(-0.16 - 0.29)	0.57	0.00 (-0.18 – 0.18)	0.99
Mean length gain (cm)	3.4±0.9	3.4±1.1	3.1±0.9	0.28	0.0(-0.49 – 0.57)	0.89	-0.3 (-0.8 – 0.1)	0.17
Mean WAZ change	-0.05±0.39	0.00±0.54	-0.05±0.35	0.86	0.05 (-0.19 – 0.29)	0.69	-0.00 (-0.20 – 0.19)	0.97
Mean Hb change	-3.4±10	-6.3±21	-1.4±11	0.42	-2.9 (-11.5 – 5.7)	0.50	2.0 (-3.8 – 7.8)	0.49

Values are Mean±SD or Mean difference (95% CI); WAZ= Weight-for-Age Z-score, Hb= blood haemoglobin concentration (g / L)

5.2 Effectiveness of LNS/CSB supplementation of moderately underweight children on growth (II)

Two hundred and ninety nine (299) children were randomized to receive CSB, LNS or no supplementation. About 94% completed the follow-up (Figure 1 in the published manuscript for II). All participants were reported to be breast-fed during the whole intervention period.

At enrollment, children in the LNS group were younger, thinner and shorter as compared to the CSB and control groups. The majority of the children in the CSB and LNS groups were enrolled at the beginning of the lean season while those in the control group were evenly distributed (Table 7). The study took place between November 2007 and April 2008.

Table 7. Baseline characteristics of participants in study II (Thakwalakwa et al., 2012).

Variable	Control	CSB	LNS
Participants (n, % male)	86 (44)	109 (55)	104 (49)
Age, months	11.6±2.3	11.1 ± 2.4	10.0± 2.4
Weight, kg	6.95± 0.74	6.97 ± 0.76	6.59± 0.89
Length, cm	67.3 ± 3.3	67.5 ± 3.6	66.3 ± 3.6
MUAC, cm	12.7 ± 0.9	12.7± 0.8	12.4 ± 0.9
HC, cm	43.9± 1.5	43.7 ± 1.6	43.2± 1.7
WAZ*	-3.11± 0.82	-2.96± 0.79	-3.06±0.92
WLZ*	-1.32 ± 0.84	-1.36 ± 0.83	-1.61±0.86
LAZ*	-2.36 ± 0.91	-2.16 ± 0.90	-2.11± .92
Hb, g/l	88± 17	89 ± 17	88± 20
Age,6-12 months (n,%)	47 (55)	67 (61)	79 (76)
Age,12.01-18 months (n,%)	39 (45)	42 (39)	25 (24)
Enrolled Nov-Dec 2007(n,%)	46(53)	63 (58)	71 (68)
Enrolled Jan 2008 (n,%)	40 (47)	46 (42)	33 (32)

Values are Mean±SD or n (%) CSB, corn–soya blend; LNS, lipid-based nutrient supplement; MUAC, mid-upper arm circumference; HC, head circumference; WAZ, weight-for-age Z-score; WLZ, weight-for-length Z-score; LAZ, length-for-age Z-score.
*Using Centers for Disease Control and Prevention 2000 growth reference

Average weight gain at the end of the 12-week intervention period was 630g, 680g and 750g in Control, CSB and LNS groups respectively (P=0.21). When adjusted for factors that were not balanced at enrollment (sex, enrolment season and baseline WLZ), children in LNS group gained 130g more weight (P=0.051) and 0.4 cm more length (P=0.053) than children in the control group. Marginal differences were observed between the CSB and control group in the average weight and length gain. For further results please refer to the attached manuscript for II.

At baseline, about 47% and 22% of children in the control group were severely underweight and severely stunted respectively; the respective measures in the CSB group were about 39% and 15% and 45% and 13% respectively in the LNS group. There were no severely wasted children in any of the three groups. At the end of the 12-week intervention period, the control group had about 56% and 22% severely underweight and severely stunted children respectively. The corresponding values were 45% and 17% in the CSB and 46% and 13% in the LNS groups respectively. The prevalence of wasting was similar in all groups. (Table 8)

Table 8. Prevalence of undenutrition at enrollment and at the end of the intervention amongst the children supplemented with LNS, CSB or no supplements (Control)

	Control	CSB	LNS
Number enrolled	86	109	104
Moderate to severe underweight at enrollment (%)	86 (100)	109 (100)	104 (100)
Moderate to severe underweight at the end (%)	72 (84)	96 (88)	89 (85)
Severe underweight at enrollment (%)	40 (47)	42 (39)	47 (45)
Severe underweight at the end (%)	48 (56)	49 (45)	48 (46)
Moderate to severe stunting at enrollment (%)	21 (24)	25 (23)	40 (38)
Moderate to severe stunting at the end (%)	43 (50)	59 (54)	52 (50)
Severe stunting at enrollment (%)	19 (22)	16 (15)	14 (13)
Severe stunting at the end (%)	19 (22)	18 (17)	13 (13)
Moderate to severe wasting at enrollment (%)	57 (66)	64 (59)	58 (56)
Moderate to severe wasting at the end (%)	30 (35)	32 (29)	39 (38)
Severe wasting at enrollment (%)	0 (0)	0 (0)	0 (0)
Severe wasting at the end (%)	5 (6)	6 (6)	7 (7)

Fifty-one study participants experienced AE during the intervention period with no significant difference among the three groups (all P>0.005) (Table 5 in manuscript for II). All SAE were assessed as unlikely related to the intervention.

5.3 Effect of LNS/CSB supplementation to healthy infants on breast milk intake (III)

A total of 41 out of the 44 enrolled mother-infant pairs completed the study (Table 9). Prevalence of the participants' exclusive breast feeding at enrollment was at 12% with the remaining 88% already introduced to foods other than breast milk. At baseline, the infants in the 25g/day LNS consumed a mean ±SD breast milk intake of 955± 189 g per day, those in the 50g/day LNS consumed about 921±165g/day, while those in the 72g/day CSB consumed about 839±109g/day (Table 10). The infants were fed 25 g/day LNS, 50 g/day LNS, or 72 g/day CSB for approximately a month before the second assessment of breast milk intake. During the second assessment their breast milk consumption was 902± 193 g/day, 931±187g/day, 797±119g/day (Table 10) showing a substantial reduction but the effects of the complementary foods were similar (P= 0.69). The reduction was greater in the children who were already on complementary foods than in those on exclusive breast feeding. The study took place between 15 September and 12 December, 2004.

Table 9. Baseline characteristics of participants in study III

Variable	25g/d LNS	50g/d LNS	72g/d CSB
Infants			
Number (% Male)	15 (67)	14 (36)	12 (42)
Weight, kg	7.02± 0.66	7.05±0.93	6.41±0.30
Age, mon	5.3± 0.3	5.5±0.4	5.5±0.4
Length, cm	64.2±1.7	64.3±1.7	63.6±1.0
WLZ	0.3±0.5	0.3±1.0	0.2±0.5
WAZ	-0.3±0.6	0.2±0.9	-0.8±0.5
LAZ	-0.7±0.4	-0.6±0.4	-0.8±0.5
Have other source of milk, n (%)	2 (13)	2 (14)	0 (0)
Consumed other foods before enrollment, n (%)	12(80)	12 (86)	12 (100)
Mothers			
Age, years	23±5	26±4	28±4
Weight, Kg	50.8±5.4	55.2±5.8	50.7±4.4

Values expressed as Mean±SD or n (%), LAZ= Length-for-Age z-scores, WAZ= Weight-for-Age z-scores; WLZ= Weight-for-Length z-scores

Table 10. Breast milk intake before and after one month of complementary feeding

Variable	25g/d LNS	50g/d LNS	72g/d CSB
Before complementary feeding			
Breast milk intake, g/d	955±189	921±165	839±109
Intake per weight, g/d	132±21	127±19	128±15
Infant weight, kg	7.02±0.66	7.05±0.93	6.45±0.33
After one month of complementary feeding			
Breast milk intake, g/d	902±193	931±187	797±119
Intake per weight, g/d	115±21	118±18	111±14
Infant weight, kg	7.32±0.58	7.50±0.85	6.85±0.35

Values are Mean±SD

5.4 Effect of LNS and CSB supplementation on energy and nutrient intake (IV)

188 of the 192 children randomized into the efficacy study (I) participated in this dietary intake assessment study when they were between 8 and 18 months of age. The control and CSB groups had slightly lower baseline age, weight, length, length-for-age (LAZ), weight-for-age (WAZ) and weight-for-length (WLZ) than the LNS group at baseline of this study (Table 11).

Table 11. Baseline characteristics of participants for IV (Thakwalakwa et al., 2014).

Variable	Control	CSB	LNS
Participants, n	58	65	65
Age, months	13.3±2.58	13.3±2.80	13.5±2.54
Weight, kg	7.35±0.79	7.23±1.10	8.29±5.75
Length, cm	67.4±8.7	68.1±4.3	69.0±3.6
MUAC, cm	13.6±0.8	14.0±4.3	13.9±0.9
HC, cm	44.8±1.5	44.4±1.6	44.6±1.3
WAZ	-3.20±0.84	-3.36±1.16	-2.91±0.85
WLZ	-1.14±0.84	-1.17±0.97	-0.90±0.94
LAZ	-2.63±0.82	-2.75±1.05	-2.47±0.74

Values are mean ±SD HC=Head circumference

During the assessment, the mean energy intake from the regular complementary foods and the food supplements was 548kcal in control group, 551kcal in CSB group and 692kcal in LNS group (P=0.01). Mean protein intakes were 13.7g, 14.9g and 18.2g in control, CSB and LNS groups respectively (P=0.03). Compared to the control group, infants in the LNS group had on average (95% CI) 144kcal (37 to 250, P=0.01) higher energy intake and 5 grams (-1.5 to 7.7, P=0.00) higher protein intake. CSB group had slightly higher energy and protein intakes as compared to the control group (both P=>0.05). Both CSB and LNS had higher calcium, iron, zinc and vitamin C intakes as compared to control (all P=<0.001) (Table 3 in the manuscript for IV).

Without the food supplements, the mean energy intake was 548kcal, 366kcal and 596 kcal for the control, CSB and LNS groups respectively (P=<0.001). Compared to the control group, LNS group had 48 kcal higher energy intake while CSB had 182 kcal lower energy intake from the other complementary foods. Similar intakes of protein, calcium, iron, zinc, vitamin A and vitamin C were observed in all the three groups

6 DISCUSSION

The present studies were carried out to compare the effect of LNS and CSB supplementation to children on their growth, intake of energy and nutrients and intake of breast milk. Studies I and II tested the effect of LNS and CSB supplementation to moderately underweight children on growth in terms of weight gain and other health benefits in a controlled setting and through public health services respectively. Study III compared the intake of breast milk in relation to supplementation of LNS and CSB to healthy infants while study IV compared intake of energy and nutrients from the regular complementary foods with the supplementation of LNS and CSB to moderately underweight children. The first part of this section discusses the strengths and weaknesses of the studies. Then it discusses possible reasons for the observed results and compares the present results with other studies.

6.1 Strengths and weaknesses of this research

A major strength of the present studies was random group allocation: all participants had an equal chance to be in any of the intervention groups. There was blinding for group allocation of the individuals assessing the outcomes and refusal rate for participation was low. Furthermore, there was a high enrollment rate and a very minimal and balanced loss-to-follow-up between the groups which make the results to be representative of the study population. Lastly, the characteristics of the participants and those who refused participation were similar and this minimized the potential for selection bias.

Despite the above strengths, there were some limitations that need to be taken into consideration when interpreting the present results. First, the study was conducted mainly during a time of the year when access to food is usually low and the study may thus have been affected by the poor availability of foods. Caution should be applied when applying the results to other times of the year when food is plenty. Secondly, there were no planned observations made to confirm if the mothers actually fed the LNS or CSB to the targeted children. However, the participants in studies I, III and IV were visited weekly in their homes where among other things, the guardian was asked how well the child ate the food supplement. In addition to this, another study in the same research area documented on how the food supplements were actually used in the home (Flax et al., 2010). Thirdly, the dietary study relied on the mothers' memory and reports to collect data on intake of complementary foods. This method could have resulted into a recall bias. This was however, reduced with the use of the structured interactive 24-hour recall method which mainly uses the local food picture calendar to aid in stimulating memory of the respondents. It is well known that diets vary considerably from day to day (Beaton et al., 1983; Herbert et al., 2000) and that a single 24-hour recall does not accurately estimate an individual's usual intake. However, the interest in this study was on group estimates which a single 24-hour recall can reliably estimate (Ferguson et al., 1995).

A further limitation in the breast milk study (III) was that breast milk intake was compared between children supplemented with either LNS or CSB, for ethical reasons without an unsupplemented (control) group. The conclusions were thus restricted to the two supplements without conclusions from an unsupplemented group. The results obtained did not clearly show whether the reduction in the intake was due to the study supplements or other factors. Therefore, there is need to conduct another study with an unsupplemented comparison group included to determine the true effect of LNS or CSB supplementation. However, the focus of the study was to compare how much breast milk intake reduction would occur with supplementation of either LNS or CSB.

It is with this background of strengths and weaknesses that the following discussions from the present studies are presented.

6.2 Promotion of growth

The energy needs of children with moderate undernutrition are high for catch-up growth. Therefore, these children require an energy dense diet. Unfortunately, the typical diet in populations like Malawi with a high prevalence of undernutrition consists predominantly of a starch-rich staple, such as a cereal (maize, rice) or tuber (cassava), with limited amounts of fruits, vegetables, legumes, and pulses, and little or no animal-source food (Dewey and Brown, 2003; Lutter and Rivera, 2003a). This type of a diet is bulky and has a low density of energy and nutrients needed for growth (Onyango et al., 1998; Allen, 2008). To complement it, the children could be supplemented with some fortified food products. Although any fortified food product given to young children in low-income countries is likely to have a positive impact on growth when compared with not giving a product at all (Dewey and Adu-Afarwuah 2008), the research presented in this thesis show that LNS promotes weight gain than CSB. These results are in agreement with other studies using LNS for moderately malnourished children (Ciliberto et al., 2005; Patel et al., 2005; Defourny et al., 2007; Phuka et al., 2008; Ackatia-Armah, 2012).

One possible explanation behind the higher weight gain with LNS supplementation than with CSB supplementation observed in the studies is that the lipid component in the LNS contains essential fatty acids which promote child growth (Huffman et al., 2011). Earlier studies from the same area suggested a sharing of the LNS and CSB supplements with other people not intended for it (Flax et al., 2008) with more sharing observed with CSB than with LNS supplementation (Maleta et al., 2004). This may also explain the lower weight gains observed with CSB supplementation than with LNS supplementation in the present studies.

LNS has also been shown to lead to an improvement in the recovery from undernutrition compared to CSB (Patel et al., 2005; Defourny et al., 2007; Matilsky et al., 2009; Nackers et al., 2010; Ackatia-Armah et al., 2012) and a reduction in the prevalence of undernutrition (Ruel et al., 2008; Isanaka et al., 2009; Defourny et al., 2009) thereby promoting growth. The present studies however do not show any recovery from undernutrition nor a reduction in prevalence of undernutrition but show that LNS helps to maintain nutritional status and prevents it from becoming

worse. This could be because the growth promoting effect observed was too marginal to lead to a recovery from undernutrition. The studies were mainly conducted during the time when food is scarce and children experience a decrease in rate of weight gain (Maleta et al., 2003). The seasonal factor is likely to have led to an underestimation of the effects of both LNS and CSB. Age and length of intervention has been shown to determine effectiveness of an intervention program (Schroeder et al., 1995; Simondon et al., 1996; Dewey and Adu-Afarwuah, 2008). It is possible that the intervention period in the present studies was too short to observe big changes. It is also possible that the positive effect was not detectable because of the consequences of the poor diet and high morbidity prior to the start of the intervention (FAO, 2010). The strong correlation between infections and undernutrition and its negative effects have well been documented (World Bank, 2008). For a better outcome, another trial should include an intervention on the infections combined with the food supplements.

These present studies suggest a stronger growth promoting effect of LNS vs CSB in poorly undernourished children. This was mainly observed in study I where children with poor nutritional status, that is, those with lower weight-for age at enrollment had higher weight gains than those with higher WAZ. A similar observation was made by Rivera and Habitch who showed a more substantial effect of LNS supplementation in the undernourished children than in those better off at enrollment (Rivera and Habitch, 2002). Overall, LNS supplementation can be a good solution to help improve the catch-up growth of undernourished children.

In the present studies, CSB and LNS were not effective in promoting length gain. However, when stratified analysis were done based on the WHO 2006 growth standards, CSB led to higher length gain as compared to the no supplement group. Other studies have documented no difference in length gain with ready to use supplementary food and CSB (Nackers et al., 2010; LaGrone et al., 2012). However, a review by Dewey and Adu-Afarwuah showed a significantly higher length gain with CSB supplementation for longer than three months as compared to no supplementation (Dewey and Adu-Afarwuah, 2008). Scientific literature has shown that length gain follows weight gain and this happens within a lag period (Costello, 1989; Heikens et al., 1989). As for Malawi, the lag period is three months (Maleta et al., 2003). The three month intervention period in the present studies was not long enough to be able to observe the effects on length gain. There is a need for further

research to determine the factors behind the higher length gains after a short period of CSB supplementation.

6.3 Promotion of intake of breast milk, energy and nutrients

Provision of high energy density diets to malnourished children has been shown to result in higher weight gains than low energy density diets (Brown et al., 1995). However, high energy diets have also been documented to displace breast milk and other complementary foods (Bajaj et al., 2005; Islam et al., 2006) implying a negative effect of high energy density food. The results from the present research do not agree with the finding that supplementation with high density foods lead to displacement of breast milk and complementary foods. Rather, the results are consistent with other studies that consumption of up to 50g/day of LNS promotes delivery of energy and nutrients without displacing breast milk (Owino et al., 2007; Owino et al., 2011) or other complementary foods (Maleta et al., 2003) more than CSB.

Studies have shown that as infant age increases, volumes of breast milk consumed also increase (da Costa et al., 2010) and remain above 800 ml/day until six to seven months of age (Islam and Brown, 2010). Our findings are in agreement with these findings. However, some studies have shown that giving infants complementary foods early may reduce breast milk intake (Cohen et al., 1994; WHO, 2000b). In the present studies infants who were already introduced to complementary feeding before the age of six months had a higher reduction of breast milk intake than those who were exclusively breast fed up to this age. Most of the previous studies used the test weighing method of assessing breast milk intake which is not very accurate and also interferes with normal feeding patterns as opposed to the present study that used a more accurate method. Therefore, the reduction in breast milk intake in the present studies may have been due to the early introduction of complementary feeding which was observed in 88% of the participants. The present study, however, did not include an unsupplemented group. It could not be concluded that the reduction in breast milk intake observed was due to the LNS and CSB supplementation or from the early introduction of complementary feeding. A later

study of 9-10 months old children in the same area included a no food supplement group (Kumwenda et al., 2014). The results showed that LNS supplementation of up to 40g/day does not lead into any reduction in breast milk intake.

The present studies show poor compliance to exclusive breastfeeding and an early introduction of complementary foods. Generally, exclusive breastfeeding rates are low in Malawi with only 41% of the infants under 6 months being exclusively breastfed (MDHS, 2010). The present studies with rates of only 12% exclusive breastfeeding before 6 months of age is lower than the national rate but reconfirms the findings of poor compliance to exclusive breast feeding practice. An explanation behind the difference in rate between the present studies and the national rate could be the methods used. The national data was collected using the questionnaire method while in the present studies, a dose-to-mother deuterium dilution method was used to overcome the practical problems associated with the questionnaire method (Butte et al., 1988; Haisma et al., 2003; Albernaz et al., 2003; Moore et al., 2007; Kumwenda et al., 2014).

The mean age for the participants in study IV was 13 months and they were all breast fed during the whole intervention time. The expected energy intake for this age group is about 900kcal/day (WHO/UNICEF, 1998; Dewey and Brown, 2003) with the complementary foods contributing about 550kcal/ day and breast milk contributing the remainder (about 350kcal/day). Compared to control group, the LNS had higher while CSB had lower energy from non-study complementary food intakes indicating displacement of other complementary foods with CSB supplementation. Children have a smaller stomach capacity (Dewey and Brown, 2003) making it difficult for them to eat much of the other complementary foods (Lucas et al., 1987; Bier et al., 1999). LNS has high nutrient density and is served in smaller portions. It is possible that this could have led to the higher intakes observed in the LNS group. In contrast, because of the lower energy and nutrient density of CSB, the child needs to eat more to meet the required energy need.

Other studies have documented a reduced energy intake from the regular foods during supplementation (Maleta et al., 2003; Koletzko, 1999; Walker et al., 1991). The present studies show an increase in energy intake with LNS and CSB supplementation with the LNS supplementation showing a higher increase than CSB supplementation.

6.4 Prevention from morbidity

The present studies show no conclusive evidence on whether LNS or CSB supplementation would or would not promote morbidity. Study I observed more illnesses in the LNS supplemented group than trial number II. Mixed results have also been reported from previous studies. A study by Ciliberto and colleagues found a lower prevalence of diarrhea, fever, and cough in a group supplemented with LNS compared to a group that received CSB (Ciliberto et al., 2005). Huybregts's study suggested that providing LNS as part of a general food distribution results in reduction in morbidity (Huybregts et al., 2012). Some studies found no evidence of difference in morbidity between the LNS and CSB supplementation (Adu-Afarwuah et al., 2007; Huybregts et al., 2012; Iannotti et al., 2014). However, it is difficult to generalize the findings from these studies since they varied in terms of age of participants, dose and duration of the supplement and morbidity assessment methods. Even though in the present studies (I and II) the parents were encouraged to present any case of illness to the hospital, participants in study I may have received frequent reminders since the data collectors visited their homes every week. This may have led to more cases being presented from study I than II. There is need for more research to be conducted to determine the effect of LNS and CSB supplementation on morbidity.

7 CONCLUSIONS

The purpose of the present studies was to assess the effect of LNS and CSB supplementation on growth, intake of breast milk and intake of energy and nutrients from the regular complementary foods. After the supplementation, the following conclusions were made:

Supplementation of LNS but not CSB boots growth when provided to moderately undernourished children in a controlled setting. The effect is more pronounced in more seriously underweight children compared to the less seriously underweight ones.

Supplementation of LNS and not CSB boosts growth when provided to moderately undernourished children through public health channels. The effect is smaller but in the same direction as that observed in more controlled settings.

LNS supplementation to breast fed children does not reduce breast milk intake more than CSB supplementation. However, a greater reduction in breast milk intake is associated with an introduction of other complementary foods to the infants before it reaches six months of age.

Intakes of energy and proteins from regular complementary foods (excluding breast milk and the study supplements) are higher with LNS supplementation than with CSB supplementation. Both LNS and CSB lead to higher micronutrient intake. LNS supplementation does not displace intake of the regular complementary foods. CSB, by contrast, leads to displacement of the regular complementary foods.

8 PUBLIC HEALTH IMPLICATIONS AND TOPICS FOR FUTURE RESEARCH

While there have been a lot of reports on the effects of food supplementation, most of the studies have looked at anthropometric gains as an outcome. The present study brings out a whole picture of the effect of LNS and CSB supplementation on intake of breast milk, intake of energy and nutrients and growth.

To ensure that the introduction of a food supplement promotes growth but does not replace or undermine breast feeding and optimal complementary feeding, the present studies provide additional evidence that LNS supplementation promotes growth in terms of weight gain. This research, though lacking a no food control group, supports the evidence that LNS supplementation does not lead to more reduction of breast milk intake than CSB supplementation (Cohen et al., 1994; Owino et al., 2007; Owino et al., 2011) and does not displace other complementary foods (Maleta et al., 2003) but disagrees with the finding that consumption of high energy density meals displace other complementary foods (Bajaj et al., 2005; Islam et al., 2006).

The studies suggest that the addition of LNS to children's diet from six months of age could provide an opportunity for dietary diversity and provide a potential intervention to manage undernutrition better than CSB. The present results would help guide policy makers, practitioners, and nutritionists for developing recommendations and planning action oriented approaches to combat child nutritional deficiencies.

The present studies demonstrate for the first time in Malawi the amount of breast milk taken by infants under six months using an objective and accurate "dose to mother" deuterium dilution method. In addition, the findings demonstrate that there is poor compliance to exclusive breastfeeding and that complementary foods are

introduced early to the infants. Exclusive breastfeeding needs to be scaled up in Malawi for optimum nutrition, growth and development.

The current study however points to the following areas in need of further research:

To carry out another study to identify the factors in LNS that makes it superior to CSB in promoting growth.

To include a no food control group in a larger trial to determine the effect of LNS and CSB supplementation on breast milk intake.

To carry out more research on the effect of CSB supplementation on length gain

Further research is also warranted to study breast milk intake across Malawi using accurate isotopic methods such as the deuterium dilution method that would give an objective estimate of the quantity of breast milk consumed by infants as well as a more accurate estimate of compliance to exclusive breastfeeding in comparison to currently available national data that reports intake of breast milk using questionnaires.

To conduct trials of LNS supplementation throughout all the three seasons in Malawi to determine actual effect of supplementation.

To conduct another study with an unsupplemented group included to determine the effect of LNS supplementation on morbidity.

Finally, there is need to identify other factors and practices that are associated with child growth. The information could be used when planning interventions such as LNS.

9 ACKNOWLEDGEMENTS

The research was carried out in the Department of International Health at University of Tampere Medical School in collaboration with the Department of Public Health of the College of Medicine, Malawi. A lot of people supported me and I would like to express my gratitude and appreciation to them all. However, the following people deserve few more words:

My supervisors, Professors Ken Maleta and Per Ashorn, for their tireless efforts and tremendous patience while I worked through a variety of duties (parenting and doing some project work among them) while completing this research. They provided great insights and offered a number of suggestions which enriched the research and dissertation. Earlier in my academic career, they provided amazing guidance and encouraged me to choose a subject matter which I am passionate about. During my challenging times, they offered empathy I never expected which I did and still appreciate more than they know.

Special thanks also goes to Professor Mark Manary for the financial, moral and physical support during the time this dissertation was being written. I do appreciate very much for your critical contribution and kind consideration throughout the time I was writing the dissertation.

My appreciation also goes to Professor Yin Bun Cheung for the statistical direction and assistance throughout the research. I very much appreciate your patience. Kiitos to Matti Katajja for the precious time that you devoted to help me do some analyses while in Tampere, Finland.

I also extend my warmest gratitude to the faculty and staff of the Department of International Health, Tampere, Finland for providing a motivating and friendly learning environment. I am appreciative of all those who helped to make my times

in Finland wonderful especially the Ashorns, Heli Kuusipalo, Kati Silvan, Anna Pulakka, Ulla Harujma, Hanna Peevo. Kiitos to you all!

The teachers in the IPPE for teaching me about epidemiology and biostatistics. Kirsi Lumme-Sandt, Catarina Ståhle-Nieminen, Hanna Peevo, and Kirsi-Maarit Lehto for assisting me with the administrative aspects of studying at the University of Tampere.

Special thanks go to the Academy of Finland, Nestle foundation and St Louis Nutrition Project for the financial assistance during my studies.

I thank the external reviewers, Professors Niinikoski and Rissanen for the thesis review work well done. The Data safety monitoring board (Paul Ndebele and Professors Kamija Phiri and Tom Heikens) for monitoring the studies. Professors Marja Ashorn and Suvi Virtanen for reviewing progress throughout my studies.

I am thankful to my colleagues: Mpumulo Jawati, John Phuka,Valerie Flax, the Tampere University Mother and Child Health Project (TUMCHP) study team (Rose Mzamu, Eunice Willy, Amina Atwabi, Rajab Allie, Falida Kasimu, Japhet Banda, Mark Dennis, Vukawaka Mbene, Laura Khanga, James Chitwanga, Mariam Pongolani, Maulidi, Halima, Prince, Lucia, Lesson, Ignasio, Dickson and Francis) for all the direction, support and fun that we had together while carrying out the research work. I enjoyed and still enjoy being part of the team.

My family (dad, mum, brothers and sisters) provided words of encouragement along the way, even when they wondered if it would ever get to the end. Indeed, hard work never killed anybody!!

Thanks to my friends Austrida Gondwe, Minyanga Kachale, Salma El Almin, John Phuka, John Njuma Libwea, Charles Mangani, Chiza Kumwenda, Jaden Bendabenda, Ngoza Chiolowa, Jenala Zulu, Ida Muwa and Odetta Thompson for being with me throughout the good and the challenging times.

My beloved husband, daughter and son (Charles, Chikondano and Chisomo) who endured countless times and long hours when I had to complete the thesis. You are such a wonderful team. I really do appreciate and look forward to life post-defense.

10 REFERENCES

Abuya BA, Onsomu EO, Kimani JK and Moore D. Influence of maternal education on child immunization and stunting in Kenya. *Matern Child Health J, 2011;* 15:1389 –1399.

Ackatia-Armah RS, McDonald C, Doumbia S, and Brown KH. Effect of selected dietary regimens on recovery from moderate acute malnutrition in young Malian children. Faseb J, 2012; 26.

Adu-Afarwuah S, Lartey A, Brown KH, Zlotkin S, Briend A and Dewey KG. Randomized comparison of 3 types of micronutrient supplements for home fortification of complementary foods in Ghana: effects on growth and motor development. *Am J Clin Nutr, 2007;* 86: 412–420.

Adu-Afarwuah S, Lartey A, Zeilani M, and Dewey KG. Acceptability of lipid-based nutrient supplements (LNS) among Ghanian infants and pregnant or lactating women. *Matern Child Nutr, 2010;* 7: 344–356.

Albernaz E, Victora CG, Haisma H, Wright A and Coward WA. Lactation counselling increases breast-feeding duration but not breast milk intake as measured by isotopic methods. *J Nutr, 2003;* 133(1):205–210.

Allen LH, Backstrand JR, Stanek EJ 3rd, Pelto GH, Chávez A, Molina E, Castillo JB and Mata A. The interactive effects of dietary quality on the growth and attained size of young Mexican children. *Am J Clin Nutr, 1992;* 56:353-364.

Allen LH and Gillespie SR. What Works? A review of the efficacy and effectiveness of nutrition interventions. ACC/SCN Nutrition Policy Paper 19. Asian Development Bank (ADB) Nutrition and Development Series 5. Geneva and Manila.United Nations Administrative Committee on Coordination/Sub-Committee on Nutrition and the Asian Development Bank, 2001.

Allen LH. To what extent can food-based approaches improve micronutrient status? *Asia Pacific Journal of Clinical Nutrition, 2008; 17*(S1): 103-105.

Almeida RM, de Marins VM and Valle J. Breastfeeding, socio-economic conditions and nutritional status of children younger than 12 months in Brazil. *Ann Trop Paediatr, 1999;* 19:257-262.

Anderson AS, Porteous LEG, Foster E, Higgins C, Stead M, Hetherington M, Ha MA and Adamson AJ. The impact of a school-based nutrition education intervention on

dietary intake and cognitive and attitudinal variables relating to fruits and vegetables. *Public Health Nutrition, 2005;* 8:650-656.

Anekwe TD and Kumar S. The effect of a vaccination program on child anthropometry: evidence from India's Universal Immunization Program. *Journal of Public Health, 2012;* 489-497.

Arifeen S, Black RE, Antelman G, Baqui A, Caulfield L and Becker S. Exclusive breastfeeding reduces acute respiratory infection and diarrhea deaths among infants in Dhaka slums. *Pediatrics, 2001;* 108 (4):E67.

Arimond M and Ruel MT. Dietary diversity is associated with child nutritional status: evidence from 11 demographic and health surveys. J Nutr 2004; 134: 2579-85.

Bahl R, Frost C, Kirkwood BR, Edmond K, Martnes J, Bhandari N and Arthur P. Infant feeding patterns and risks of death and hospitalization in the first half of infancy: multicentre cohort study. *Bull World Health Organ, 2005;* 83: 418–426.

Bajaj M, Dubey AP, Nagpal J, Singh PK and Sachdev HPS. Short-term effect of oil supplementation of complementary food on total ad libitum consumption in 6- to 10-month-old breastfed Indian infants. *J Pediatr Gastroenterol Nutr, 2005;* 41:61-65.

Beaton GH and Ghassemi H. Supplementary feeding programs for young children in developing countries. *Am J Clin Nutr, 1982; 35 (4):*864-916.

Beaton GH, Milner J, McGuire V, Feather TE, and Little JA. Source of variance in 24-hour dietary recall data: Implications for nutrition study design and interpretation. Carbohydrate sources, vitamins, and minerals. *Am J Clin Nutr, 1983;* 37:986–995.

Beaton GH: Approaches to analysis of dietary data: relationship between planned analyses and choice of methodology. *Am J Clin Nutr*,1994; 59:253S-261S.

Berti PR, Krasevec J and FitzGerald S. A review of the effectiveness of agricultural interventions in improving nutrition outcomes. *Public Health and Nutr, 2003;* 7: 599-609.

Bhandari N, Bahl R, Nayyar B, Khokhar P, Rohde J.E, and Bhan M. Food supplementation with encouragement to feed it to infants from 4 to 12 months of age has a small impact on weight gain. *Journal of Nutrition, 2001;* 131:1946–1951.

Bhandari N, Mazumder S, Bahl R, Martines J, Black RE, Bhan MK, and other members of the infant feeding study group. An educational intervention to promote appropriate complementaryfeeding practices and physical growth in infants and young children in rural Haryana, India. *J Nutr, 2004;* 134: 2342–2348.

Bhutta ZA, Ahmed T, Black RE, Cousens S, Dewey K, Giugliani E, Haider BA, Kirkwood B, Morris SS, Sachdev HPS, Shekar M for the Maternal and Child Undernutrition

Study Group. What works? Interventions for maternal and child undernutrition and survival. *Lancet, 2008;* 371:417-440.

Bhutta Z, Das JK, Rizvi A, Gaffey MF, Walker N, Horton S, Webb P, Lartey A, Black RE, The Lancet nutrition intervention Review Group, and the maternal and child nutrition study Group 2013. Evidence-based interventions for improvement of maternal and child nutrition: what can be done and at what cost?. Lancet 2013; http://dx.doi.org/10.1016/S0140-6736(13)60996-4

Bier DM, Brosnan JT, Flatt JP, Hanson RW, Heird W, Hellerstein MK, Jequiler E, Kalhan S, Koletzko B, Macdonal I, Owen O and Uauy R. Report of the IDECG working group on lower and upper limits of carbohydrates and fat intake: International dietary energy consultative group. Eur J Clin Nutr, 1999; 53 (1): 177-178

Black RE and Sazawal ES. Zinc and childhood infectious disease morbidity and mortality. *Br J Nutr, 2001;* 85:. S125-S129.

Black RE, Morris SS and Bryce J. Where and why are 10 million children dying each year? *Lancet, 2003; 361*:*2226*–2234.

Black RE, Allen LH, Bhutta ZA, Caulfield LE, de Onis M, Ezzati M, Mathers C, Rivera J for the maternal and child undernutrition study group. Global and regional exposures and health consequences. *Lancet, 2008;* 371:243–260.

Black RE, Cousens S, Johnson HL, Lawn JE, Rudan I, Bassani DG, Jha P, Campbell H, Walker CF, Cibulskis R, Eisele T,Liu L, and Mathers C, for the Child Health Epidemiology Reference Group of WHO and UNICEF. Global, regional and national causes of child mortality in 2008: A systematic analysis. *Lancet, 2010;* 375: 1969-1987.

Black RE, Victora CG, Walker SP, Bhutta ZA, Christian P, de Onis M, Ezzati M, Grantham-Mc Gregor S, Katz J, Martorell R, Uauy R and the Maternal and Child Nutrition Study Group. Maternal and child undernutrition and overweight in low-income and middle-income countries. *Lancet,2013:* http://dx.doi.org/10.1016/S0140-6736(13)60937-X

Blom-Hoffman J, Kelleher C, Power TJ and Leff SS. Promoting healthy food consumption among young children: Evaluation of a multi-component nutrition education programme. *Journal of School Psychology, 2004;* 42:45-60.

Blossner M and de Onis M. Malnutrition: Quantifying the health impact at national and local levels. Geneva. WHO, 2005. (WHO Environmental burden of disease series, No 12).

Briend A, Lacsala R, Prudhon C, Mounier B, Grellety Y and Golden MH. Ready to use therapeutic food for treatment of marasmus. *Lancet, 1999;* 353:1767-1768.

Briend A. Highly nutrient-dense spreads: a new approach to delivering multiple micronutrients to high-risk groups. *Br J Nutr, 2001;* 85 (suppl. 2):S175-S179.

Brown KH, Black RE, Becker S, Nahar S and Sawyer J. Consumption of foods and nutrients by weanlings in rural Bangladesh. Am J Clin Nutr, 1982; 36: 878-89.

Brown KH, Black RE, Lopez de Romana G and Creed de Kanashiro H. Infant feeding practices and their relationship with diarrheal and other diseases in Huascar (Lima), Peru. *Pediatrics, 1989;* 83:31-40.

Brown KH, Sanchez-Griñan M, Perez F, Peerson JM, Ganoza L and Stern JS. Effects of dietary energy density and feeding frequency on total daily energy intakes of recovering malnourished children. *Am J Clin Nutr, 1995;* 62:13-18.

Brown K. Complementary feeding in developing countries: factors affecting energy intake. *Proceedings of the Nutrition Society, 1997;* 56: 139-148.

Burke BS and Stuart HC. A method of diet analysis: application in research and pediatric practice: *J. Pediatr*:12, 1938; 493-503.

Burke BS. The dietary history as a tool in research: *J. Am. Diet. Assoc, 1947;* 23: 1041-1046.

Butte NF, Wong WW, Patterson BW, Garza C and Klein PD. Human-milk intake measured by administration of deuterium oxide to the mother: a comparison with the test-weighing technique. *Am J Clin Nutr, 1988;* 47(5):815–821.

Cameron M. The monitoring of growth and nutritional status in South Africa. *Am J Hum* Biol, 1992; 4: 223-234.

Caulfield LE, Huffman SL and Piwoz EG. Interventions to improve intake of complementary foods by infants 6 to 12 months of age in developing countries: impact on growth and on the prevalence of malnutrition and potential contribution to child survival. *Food Nutr Bull, 1999;* 20:183–200.

Caulfield LE, de Onis M, Blossner M and Black R.E. Undernutrition as an underlying cause of child deaths associated with diarrhea, pneumonia, malaria and measles. *Am J Clin Nutr, 2004;* 80:193-198.

Caulfield LE, Richard SA, Rivera JA, Musgrove P, and Black R. Stunting, Wasting, and Micronutrient Deficiency Disorders, 2006." In *Disease Control Priorities in Developing Countries*, 2nd ed. Dean T. Jamison, Joel G. Breman, Anthony R. Measham, George Alleyne, Mariam Claeson, David B. Evans, Prabhat Jha, Anne Mills, Philip Musgrove, chapter 28. Washington, DC: World Bank.

Child Health Research. A foundation for improving child health. Geneva: World Health Organization, 2002.

Ciliberto MA, Sandige H, Ndekha MJ, Ashorn P, Briend A, Ciliberto HM and Manary MJ. Comparison of home based therapy with ready-to-use therapeutic food with standard

therapy in the treatment of malnourished Malawian children : a controlled, clinical effectiveness trial. *Am J Clin Nutr, 2005;* 81: 864-870.

Cissé AS, Dossou N, Ndiaye M, Guèye AL, Diop el HI, Diaham B, Guiro AT, Cissé D, Sarr CS and Wade S. Stable isotope aided evaluation of community nutrition program: effect of food supplementation schemes on maternal and infant nutritional status. *Food Nutr Bull,* 2002; 23(3):169–173.

Cleland JG and van Ginneken J. Maternal education and child survival in developing countries: the search for pathways of influence. Soc. Sci. Med, 1988; 27 (2):1357-1368.

Cogill B. Anthropometric indicators measurement guide. Food and Nutrition Technical Assistance Project. Academy for Educational Development: Washington, DC, 2003.

Cohen RJ, Brown KH, Dewey KG, Canahuati J, Rivera LL and Dewey KG. Effects of age of introduction of complementary foods on infant breast milk intake, total energy intake, and growth: a randomised intervention study in Honduras. *Lancet, 1994;* 344: 288 - 293.

Collins S. Changing the way we address severe malnutrition during famine. *Lancet, 2001;* 358:498-501.

Coovadia HM, Rollins NC, Bland RM, Little K, Coutsoudis A, Bennish ML and Newell ML. Mother-to- child transmission of HIV-1 infection during exclusive breastfeeding in the first 6 months of life: an intervention cohort study. *Lancet, 2007;* 369:1107–1116.

Costello A.M. Growth velocity and stunting in rural Nepal. *Archives of Disease in Childhood, 1989;* 64: 1478–1482.

Coutsoudis A. Breastfeeding and the HIV positive mother: the debate continues. *Early Hum Dev, 2005;* 81:87–93.

Coward WA, Sawyer MB, Whitehead RG, Prentice AM and Evans J. New method for measuring milk intakes in breast-fed babies. *Lancet, 1979;* 2 (8132):13–14.

Coward WA, Cole TJ, Sawyer MB and Prentice AM. Breast-milk intake measurement in mixed-fed infants by administration of deuterium oxide to their mothers. *Hum Nutr Clin Nutr, 1982;* 36:141–148.

da Costa THM, Hasima H, Wells JCK, Mander AP, Whiteheat RG and Bluck LJC. How much human milk do infants consume? Data from 12 countries using standardized stable isotope methodology. *J Nutr, 2010;* 140:2027-2032.

de Onis M. Measuring nutritional status in relation to mortality. Bulletin of the World Health Organization, 2000; 78(10):1271-1274.

de Onis M, Garza C, Onyango AW, and Martorell R. (Eds.). WHO growth standards. *Acta Paediatrica, 2006; 450:1-101.*

de Pee S and Bloem MW. Current and potential role of specially formulated foods and food supplements for preventing malnutrition among 6 to 23-month-old children and for treating moderate malnutrition among 6 to 59 month-old children. *Food and Nutrition Bulletin, 2009;* 30: S434-S463.

Defourny I, Seroux G, Abdelkader I and Harczi G. Management of moderate acute malnutrition with RTUF in Niger. *Field Exchange, 2007;* 31:2-4.

Defourny I, Minetti A, Harczi G, Doyon S, Shepherd S, Tectonidis M, Bradol JH and Golden M. A large-scale distribution of milk-based fortified spreads: Evidence for a new approach in regions with high burden of acute malnutrition. *PLoS One, 2009;* 4(5):e5455.

Delisle H. Early nutritional influences on obesity, diabetes and cardiovascular disease risk. International Workshop, 6–9 June 2004, Montreal University, Quebec, Canada. *Maternal and Child Nutrition, 2005;* 1(3): 128–129.

Department for International Development (DFID): The neglected crisis of undernutrition (2012): Evidence for action. Available at:https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/67319/undernutrition-finalevidence-oct12.pdf.

Desai S and Alva S. Maternal education and child health: is there a strong causal relationship? *Demography, 1998;* 35 (1):71–81.

Dewey KG, Peerson JM, Heinig MJ, Nommsen LA, Lonnerdal B, Lopez de Romana G, de Kanashiro HC, Black RE and Brown KH. Growth patterns of breastfed infants in affluent (United States) and poor (Peru) communities: Implications for timing of complementary feeding. *Am J Clin Nutr, 1992;* 56: 1012–1018.

Dewey KG. The challenges of promoting optimal infant growth. *J Nutr, 2001;* 131:1879–1880.

Dewey KG and Brown KH. Update on technical issues concerning complementary feeding of young children in developing countries and implications for intervention programs. *Food Nutr Bull, 2003; 24*:5–28.

Dewey KG and Adu-Afarwuah S. Systematic review of the efficacy and effectiveness of complementary feeding interventions in developing countries. *Maternal & Child Nutrition, 2008;* 4:24–85.

Dewey KG, Yang Z and Boy E. Systematic review and meta-analysis of home fortification of complementary foods. *Matern Child Nutr, 2009;* 5:283–321.

Dewey KG and Mayers DR. Early child growth: how do nutrition and infection interact? *Matern Child Nutr, 2011;* 7(3):129-42.

Dewey KG and Arimond M. Lipid-based nutrient supplements: How can they combat child malnutrition? PLoSMed 2012; 9 (9): e1001314.

Dewey K G and Vitta B S. Strategies for ensuring adequate nutrient intake for infants and young children during the period of complementary feeding (2013). Available at: www.aliveandthrive.org

Dijkhuisen P. Processed complementary foods in the World Food Programme. *Food Nutr Bull, 2000;* 21:62-64.

Diop EHl, Dossou NI, Ndour MM, Briend A and Wade S. Comparison of the efficacy of a solid ready-to-use food and a liquid, milk-based diet for the rehabilitation of severely malnourished children: a randomized trial. *Am J Clin Nutr,2003;* 78:302–307.

Doherty T, Chopra M, Tomlinson M, Oliphant N, Nsibande D and Mason J. Moving from vertical to integrated child health programmes: experiences from a multi-country assessment of the Child Health Days approach in Africa. *Trop med int health, 2010;* 15: 296-305.

Dubois L, Girard M, Girard L, Tremblay R, Boivin M, Perusse D. Genetic and environmental influences on body size in early childhood: A twin-birth cohort study. *Twin Res Hum Genet*,2007; 10 (3): 479-485.

Ehreth J. The global value of vaccination. *Vaccine, 2003;* 21: 596-600.

Ejemot RI, Ehiri JE, Meremikwu MM and Critchley JA. Hand washing for preventing diarrhea: *Cochrane database systematic review, 2008;* 23:CD004265

Ettyang GA, van Marken Lichtenbelt WD, Esamai F, Saris WHM, and Westerterp KR. Assessment of body composition and breast milk volume in lactating mothers in pastoral communities in Pokot, Kenya, using deuterium oxide. *Ann Nutr Metab, 2005;* 49:815:1-8.

FAO: Nutrition country profiles (2010). Available at http://www.fao.org/ag/agn/nutrition/mwi_en.stm)

FAO: Preparation and use of food based dietary guidelines. Available at http://www.fao.org/docrep/x0243e/x0243e05.htm

FAO/WHO. Vitamin and mineral requirements in human nutrition, 2nd edition. Geneva, World Health Organization and Food and Agriculture Organisation, 2004.

FAO. Nutrition Education for the public is essential. Global Forum on Food Security and Nutrition Policies and Strategies (FSN Forum), 2008. Available at: <http://www.fao.org/fsn/>.

Ferguson EL, Gibson RS, Ounpuu S and Sabry JH. The validity of the 24-hour recall for estimating the energy and selected nutrient intakes of a group of rural Malawian pre-school children. *Ecol Food Nutr, 1989;* 23: 273-285.

Ferguson EL, Gibson RS, Opare-Obisaw C, Osei-Opare F, Stephen AM, Lehrfeld J and Thompson RU. The zinc, calcium, copper, manganese, nonstarch polysaccharide and phytate content of seventy-eight locally grown and prepared African foods. *Journal of Food Composition and Analysis, 1993;* 6:87-99.

Ferguson EL, Gadowsky SL, Huddle JM, Cullinan TR, Lehrfeld J and Gibson RS. An interactive 24-h recall technique for assessing the adequacy of trace mineral intakes of rural Malawian women; its advantages and limitations. *Eur J Clin Nutr, 1995;* 49:565-578.

Fishman SM, Caulfield LE, de Onis M, Blossner M, Hyder AA, Mullany L and Black RE. Childhood and maternal underweight. In: Ezzati M, Lopez AD, Rodgers A, Murray CJL, eds. Comparative quantification of health risks: global and regional burden of disease attributable to selected major risk factors . Geneva : WHO; 2004. pp. 39 -161.

Flax VL, Ashorn U, Phuka J, Maleta K, Manary MJ and Ashorn P. Feeding patterns of underweight children in rural Malawi given supplementary fortified spread at home. *Matern Child Nutr, 2008;* 4: 65–73.

Flax VL, Phuka J, Cheung YB, Ashorn U, Maleta K and Ashorn P. Feeding patterns and behaviors during home supplementation of underweight Malawian children with lipid-based nutrient supplements or corn-soy blend. *Appetite, 2010;* 54 (3): 504-511.

Frost MB, Forste R, and Haas DW. Maternal education and child nutritional status in Bolivia: Finding the links. *Social Science and Medicine, 2005;* 60: 395-407.

Galpin L, Thakwalakwa C, Phuka J, Ashorn P, Maleta K, Wong WW and Manary M. Breast milk intake is not reduced more by the introduction of energy dense complementary food than by typical infant porridge. *J Nutr, 2007;* 137: 1828-1833.

Gibson R. Principles of nutritional assessment. 2nd ed. Oxford University Press. New York, 2005.

Glewwe P. Why does mother's schooling raise child health in developing countries? Evidence from Morocco. *J. Hum Res, 1999;* 34:124–159.

Golden MHN. Specific deficiencies versus growth failure: Type 1 and type 11 nutrients. *Journal of Nutritional and Environmental medicine, 1996;* 6 (3): 301-308.

Griffiths Marcia and Del Rosso Joy. Growth monitoring and the promotion of healthy young child growth: Evidence of Effectiveness and Potential to Prevent Malnutrition, 2007: http://www.manoffgroup.com/documents/GMP_UNICEF_Nov_1608.pdf.

Guerrant RL, Deboer MD, Moore SR, Scharf RJ and Lima AAM. The impoverished gut – a triple burden of diarrhoea, stunting and chronic disease, *National Review Gastroenterology & Hepatology, 2013;* 10: 220-229.

Guldan GS, Fan H-C, Ma X, Ni Z-Z, Xiang X and Tang M-Z. Culturally appropriate nutrition education improves infant feeding and growth in rural Sichuan, China. J Nutr, 2000; 130:1204-1211.

Haider BA, Bhutta ZA. Multiple micronutrient supplementation for women during pregnancy: Cochrane Database Syst Rev 2012; 11: CD004905.

Habicht. Height and weight standards for preschool children. How relevant are ethnic differences in growth potential? *Lancet*, 1974; 1: 611-614.

Habicht JP. 'Malnutrition kills directly not indirectly: *Lancet, 2008;* 371 (9626): 1749–1750.

Haisma H, Coward WA, Albernaz E, Visser H, Wells JCK, Wright A and Victora CG. Breast milk and energy intake in exclusively, predominantly, and partially breast-fed infants. *Eur J Clin Nutr*, 2003; 57:1633–1642.

Handa S. Maternal Education and Child Height. *Econ. Devel. Cult. Change, 1999;* 47 (2):421 – 439.

Haroon S, Das JK, Salam RA, Bhutta ZA. Breastfeeding promotion interventions and breastfeeding practices. A systematic revew. *BMC Public Health, 2013;* 13(3): S20.

Harvey PWJ and Dary O. Governments and academic institutions play vital roles in food fortification: iron as an example. *Public Health Nutr, 2012;* 1:1–5.

Hebert JR, Gupta PC, Mehta H, Ebbeling CB, Bhonsle RR and Varghese F. Sources of variability in dietary intake in two distinct regions of rural India: implications for nutrition study design and interpretation. *Eur J Clin Nutr, 2000;* 54:479–486.

Heikens GT, Schofield WN, Dawson S and McGregor S. The Kingston project. I. Growth of malnourished children during rehabilitation in the community, given a high energy supplement. *Eur J Clin Nutr, 1989;* 43 (3):145–160.

Hendrata L and Rohde JE. Ten Pitfalls of Growth Monitoring and Promotion. *Indian Journal of Pediatrics, 1998;* 55: S9-S15.

Hess SY, Bado LL, Aaron GJ, Ouédraogo JB, Zeilani M and Brown KH. Acceptability of zinc-fortified, lipid-based nutrient supplements (LNS) prepared for young children in Burkina Faso. *Matern Child Nutr, 2011;* 7: 357–367.

Huffman SL, Rajwinder KH, Eilander A and Osendarp SJM. Essential fats: how do they affect growth and development of infants and young children in developing countries? A literature review. *Matern Child Nutr, 2011;* 7 (3): 44–65.

Huybregts L, Houngbé F, Salpéteur C, Brown R, Roberfroid D, Ait-Aissa M and Kolsteren P. The effect of adding Ready-to-Use Supplementary Food to a General Food Distribution on child nutritional status and morbidity: A Cluster-Randomized Controlled Trial. *PLoS Med, 2012;* 9: e1001313.

Iannotti LL, Dulience SJ, Green J, Joseph S, François J, Anténor ML, Lesorogol C, Mounce J and Nickerson NM. Linear growth increased in young children in an urban slum of Haiti: a randomized controlled trial of a lipid-based nutrient supplement. *Am J Clin Nutr, 2014;* 99:198-208.

Imdad A, Yakoob MY, Bhutta ZA. Effect on breast feeding promotion interventions on breast feeding rates with special focus on developing countries. BMC Public Health 2011; 11 (Suppl 3): S24.

Imdad A, Bhutta ZA. Maternal nutrition and birth outcomes: effect of balanced protein energy supplementation. Paediatr perinat epidemiol 2012; 26 (Supp 1): 178-90.

Isanaka S, Nombela N, Djibo A, Poupard M, Van Beckhoven D, Gaboulaud V, Guerin PJ and Grais RF. Effect of preventive supplementation with ready-to-use therapeutic food on the nutritional status, mortality, and morbidity of children aged 6 to 60 months in Niger. A cluster randomized trial. *JAMA, 2009;* 301(3):277–285.

Islam MM, Peerson JM, Ahmed T, Dewey KG and Brown KH. Effects of varied energy density of complementary foods on breast-milk intakes and total energy consumption by healthy breastfed Bangladeshi children. *Am J Clin Nutr, 2006;* 83:851–858.

Islam MM and Brown KH. Breast milk zinc transfer to appropriate- for-gestational-age (AGA) and small-for-gestational-age (SGA) Bangladeshi infants: Studies of milk volume, using deuterium-to-mother and milk zinc concentrations. *FASEB* J, 2010; 24 (Meeting Abstract Supplement) 718.6.

Jones G, Steketee RW, Black RE, Bhutta ZA, Morris SS and the Bellagio Survival Study Group. How many child deaths can we prevent this year? *Lancet, 2003;* 362: 65–71.

Kabubo-Mariara J, Ndenge GK, and Mwabu DK. Determinants of Children's Nutritional Status in Kenya: Evidence from Demographic and Health Surveys. *J Afr Econ, 2008;* doi:10.1093/jae/ejn024.

Kalanda BF, Verhoeff FH and Brabin BJ. Breast and complementary feeding practices in relation to morbidity and growth in Malawian infants. *Eur J Clin Nutr, 2006;* 60:401-407.

Koletzko B. Response to and range of acceptable fat intakes in infants and children. *Eur J Clin Nutr, 1999;* 53 (1): S78-83.

Kramer MS, Chalmers B, Hodnett ED, Sevkovskaya Z, Dzikovich I, Shapiro S, Helsing E. Promotion of breastfeeding Intervention Trial (PROBIT): A randomized trial in the Republic of Belarus. *JAMA, 2001;* 285 (4): 423-420.

Kramer MS, Guo T, Platt RW, Sevkovskaya Z, Dzikovich I, Collet JP, Shapiro S, Chalmers B, Hodnett E, Vanilovich I, Mezen I, Ducruet T, Shishko G, Bogdanovich N. Infant growth and health outcomes associated with 3 compared with 6 months of exclusive breastfeeding. *Am J Clin Nutr, 2003;* 78: 291-295.

Kramer MS and Kakuma R. Optimal duration of exclusive breast feeding. *Cochrane Database of systematic reviews* 8, 2012.

Kuczmarski RJ, Ogden CL, Guo SS, Grummer-Strawn LM, Flegal KM, Mei Z, Wei R, Curtin LR, Roche AF and Johnson CL. 2000 CDC Growth Charts for the United States: methods and development. *Vital Health Stat, 2002;* 11:1–190.

Kumwenda C, Dewey KG, Hemsworth J, Ashorn P, Maleta K and Haskell MJ. Lipid-based nutrient supplements do not decrease breast milk intake of Malawian infants. *Am J Clin Nutr, 2014;* 99:617-23.

Kuusipalo H, Maleta K, Briend A, Manary M and Ashorn P. Growth and change in blood haemoglobin concentration among underweight Malawian infants receiving fortified spreads for 12 weeks. A preliminary trial. *J Pediatr Gastroenterol Nutr, 2006;* 43:525-532.

LaGrone LN, Trehan I, Meuli GJ, Wang RJ, Thakwalakwa C, Maleta K and Manary MJ. A novel fortified blended flour, corn-soy blend "plus-plus," is not inferior to lipid-based ready-to-use supplementary foods for the treatment of moderate acute malnutrition in Malawian children. *Am J Clin Nutr, 2012;* 13(1):212–219.

Lartey AA, Manu AA, Brown KH, Peerson JM and Dewey KG. A randomized, community-based trial of the effects of improved, centrally processed complementary foods on growth and micronutrient status of Ghanaian infants from 6 to 12 months of age. *Am J Clin Nutr, 1999;* 70(3): 391–404.

Lawrence RA, Lawrence RM. Breastfeeding: A guide for the medical profession. 6th ed. Philadelphia, PA: Elsevier Mosby, 2005.

Linneman Z, Matilsky D, Ndekha M, Manary MJ, Maleta K and Manary MJ. A large-scale operational study of home-based therapy with ready-to-use therapeutic food in childhood malnutrition in Malawi. *Matern Child Nutr, 2007;* 3(3): 206–215.

Lucas A, Ewing G, Roberts SB and Coward WA. Measurement of milk intake by deuterium dilution. *Arch. Dis. Child, 1987;* 62: 796–800.

Lutter CK, Rivera JA. Nutritional status of infants and young children and characteristics of their diets. J Nutr, 2003; 133:2941S–2949S.

Mahgoub SED, Nnyepe M. and Bondeke T. Factors affecting prevalence of malnutrition among children under three years of age in Botswana. *African Journal of Food, Agriculture, Nutrition and Development, 2006;* 6:(1): 1-15.

Malawi Country Presentation to CAADP Nutrition Meeting in Botswana, 2013. Available at: http://www.fao.org/fileadmin/user_upload/wa_workshop/PPT_SA/DAY4_Capacity_devt_Malawi.pdf.

Malawi Demographic and Health Survey. Calverton, Maryland: NSO and ORC Macro, 2004. Available at: http://www.measuredhs.com/publications/publication-FR175-DHS-Final-Reports.cfm

Maleta K, Kuittinen J, Duggan MB, Briend A, Manary MJ, Wales J, Kulmala T and Ashorn P. Supplementary feeding of underweight, stunted Malawian children with a ready-to-use food. *J Pediatr Gastroenterol Nutr, 2004;* 38:152-158.

Maleta K, Virtanen S, Espo M, Kulmala T and Ashorn P. Timing of growth faltering in rural Malawi. Arch Dis Child, 2003; 88:574–578.

Manary MJ, Ndekha M, Ashorn P, Maleta K and Briend A. Home-based therapy for severe malnutrition with ready-to-use food. *Arch Dis Child,2004;* 89:557-561.

Manary MJ and Sandige HL. Management of acute moderate and severe childhood malnutrition. *BMJ, 2008;* 337: a2180.

Marquis GS, Habict JP, Lanata CF, Black RE, and Rasmussen KM. Breast Milk or Animal-product foods Improve Linear Growth of Peruvian Toddlers Consuming Marginal Diets. *Am J Clin Nutr, 1997;* 66:1102-1109.

Marriott BP, White A, Hadden L, Davies JC, Wallingford JC. World Health Organisation. Infant and young child feeding indicators: associations with growth measures in 14 low-income countries. Matern Child Nutr 2012; 8: 354-70.

Martorell R, and Habicht J-P. Growth in Early Childhood in Developing Countries. In: F. Falkner and J. Tanner, editors. Human Growth: A Comprehensive Treatise. Second edition. New York: Plenum Press, 1986.

Martorell R, Khan LK and Schroeder DG. Reversibility of stunting: Epidemiological findings in children from developing countries. Eur J Clin Nutr, 1994; 48 (Suppl. 1): S45-57.

Martorell R, Schroeder DG, Rivera JA, Kaplowitz HJ. Patterns of linear growth in rural Guatemalan adolescents and children. J Nutr, 1995; 125 (4 Suppl): 1060S-1067S.

Matilsky DK, Maleta K, Castleman T and Manary MJ. Supplementary feeding with fortified spreads results in higher recovery rates than with a corn/soy blend in moderately wasted children. J *Nutr, 2009; 139(4):773-778*.

Matvienko O. Impact of a nutrition education curriculum on snack choices of children aged six and seven years. *Journal of Nutrition Education and Behaviour (JNEB), 2007;* 39(5):281-285.

Meerman J, Carisma B, Thompson B. Global, regional and subregional trends in undernourishment and malnutrition, 2012. Available at: http://www.fao.org/fileadmin/user_upload/agn/pdf/SOFA_2013global.regional.subregional.trends.pdf .

Meier PP. Breastfeeding in the special care nursery: Premature and infants with medical problems. *Pediatr Clin North Am, 2001;* 48:425-442.

Mensah P and Tomkins A. Household-level technologies to improve the availability and preparation of adequate and safe complementary foods. *Food Nutr Bull, 2003;* 24: 104–125.

Monterossa EC, Frongillo EA, Vasquez-Garibay EM, Romero-Velarde E, Casey LM, Willows ND. Predominant breast-feeding from birth to 6 months is associated with fewer gastrointestinal infections and increased risk for iron deficiency among infants. *J Nutr, 2008;* 138 (8): 1499-1504.

Moore SE, Prentice AM, Coward WA, Wright A, Frongillo EA, Fulford AJC, Mander AP, Persson L, Arifeen SE and Kabir I. Use of stable-isotope techniques to validate infant feeding practices reported by Bangladeshi women receiving breastfeeding counseling. *Am J Clin Nutr, 2007;* 85(4):1075-1082.

Moore SR, Lima NL, Soares AM, Oria RB, Pinkerton RC, Barret LJ, Guerrant RL, and Lima AAM. Prolonged episodes of acute diarrhea reduce growth and increase risk of persistent diarrhea in children. *Gastroenterology, 2010;* 139:1156–1164.

Nackers F, Broillet F, Oumarou D, Djibo A, Gaboulaud V, Guerlin P, Rusch B, Grais RF, and Captier V. Effectiveness of ready-to-use therapeutic food compared to a corn/soy-blend-based pre-mix for the treatment of childhood moderate acute malnutrition in Niger. *J. Trop. Pediatr, 2010; 56:407-413*.

National Nutrition Policy and Strategic Plan 2007-2011. Available at: http://www.moafsmw.org/Key Documents/National Nutrition Policy & Strategic Plan Final 2009.pdf.

National Statistical Office (Malawi) and MEASURE DHS, ICF Macro Calverton, Maryland, USA. Malawi Demographic and Health Survey. National Statistical Office, 2010.

Navarro-Colorado C. A retrospective study of emergency supplementary feeding programmes. Save the Children/ENN, 2007. Available from:

http://www.ennonline.net/pool/files/research/Retrospective_Study_of_Emergency_Supplementary_Feeding_Programmes_June%20 2007.pdf.

Ndekha M, Kulmala T, Vaahtera M, Cullinan T, Salin M-L and Ashorn P. Seasonal variation in the dietary sources of energy for pregnant women in Lungwena rural Malawi. *Ecol Food and Nutr, 2000;* 38:605-622.

Ndekha M, Manary M, Ashorn P and Briend A. Home-based therapy with ready-to-use therapeutic food is of benefit to malnourished, HIV-infected Malawian children. *Acta Paediatrica, 2005;* 94: 222–225.

Oddy WH, Sly PD, de Klerk NH, Landau LI, Kendall GE, Holt PG, Stanley FJ. Breast feeding and respiratory morbidity in infancy: a birth cohort study. *Arch Dis Child, 2003;* 88 (3):224-228.

Oelofse A, Van Raaij JM, Benade AJ, Dhansay AM, Tolboom JJ, and Hautvast JG. The effect of a micronutrient-fortified complementary food on micronutrient status, growth and development of 6- to 12-month-old disadvantaged South African infants. *International Journal of Food Sciences and Nutrition, 2003;* 54(5): 399–407.

Olofin I, McDonald CM, Ezzati M, Flaxman S, Black RE, Fawzi WW, Caulfield LE, Danaei G. 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): e64636.

Onyango A, Koski KG and Tucker KL. Food diversity versus breastfeeding choice in determining anthropometric status in rural Kenyan toddlers *International Journal of Epidemiology, 1998;* 27:484-489.

Ota E, Tobe-Gai R, Mori R, Farrar D. Antenatal dietary advice and supplementation to increase energy and protein intake. *Cochrane database of systematic reviews, 2012;* (9): CD000032.

Owino VO , Kasonka LM, Sinkala MM, Wells JK, Eaton S , Darch T, Coward A, Tomkins AM, and Filteau SM. Fortified complementary foods with or without amylase treatment increase hemoglobin but do not reduce breast milk intake of 9-mo-old Zambian infants. *Am J Clin Nutr, 2007;* 86 (4):1094–1103.

Owino V, Bahwere P, Bisimwa G, Mwangi CM and Collins S. Breast-milk intake of 9–10-mo-old rural infants given a ready-to-use complementary food in South Kivu, Democratic Republic of Congo. *Am J Clin Nutr, 2011;* 93(6):1300–1304.

PAHO/WHO. Guiding principles for complementary feeding of the breastfed child.Pan American Health Organization, Washington, DC, 2003.

Patel MP, Sandige HL, Ndekha MJ, Briend A, Ashorn P and Manary MJ. Supplemental feeding with ready-to-use therapeutic food in Malawian children at risk of malnutrition. *J Health Popul Nutr, 2005;* 23(4):351-357.

Pelletier DL, Frongillo EA, Jr, and Habicht JP. Epidemiologic evidence for a potentiating effect of malnutrition on child mortality. *Am J Public Health, 1993;* 83(8):1130–1133.

Pelletier D, Frongillo EA, Schroeder DG, and Habicht JP. A methodology for estimating the contribution of malnutrition to child mortality in developing countries. *J Nutr, 1994;* 124:2106S- 2122S.

Pelletier D, Frongillo EA Jr, Schroeder D, and Habicht JP. The effects of malnutrition on child mortality in developing countries. *Bull WHO, 1995;* 7(4):443–448.

Penny ME, Creed-Kanashiro HM, Robert RC, Rocio Norro M, Caulfield LE and Black R. Effectiveness of an educational intervention delivered through the health services to improve nutrition in young children: A cluster-randomised controlled trial. *Lancet, 2005;* 365: 1863–1872.

Perez-Rodrigo C and Aranceta J. Nutrition education in schools: experiences and challenges. *Eur J Clin Nutr, 2003;* 57(1):S82–S85.

Phuka JC, Maleta K, Thakwalakwa C, Cheung YB, Briend A, Manary MJ and Ashorn P. Complementary feeding with fortified spread and incidence of severe stunting in 6- to 18-month-old rural Malawians. *Arch Pediatr Adolesc Med, 2008;* 162: 619–626.

Phuka JC, Thakwalakwa C, Maleta K, Cheung YB, Briend A, Manary MJ, and Ashorn P. Post intervention growth of Malawian children who received 12-month dietary complementation with a lipid-based nutrient supplement or maize–soy flour. *Am J Clin Nutr, 2009;* 89: 382–390.

Phuka J, Ashorn U, Ashorn P, Zeilani M, Cheung YB, Dewey KG. and Maleta, K. Acceptability of three novel lipid-based nutrient supplements among Malawian infants and their caregivers. *Maternal & child nutrition, 2011; 7*(4): 368-377.

Picciano MF. Pregnancy and lactation: physiological adjustments, nutritional requirements and the role of dietary supplements. *J Nutr, 2003;* 133: 1997S–2002S.

Rice AL, Sacco L, Hyder A. and Black RE. Malnutrition as an underlying cause of childhood deaths associated with infectious diseases in developing countries. *Bulletin WHO, 2000;* 78: 1207-1221.

Rivera JA and Habicht J-P. Effect of supplementary feeding on the prevention of mild-to-moderate wasting in conditions of endemic malnutrition in Guatemala. *Bull WHO, 2002;* 80:926-932.

Roy SK, Fuchs GJ, Mahmud Z, Ara G, Islam S, Shafique S, Akter SS and Chakraborty B. Intensive nutrition education with or without supplementary feeding improves the nutritional status of moderately-malnourished children in Bangladesh. *J Health Popul Nutr, 2005;* 23:320-330.

Ruel MT, Menon P, Habicht JP, Loechl C, Bergeron G, Pelto G, Arimond M, Maluccio J, Michaud L and Hankebo B. Age-based preventive targeting of food assistance and behaviour change and communication for reduction of childhood undernutrition in Haiti: a cluster randomised trial. *Lancet, 2008;* 371(9612): 588–595.

Salam RA, MacPhail C, Das JK, Bhutta ZA. Effectiveness of micronutrient powders (MNP) in women and children. MBC Public Health, 2013; 13 (Suppl 3): S22.

Sandige H, Ndekha MJ, Briend A, Ashorn P and Manary MJ. Locally produced and imported ready-to-use-food in the home-based treatment of malnourished Malawian children. *J Paed Gastr Nutr, 2004;* 39:141-146.

Savenije OE and Brand PL. Accuracy and precision of test weighing to assess milk in newborn infants. *Arch Dis Child Fetal Neonatal* Ed, 2006; 91(5): F330–F332.

Scanlon KS, Alexander MP, Serdula MK, Davis MK and Bowman BA. Assessment of Infant Feeding: The Validity of Measuring Milk Intake. *Nutrition Reviews, 2002;* 60: 235–251.

Schroeder DG, Martorell R, Rivera JA, Ruel MT and Hbicht JP. Age differences in the impact of nutritional supplementation on growth. *J Nutr, 1995;* 125 (4): 1051S–1059S.

Scrimshaw NS, Taylor CE and Gordon AJE. Interactions of Nutrition and Infection. WHO monograph series no. 57. World Health Organization. Geneva, Switzerland, 1968.

Scrimshaw NS, Waterlow JC, Schurch B, eds. Energy and protein requirements: Proceedings of an IDECG workshop. Eur J Clin Nutr, 1996; 50 (1): S1-197.

Sempos CT, Liu K, Ernst ND. Food and nutrient exposures: what to consider when evaluating epidemiologic evidence. *Am J Clin Nutr, 1999;* 69:1330S-1338S.

Shi L and Zhang J. Recent evidence of the effectiveness of educational interventions for improving complementary feeding practices in developing countries. *J Trop Pediatr, 2011;* 57(2):91–98.

Shrimpton R, Victoria CG, de Onis M, Lima RC, Blossner M, and Clugston G. Worldwide timing of growth faltering: Implications of nutritional interventions. *Pediatrics, 2001;* 107(5):E75:1-7.

Simondon KB, Gartner A, Berger J, Cornu A, Massamba JP, San Miguel JL, Ly C, Missotte I, Simondon F, Traissac P, Delpeuch F, Maire B. Effect of early, short-term supplementation on weight and linear growth of 4-7-mo-old infants in developing countries: a four-country randomized trial. *Am J Clin Nutr, 1996;* 64: 537–545.

Simondon KB, Simondon F, Costes R, Delaunay V and Diallo A. Breast-feeding is associated with improved growth in length but not weight in rural Senegalese toddlers. *Am J Clin Nutr, 2001;* 73: 959-967.

Singh M. Essential fatty acids, DHA and human brain. Indian J Pediatr, 2005; 72: 239-242.

Soofi SB, Cousens S, Iqbal SP, Akhund T, Khan J, Ahmed I, Zaidi AKM, Bhutta ZA. Effect of provision of daily zinc and iron with several micronutrients on growth and morbidity among young children in pakistan: a cluster randomized trial. Lancet 2013; 382: 29-40

Strebel PM, Papania MJ, and Halsey NA. Measles vaccine: In: Plotkin SA, Orenstein WA, eds. *Vaccines*, 4th ed. Philadelphia: WB Saunders; 389-440, 2004.

Thakwalakwa C, Ashorn P, Phuka J, Cheung YB, Briend A, Puumalainen T, Maleta K. A Lipid-Based Nutrient Supplement but Not Corn-Soy Blend Modestly Increases Weight Gain among 6- to 18-Month-Old Moderately Underweight Children in Rural Malawi. *J Nutr, 2010;* 140 (11):2008–2013.

Thakwalakwa CM, Ashorn P, Jawati M, Phuka JC, Cheung YB and Maleta KM. An effectiveness trial showed lipid-based nutrient supplementation but not corn-soy blend offered a modest benefit in weight gain among 6-18 month-old underweight children in rural Malawi. *Public Health Nutr, 2012;* 15: 1755-1762.

Thakwalakwa CM, Kuusipalo HM, Maleta KM, Phuka JC, Ashorn P and Cheung YB. The validity of a structured interactive 24h recall in estimating energy and nutrient intakes in 15-month old rural Malawian children. *Matern Child Nutr, 2012b;* 8(3):380-389.

Thakwalakwa CM, Ashorn P, Phuka JC, Cheung YB, Briend A and Maleta KM. Impact of lipid-based nutrient supplements and corn–soy blend on energy and nutrient intake among moderately underweight 8–18-month-old children participating in a clinical trial. *Maternal & Child Nutrition, 2014;* doi:10.1111/mcn.12105.

UN Millennium Project. Halving hunger: it can be done. Task Force on Hunger. London and Sterling, VA, 2005. Available at http://www.unicef.org/publications/index-42623.html.

UNICEF/UNU/WHO. Composition of a multi-Micronutrient supplement to be used in pilot programmes among pregnant women in developing countries. Report of a Workshop . New York, UNICEF, 1999.

UNICEF. Progress for children –What is undernutrition? 2006. Available at:www.unicef.org/progressforchildren/2006n4/index_undernutrition.html

UNICEF. The state of the World's children. New York, 2009.

UNICEF. Committing to child survival: a promise renewed: progress report. New York, United Nations Children Fund, 2012.

UNICEF-WHO-The World Bank Joint Child Malnutrition Estimates. Levels and Trends in Child Malnutrition. 2012: available online at: http://www.who.int/entity/nutgrowthdb/jme_unicef_who_wb.pd.

UNICEF. Improving child nutrition. The achievable imperative for global progress, 2013. Available at http://www.unicef.org/gambia/Improving_Child_Nutrition_-_the_achievable_imperative_for_global_progress.pdf

Vazir S, Engle P, Balakrishna N, Griffiths PL, Johnson SL, Creed-Kanashiro H, Fernandez Rao S, Shroff MR, Bentley ME. Cluster-randomized trial on complementary and responsive feeding education to caregivers found improved dietary intake, growth and development among rural Indian toddlers: *Matern Child Nutr, 2012;* 24 (9): 99-117.

Victora CG, Adair L, Fall C, Hallal PC, Martorell R, Richter L, Sachdev HS for the Maternal and child undernutrition study group. Consequences for adult and human capital. *Lancet, 2008;* 371:340–357.

Walker SP, Powell CA, Grantham-McGregor SM, Himes JH, Chang SM. Nutritional supplementation, psychosocial stimulation, and growth of stunted children: The Jamaican study. *Am J Clin Nutr, 1991;* 54: 642–648.

Walsh C, Dannhauser A, Joubert G. The impact of a nutritional education programme on the anthropometric nutritional status of low-income children in South Africa. *Public Health Nutrition, 2002;* 5: 3-9.

WHO. Infant feeding recommendation. Available at: http://www.who.int/nutrition/topics/infantfeeding_recommendation/en/index.html

WHO working group. Use and interpretation of anthropometric indicators of nutritional status. *Bull WHO, 1986;* 64:929-941.

WHO. Physical status: the use and interpretation of anthropometry, 1995. Available at: http://whqlibdoc.who.int/trs/WHO_TRS_854.pdf

WHO/UNICEF. Complementary feeding of young children in developing countries: a review of current scientific knowledge. Geneva: World Health Organisation, WHO/NUT/98.1, 1998.

WHO Collaborative Study Team on the Role of Breastfeeding on the Prevention of Infant Mortality. Effect of breastfeeding on infant and child mortality due to infectious diseases in less developed countries: a pooled analysis. *Lancet, 2000b;* 355: 451–455.

WHO Complementary feeding. Family foods for breastfed children. Geneva: World Health Organization. WHO/NHD/00.1; WHO/FCH /CAH/00.6., 2000.

WHO. Fifty-Fourth World Health Assembly. Global strategy for infant and young child feeding: The optimal duration of exclusive breastfeeding. Geneva, Switzerland: World Health Organization, 2001.

WHO Global strategy for infant and young child feeding. WHA55/2002/REC/1, Annex 2, 2002a.

WHO global burden of disease (GBD) estimates (revised) (2002b). Available from: http://www.who.int/healthinfo/bodestimates/en/

World Health Organization. Global strategy for infant and young child feeding. Geneva, Switzerland: World Health Organization, 2003.

World Health Organization (WHO). WHO global database on child growth and malnutrition. World Health Organization/Programme of Nutrition, 2004.

WHO Child Growth Standards. Training course on child growth assessment: investigating causes of undernutrition. . Geneva: WHO, 2006. http://www.who.int/childgrowth/training/jobaid_investigating_causes.pdf

WHO multicentre growth reference study group. WHO Child Growth Standards: Length/height-for-age, Weight-for-age, Weight-for-length, Weight-for-height and Body mass index-for-age: Methods and Development. Geneva: World Health Organization, 2006.

WHO, FAO. Guidelines on food fortification with micronutrients. Geneva: World Health Organisation; Food and Agriculturual organisation, 2006.

WHO/WFP/SCN/UNICEF. Joint statement on community-based management of severe acute malnutrition, 2007. Available at: http://www.unicef.org/publications/files/Community_Based_Management_of_Sever_Acute__Malnutirtion.pdf

World Health Organization. Indicators for assessing infant and young child feeding practices: Part 1 definitions. Geneva, Switzerland: World Health Organization, 2008.

WHO. Global prevalence of vitamin A deficiency in populations at risk 1995–2005: WHO global database on Vitamin A deficiency. Geneva, World Health Organization, 2009.

WHO: Guideline: Vitamin A supplementation in infants and children 6-59 months of age.2011

Willet WC. Nutritional Epidemiology, Oxford University Press, New York, 1998.

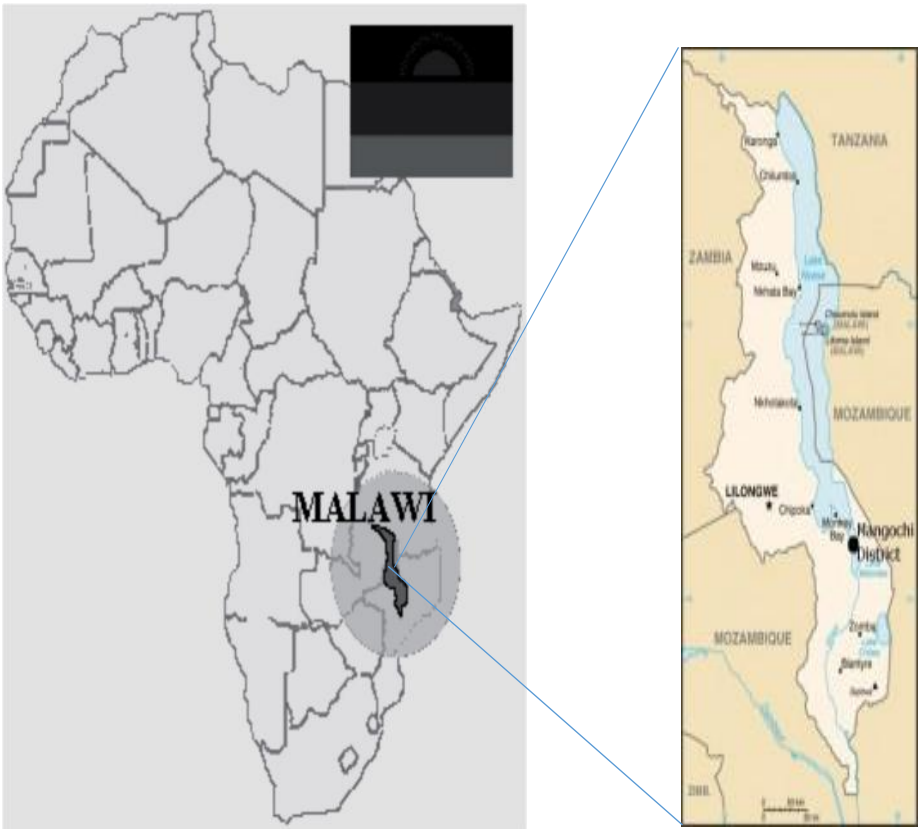
Wong HJ, Moy FM, Nair S. Risk factors of malnutrition among preschool children in Terengganu, Malaysia: a case control study. BMC Public Health, 2014; 14: 785.

Wood J and Sibanda-Mulder F: Improvement of fortified blended foods CSB products and Unimix (2011). Available from: http://www.unicef.org/supply/files/8._Improvement_of_Fortified_Blended_Foods_CSB_Products_and_Unimix.pdf.

World Bank. Environmental health and child survival: Epidemiology, economics and experience, World Bank. Washington DC, 2008.
Zulkifli SN, Yu SM. The food frequency method for dietary assessment: *J Am. Diet. Assoc, 1992;* 92:681-685.

11 APPENDICES

Appendix I: Map of research area



Appendix II: Local food picture calendar

12 ORIGINAL PUBLICATIONS

Public Health Nutrition: 15(9), 1755–1762 doi:10.1017/S1368980012003023

An effectiveness trial showed lipid-based nutrient supplementation but not corn–soya blend offered a modest benefit in weight gain among 6- to 18-month-old underweight children in rural Malawi

Chrissie M Thakwalakwa[1,2], Per Ashorn[2,3], Mpumulo Jawati[1], John C Phuka[1], Yin Bun Cheung[4] and Kenneth M Maleta[1,*]

[1]Department of Community Health, College of Medicine, University of Malawi, Private Bag 360, Chichiri Blantyre 3, Malawi: [2]Department of International Health, University of Tampere School of Medicine, Tampere, Finland: [3]Department of Paediatrics, Tampere University Hospital, Tampere, Finland: [4]Centre for Quantitative Medicine, Duke-NUS Graduate Medical School, Singapore

Submitted 3 October 2011: Final revision received 26 April 2012: Accepted 6 May 2012: First published online 13 June 2012

Abstract

Objective: To determine if supplementation with corn–soya blend (CSB) or lipid-based nutrient supplement (LNS) improved the weight gain of moderately underweight infants and children when provided through the national health service.

Design: A randomised, controlled, assessor-blinded clinical trial. Infants and children were randomised to receive for 12 weeks an average daily ration of 71 g CSB or 43 g LNS, providing 1188 kJ and 920 kJ, respectively, or no supplement (control). Main outcome was weight gain. Secondary outcomes included changes in anthropometric indices and incidence of serious adverse events. Intention-to-treat analyses were used.

Setting: Kukalanga, Koche, Katema and Jalasi health centres in Mangochi District, rural Malawi.

Subjects: Underweight (weight-for-age *Z*-score <-2) infants and children aged 6–15 months (*n* 299).

Results: Mean weight gain was 630 g, 680 g and 750 g in control, CSB and LNS groups, respectively ($P=0{\cdot}21$). When adjusted for baseline age, children receiving LNS gained on average 90 g more weight ($P=0{\cdot}185$) and their weight-for-length *Z*-score increased 0·22 more ($P=0{\cdot}049$) compared with those receiving no supplementation. No statistically significant differences were observed between the CSB and control groups in mean weight and length gain.

Conclusions: LNS supplementation provided during the lean season via through the national health service was associated with a modest increase in weight. However, the effect size was lower than that previously reported under more controlled research settings.

Keywords
Corn–soya blend
Lipid-based nutrient supplement
Undernutrition
Infant

The efficacy of providing ready-to-use therapeutic food has been demonstrated in the management of severe acute malnutrition[1–4] in institutional settings, as well as in home-based therapy for moderate acute malnutrition[5,6]. Because of this success, there has been growing interest in the efficacy of lipid-based nutrient supplements (LNS), modelled on ready-to-use therapeutic food, on growth and other health benefits in moderately undernourished children. Among mild to moderately underweight and/or stunted children, LNS has been shown to have modest effects on weight and height gains by several studies in different settings[4,7–9]. Most of the information on the efficacy of LNS has been shown in controlled research settings where compliance is intensely encouraged. It is well documented that the effectiveness of supplementation approaches differs in controlled *v.* operational settings[10]. The present study attempted to determine whether the documented efficacy of LNS on growth and other health benefits was achievable in operational settings when supplementation was through the national health system.

Fortified blended foods, such as fortified cereal and legume mixtures that resemble the indigenous diet and are prepared in a manner similar to staple food, have been recommended for supplementary feeding of moderately undernourished children[11]. In Malawi, treatment of moderate undernutrition (underweight, weight-for-age

*Corresponding author: Email kmaleta@medcol.mw

Z-score (WAZ) <-2) and wasting (weight-for-length *Z*-score (WLZ) <-2)) is done through the national health system whereby guardians are given fortified corn–soya blend (CSB) to make a soft porridge and feed the children in their homes. However, the effectiveness of using CSB remains under debate[12]. Apart from the appropriateness of the intervention, there is paucity of good data to document its effectiveness when supplementation is through the national health system.

To assess the effectiveness of LNS and CSB when administered through the national health system, we conducted a three-arm clinical trial, where moderately underweight infants and children aged 6–15 months received monthly either CSB or LNS or no supplementation (control) during the lean season of the year.

Methods

Study design

The study was a randomised, controlled, assessor-blinded clinical trial conducted at four health centres (Kukalanga, Koche, Katema and Jalasi) in Mangochi District, rural Malawi, south-east Africa. The main aim of the trial was to test the growth-promoting effect and other health benefits to infants and children of daily provision of CSB or LNS. The primary outcome measure was weight change during the 12-week follow-up period. Secondary outcomes included mean changes in length (mm), blood Hb concentration (g/l), anthropometric indices (WAZ, WLZ and length-for-age *Z*-score (LAZ)), mid-upper arm circumference (MUAC), head circumference and incidence of adverse events (AE) and serious adverse events (SAE).

Study participants

Participants were identified and screened at home. During the home visit, infants were weighed and their WAZ calculated. During the implementation of the trial, WAZ was being used nationally to assess the nutritional status of children <5 years old; as such, it was also used in screening participants for the present trial. Those whose guardians showed initial interest, were aged between 5·0 and 14·5 months and had WAZ $<-1·7$ were invited to the health centre for more thorough screening for enrolment criteria. The inclusion criteria were: a signed informed consent from at least one guardian, aged between 6·0 and 15·0 months, WAZ $<-2·0$, availability during the period of the study and permanent residence in the catchment area. Exclusion criteria included WLZ $<-3·0$ or presence of oedema, history of peanut allergy, history of any serious allergic reaction to any substance requiring emergency medical care, history of anaphylaxis, severe illness warranting hospital referral and concurrent participation in another clinical trial with intervention to the child. Those who met all inclusion criteria and whose guardians signed a consent form were randomised into one of three study groups. An independent statistician not involved in the study developed the random list, packed and sealed the randomisation codes into envelopes, then handed the sealed envelopes over to the research team. There was block randomisation. Participants picked an envelope from the remaining reshuffled envelopes which contained the randomisation group. The randomisation code was broken when all data collection was finished.

Enrolment in the trial was during the lean season between November 2007 and January 2008. No enrolment took place between 21 December 2007 and 6 January 2008 due to Christmas holiday. The 12-week follow-up of the last participant ended in April 2008 at the beginning of harvest season. The period between December and March is the rainy season during which the staple food (maize) and other crops are grown, and food levels and weight gains are at their lowest.

Sample size

The target sample size was ninety-seven infants per group (291 in total), calculated from the expected difference in the primary outcome, i.e. weight gain, among infants provided with either CSB or LNS and those provided with nothing. This expected difference was based on an assumed mean weight gain of 550 (SD 440) g in the control infants and 750 (SD 440) g among infants receiving either CSB or LNS supplementation[13]. This gave the trial 85 % power and a type 1 error rate of no more than 5 % to detect a difference of 200 g or more in mean weight gain between the control and intervention groups and allowed a 10 % loss to follow-up since the trial was done in less controlled conditions than the earlier studies.

Interventions and follow-up

Participants in the control group did not receive any food supplement during the trial period. Those in the first intervention group received 2 kg of CSB while those in the second intervention group received 1·2 kg of LNS. Both supplements were received from the health centre once every 4 weeks for 12 weeks. All participants were scheduled for a follow-up visit at the health centre every 4 weeks. CSB contains corn, soya and sugar. This was locally produced in Malawi by Rab Processors (Blantyre, Malawi). LNS was produced at a Malawian non-governmental organization, Project Peanut Butter (Blantyre, Malawi), from locally purchased peanut butter (26 %), dried skimmed milk (25 %), vegetable oil (20 %), icing sugar (27·5 %) and a pre-made mineral and vitamin mix (1·5 %; Nutriset Inc., Malaunay, France), where all percentages are by weight. All the supplements were fortified with micronutrients, but the level of fortification varied between the products.

During the follow-up visits every 4 weeks, the participants' medical condition was checked and their anthropometric measurements taken. Rations for the CSB and LNS participants were handed out during these visits. The guardians were provided with spoons and advised to give

Table 1 Nutrient composition of the participants' daily dose of corn–soya blend (CSB) or lipid-based nutrient supplement (LNS)

	CSB	LNS
Weight (g)	71	43
Energy (kJ)*	1188	920
Protein (g)	10·4	6·0
Carbohydrates (g)	NA†	11·9
Fat (g)	3·1	13·5
Retinol (μg RE)	139	400
Folate (μg)	43·2	160
Niacin (mg)	3·5	6
Pantothenic acid (mg)	NA†	2
Riboflavin (mg)	0·3	0·5
Thiamin (mg)	0·13	0·5
Vitamin B_6 (mg)	0·3	0·5
Vitamin B_{12} (μg)	0·9	0·9
Vitamin C (mg)	48	30
Cholecalciferol (μg)	NA†	5
Ca (mg)	72	366
Cu (mg)	NA†	0·4
Iodine (μg)	NA†	135
Fe (mg)	5·46	8
Mg (mg)	NA†	60
Zn (mg)	3·6	8·4

RE, retinol equivalants.
*1 kcal = 4·184 kJ.
†No information provided by the manufacturer.

their infants, twice daily, either three spoonfuls of LNS or porridge containing five spoonfuls of CSB. The guardians were encouraged to give the supplement in addition to breast milk. Interventions were handed out by a research assistant not involved in outcome assessment. Table 1 provides the energy and nutrient contents of a daily ration of each supplementation.

Measurement of outcome variables

Infant nude weights were measured to the nearest 10 g using an electronic infant weighing scale (SECA 735; Chasmors Ltd, London, UK). Head circumference and MUAC were measured to the nearest 1 mm by a non-stretchable measuring tape (Lasoo-o-tape; Harlow Printing Ltd, South Shields, UK). Length was measured to the nearest 0·1 cm using a length board (infantometer; Child Growth Foundation, London, UK). Anthropometric indices (WAZ, WLZ, LAZ) were calculated using Epi Info 3·3·2 software (Centers for Disease Control and Prevention, Atlanta, GA, USA), based on the Centers for Disease Control and Prevention 2000 growth reference[14]. All anthropometric measurements were done in triplicate by one investigator (M.J.), assisted by one trained research assistant. The first measurements were taken on enrolment day and then every 4 weeks until the end of the 12-week follow-up period. The last follow-up measurements were taken within 2 weeks of the scheduled date.

In the trial, the following medical occurrences were recorded as AE: abdominal discomfort, vomiting or diarrhoea for more than two consecutive days; skin rash for two or more consecutive days; noisy, wheezy, rapid or difficult breathing; and any other medical conditions that were judged abnormal or not typical childhood illnesses by the study physician. The SAE included: death; life-threatening condition; in-patient hospitalisation or prolongation of existing hospitalisation; persistent or significant disability or incapacity; or any other serious medical condition. Participants were advised to report to the clinical officer at the health centre if they had any of these symptoms or any problems during the study period. The clinical officer determined if the problem was an AE or SAE. An independent data safety and monitoring board (DSMB) also determined if the condition was an AE or SAE.

Ethics

The trial was performed according to International Conference of Harmonization–Good Clinical Practice guidelines (ICH-GCP) and the ethical standards of the Helsinki Declaration. The protocol was reviewed and approved by the College of Medicine Research and Ethics Committee, University of Malawi and the Ethical Committee of Pirkanmaa Hospital District, Finland. At least one guardian signed or thumb-printed an informed consent form before enrolment of each participant. The trial was registered with a registration ID of NCT00420368 at http://www.clinicaltrials.gov/. The DSMB monitored the incidence of suspected SAE.

Statistical analysis

All statistical analyses were conducted using the STATA statistical software package version 9·0 (StataCorp, College Station, TX, USA) based on an intention-to-treat principle. We compared group means between control and each of the supplemented groups at a single time point using the *t* test and results are expressed as absolute differences and their 95 % confidence intervals. We estimated the risk ratio and risk difference for comparison of binary endpoints between the control and each of the supplemented groups and tested the difference in proportions using Fisher's exact test. To prevent inflated type 1 errors due to multiple comparisons, we began hypothesis testing by testing the global null hypothesis of all three groups being identical, using Fisher's exact test (categorical variables) and ANOVA (continuous variables). Only if the global null hypothesis was rejected would the pairwise comparisons be interpreted in a confirmatory manner. No *post hoc* test was used for pairwise comparison after the aforementioned procedures. Linear regression modelling was used to determine whether, if controlled for baseline age, the type of food supplement given would be associated with weight gain. Values in the text are given as mean (SD), mean difference (95 % CI) or *n* (%). All confirmatory analyses were considered significant if $P < 0{\cdot}05$.

Results

Of the 1711 infants and children screened at home, 1066 (62 %) did not meet criteria for enrolment screening at the

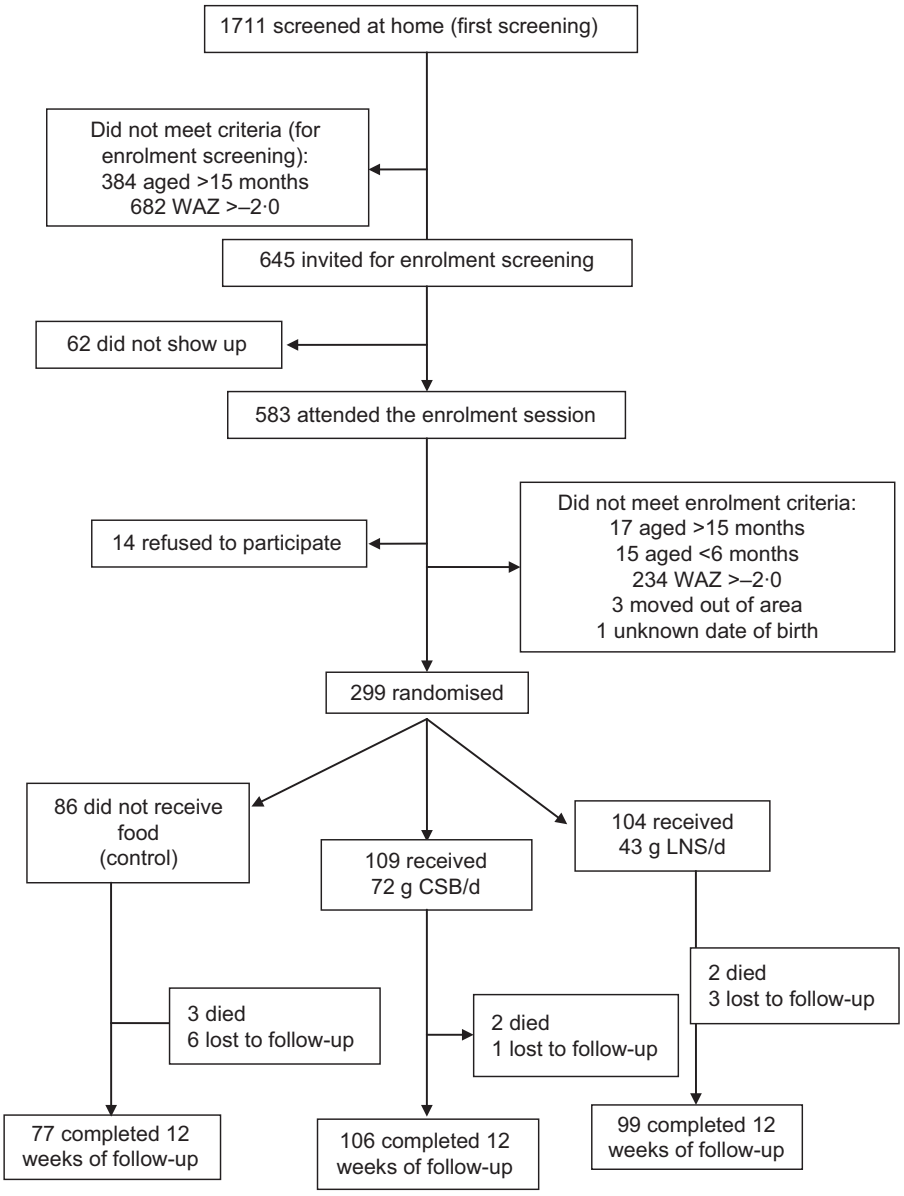


Fig. 1 Participant flow (WAZ, weight-for age *Z*-score; CSB, corn–soya blend; LNS, lipid-based nutrient supplement)

health centre (they were older and/or had WAZ $>-2{\cdot}0$); sixty-two (10 %) of the 645 invited did not show up. Of the 583 who attended enrolment screening, fourteen (2 %) refused to participate and 270 (46 %) did not meet enrolment criteria. We randomised the remaining 299 infants and children into three groups: control, CSB and LNS (Fig. 1). Two hundred and eighty-two participants (94 %) completed the follow-up, i.e. underwent medical and anthropometric assessment after the 12-week intervention. All participants were breast-fed from enrolment to the end of the follow-up period. Baseline WAZ values of participants who completed the follow-up were $-3{\cdot}14$, $-2{\cdot}95$ and $-3{\cdot}03$ ($P=0{\cdot}352$) for the control, CSB and LNS groups, respectively; corresponding values for those who died or were lost to follow-up were $-2{\cdot}88$, $-3{\cdot}33$ and $-3{\cdot}67$ ($P=0{\cdot}793$). These did not suggest that they came from different populations. The losses to follow-up were not significantly different between the intervention groups and the control group ($P=0{\cdot}341$ for deaths and $P=0{\cdot}929$ for total loss to follow-up; Fisher's exact test; Fig. 1).

At baseline, children in the LNS group were thinner and shorter compared with children in the CSB and control groups. There were more children in the younger age group, 6–9 months, in the LNS group than in the control and CSB groups: 38 % *v.* 15 % and 23 %, respectively. The proportions of children between the ages of 9 and 12 months and 12 and 15 months were, however, comparable across the groups (Table 2). At baseline, forty (47 %), forty-two (39 %) and seven (7 %) of the study participants were severely underweight in the control, CSB and

Table 2 Characteristics of participants at enrolment by study group: underweight infants and children aged 6–15 months (*n* 299), rural Malawi, 2007–2008

	Control		CSB		LNS	
Variable	Mean or *n*	% or SD	Mean or *n*	% or SD	Mean or *n*	% or SD
Participants (*n*, % male)	86	44	109	55	104	49
Age (months)	11·6	2·3	11·1	2·4	10·0	2·4
Weight (kg)	6·95	0·74	6·97	0·76	6·59	0·89
Length (cm)	67·3	3·3	67·5	3·6	66·3	3·6
MUAC (cm)	12·7	0·9	12·7	0·8	12·4	0·9
HC (cm)	43·9	1·5	43·7	1·6	43·2	1·7
WAZ*	−3·11	0·82	−2·96	0·79	−3·06	0·92
WAZ†	−2·42	0·71	−2·31	0·69	−2·50	0·77
WLZ*	−1·32	0·84	−1·36	0·83	−1·61	0·86
WLZ†	−1·23	0·68	−1·23	0·72	−1·45	0·75
LAZ*	−2·36	0·91	−2·16	0·90	−2·11	0·92
LAZ†	−2·77	0·94	−2·54	0·97	−2·49	0·97
Hb (g/l)	88	17	89	17	88	20
Age 6·00–9·00 months (*n*, %)	13	15	25	23	39	38
Age 9·01–12·00 months (*n*, %)	34	40	42	39	40	38
Age 12·01–15·00 months (*n*, %)	38	44	41	38	25	24
Age 15·01–18·00 months (*n*, %)	1	1	1	1	0	0
Enrolled 26 Nov–20 Dec 2007 (*n*, %)	46	53	63	58	71	68
Enrolled 7–23 Jan 2008 (*n*, %)	40	47	46	42	33	32

CSB, corn–soya blend; LNS, lipid-based nutrient supplement; MUAC, mid-upper arm circumference; HC, head circumference; WAZ, weight-for-age *Z*-score; WLZ, weight-for-length *Z*-score; LAZ, length-for-age *Z*-score.
Data are presented as mean and standard deviation unless indicated otherwise.
*Using Centers for Disease Control and Prevention 2000 growth reference[14].
†Using WHO 2006 growth reference[26].

Table 3 Comparison of mean quantitative anthropometric outcomes among participants receiving CSB or LNS for 12 weeks or no supplementation (control): underweight infants and children aged 6–15 months (*n* 299), rural Malawi, 2007–2008

	Results by study group							Comparison of CSB *v.* control			Comparison of LNS *v.* control		
	Control		CSB		LNS								
Outcome	Mean	SD	Mean	SD	Mean	SD	*P**	Difference†	95 % CI	*P*‡	Difference†	95 % CI	*P*‡
Weight increase (kg)	0·63	0·40	0·68	0·50	0·75	0·41	0·211	0·05	−0·09, 0·18	0·504	0·12	−0·00, 0·24	0·058
Length increase (cm)	3·4	1·2	3·3	1·3	3·6	1·3	0·290	−0·1	−0·4, 0·3	0·710	0·2	−0·2, 0·6	0·294
MUAC increase (cm)	0·3	0·8	0·3	0·9	0·4	0·7	0·743	−0·0	−0·2, 0·3	0·716	0·0	−0·3, 0·2	0·722
HC increase (cm)	0·9	0·9	0·7	0·9	0·8	0·8	0·410	−0·2	−0·4, 0·1	0·200	−0·1	−0·4, 0·1	0·377
WAZ change	−0·13	0·61	−0·13	0·71	−0·12	0·60	0·984	0·00	−0·19, 0·20	0·967	0·02	−0·16, 0·20	0·858
WLZ change	−0·25	0·71	−0·14	0·81	−0·10	0·64	0·409	0·11	−0·12, 0·34	0·341	0·14	−0·06, 0·35	0·162
LAZ change	0·06	0·44	−0·02	0·47	0·02	0·47	0·457	−0·09	−0·22, 0·05	0·207	−0·04	−0·18, 0·09	0·543
Hb change (g/l)	1·9	20	3·4	21	6·3	23	0·398	1·5	−4·7, 7·7	0·637	4·3	−2·2, 10·9	0·195

CSB, corn–soya blend; LNS, lipid-based nutrient supplement; MUAC, mid-upper arm circumference; HC, head circumference; WAZ, weight-for-age *Z*-score; WLZ, weight-for-length *Z*-score; LAZ, length-for-age *Z*-score.
*ANOVA.
†Differences are mean value in intervention group – mean value in control group.
‡*t* Test.

LNS groups, respectively. None of the participants were severely wasted but about 66 %, 59 % and 56 % of the participants in the control, CSB and LNS groups, respectively, were moderately wasted (data not shown). Attendance to the scheduled health centre visits was good in all groups. Among participants who did not die or drop out of the follow-up, the proportion that attended up to the last scheduled health centre follow-up visit was 94 %, 99 % and 98 % among control, CSB, and LNS groups, respectively.

During the 12-week follow-up, mean weight gain was 630 g, 680 g and 750 g in the control, CSB and LNS groups, respectively, with no statistically significant differences among the groups ($P = 0{\cdot}211$). Changes in the secondary outcomes (WAZ, LAZ, WLZ, length, head circumference, MUAC and Hb concentration) were not statistically significantly different in the three groups (Table 3). When controlled for baseline age, children receiving LNS gained on average 90 g more weight ($P = 0{\cdot}185$) and their WLZ increased by 0·22 more ($P = 0{\cdot}049$) compared with those receiving no supplementation. Children receiving CSB gained 40 g more weight ($P = 0{\cdot}571$) and their WLZ increased by 0·14 more ($P = 0{\cdot}205$) compared with controls. Changes in weight and other secondary outcomes (length, WAZ, LAZ, Hb) were comparable among the groups (Table 4).

At the end of the follow-up period, slightly more children in the control group (56 %) were severely underweight

Table 4 Comparison of mean quantitative outcomes among participants receiving CSB or LNS for 12 weeks or no supplementation (control), controlling for baseline age: underweight infants and children aged 6–15 months (*n* 299), rural Malawi, 2007–2008

	Comparison of CSB *v.* control			Comparison of LNS *v.* control		
Outcome	Difference*	95 % CI	*P*†	Difference*	95 % CI	*P*†
Weight increase (kg)	0·04	−0·09, 0·17	0·571	0·09	−0·04, 0·23	0·185
Length increase (cm)	−0·1	−0·5, 0·2	0·433	−0·0	−0·4, 0·4	0·942
WAZ change	0·04	−0·14, 0·22	0·656	0·12	−0·07, 0·31	0·198
WLZ change	0·14	−0·08, 0·35	0·205	0·22	−0·00, 0·44	0·049
LAZ change	−0·08	−0·22, 0·06	0·249	−0·02	−0·17, 0·12	0·731
Hb change (g/l)	2·1	−4·3, 8·5	0·513	6·2	−0·4, 12·9	0·067

CSB, corn–soya blend; LNS, lipid-based nutrient supplement; WAZ, weight-for-age *Z*-score; WLZ, weight-for-length *Z*-score; LAZ, length-for-age *Z*-score.
*Differences are mean value in intervention group – mean value in control group.
†From multiple linear regression models of changes in weight, length, WAZ, WLZ, LAZ and Hb with intervention (CSB, LNS and no food) and age.

Table 5 Proportion with confirmed AE and SAE among participants who received CSB or LNS for 12 weeks or no supplementation (control): underweight infants and children aged 6–15 months (*n* 299), rural Malawi, 2007–2008

	Number of outcomes/participants												
	Control		CSB		LNS			CSB *v.* control			LNS *v.* control		
Outcome	*n*	%	*n*	%	*n*	%	*P**	RR	95 % CI	*P**	RR	95 % CI	*P**
Participants (*n*)	86		109		104								
SAE	4	5	2	2	3	3	0·536	2·5	0·5, 13·5	0·237	1·6	0·4, 7·0	0·396
Any AE	14	16	19	17	18	17	0·981	0·9	0·5, 1·8	0·494	0·9	0·5, 1·8	0·504
Vomiting symptoms	4	5	1	1	2	2	0·267	5·1	0·6, 44·5	0·119	2·4	0·5, 12·9	0·256
Abdominal discomfort	3	3	3	3	2	2	0·903	1·3	0·3, 6·1	0·541	1·8	0·3, 10·6	0·411
Diarrhoea	8	9	12	11	12	12	0·892	0·8	0·4, 2·0	0·443	0·8	0·3, 1·9	0·399
Skin rash	3	3	3	3	4	4	0·923	1·3	0·3, 6·1	0·541	0·9	0·2, 3·9	0·604

AE, adverse effect.; SAE, severe adverse effect; CSB, corn–soya blend; LNS, lipid-based nutrient supplement; RR, risk ratio.
*Fisher's exact test.

compared with CSB (45 %) and LNS (46 %) groups. For severe stunting, the prevalence was 22 % in controls, 17 % in the CSB group and 13 % in the LNS group. Severe wasting was comparable among the groups: five (6 %), six (6 %) and seven (7 %) children in the control, CSB and LNS groups, respectively (data not shown).

During the intervention period, the incidence of AE did not differ significantly among the three groups (all $P > 0{\cdot}05$). Fifty-one children experienced a clinician-documented AE, nine of which were SAE, with no differences in the incidence of any AE among the groups (Table 5). All SAE were assessed as unlikely related to the intervention since they did not follow a reasonable time sequence from administration of the study food.

Discussion

In this sample, LNS supplementation to moderately underweight 6- to 18-month-old children through the national health system was associated with a modest increase in weight gain compared with supplementation with CSB or no supplementation. The amount of weight gain improvement (120 g/12 weeks) was in the same direction but lower than weight gains reported when LNS has been offered for a similar duration in more controlled settings (150 g)[15]. Although the findings were statistically only marginally significant with or without adjustment for covariates, the effectiveness estimate is plausible in the context of the previous efficacy trials.

The utility of any dietary supplementation regimen is dependent on its biological efficacy and its operational feasibility and practical acceptability. Results from the current study suggest that the effectiveness of LNS is maintained in a less controlled setting, albeit at a rather modest level. In a recent efficacy trial under controlled conditions from the same study area, there was a modest weight gain with LNS supplementation as compared with control[15]. The current observation from less controlled conditions is therefore not surprising. Weight gain in this setting is likely to be lower than that in a controlled setting because the LNS might be shared with family members and siblings[16]. The effects observed could easily be applied to similar settings where interventions are given at health facilities and the patients are not followed up to check compliance. However, the weakness is that compliance/adherence to the study food was not checked, limiting our understanding of how the supplement was

used by each child and within the household. The positive impact of LNS in these settings is likely to be associated with its good taste and acceptability among infants and young children[17–19], its high energy and nutrient density, and its non-resemblance to normal family foods[5,20]. CSB, on the other hand, is normally consumed by infants as high-volume porridge, similar to many traditional foods. All of these characteristics make LNS more likely than CSB to actually complement existing diets for the intended beneficiaries, rather than just displacing traditional foods or ending up as shared commodities with other individuals than the undernourished child.

Apart from their intrinsic differences, the modest effects of LNS and CSB could also be explained by the higher proportion of infants and children recruited at the beginning of the lean season (68% and 58%, respectively), when some families still had some food left, compared with the non-supplemented children, who were mostly evenly distributed. We have previously documented reduced rates of weight gain in these months[21] compared with the latter months of the year. This could result in underestimation of the effect size of either of the interventions.

The efficacy of any intervention programme is also dependent on the age of the participant[22] and the length of the supplementation[23]. In the present study, the intervention length was relatively short and the groups were not homogeneous in age, such that we had to estimate if the intervention had a differential effect based on baseline age. Controlling for age, a higher but still modest effect was observed on changes in WLZ. The modest impact of the intervention in the current trial could therefore also have been explained by the shorter duration of supplementation.

Undernutrition impacts on morbidity and morbidity affects an individual's nutritional status. Undernutrition and morbidity have a synergistic relationship in such a way that, on the one hand, nutritional deficiencies increase the susceptibility of the child to infectious diseases such as diarrhoea, fevers and malaria, and on the other, illness can suppress a child's appetite leading to undernutrition[24,25]. In the current study, the incidence of any AE (diarrhoea, vomiting and skin rash) in the CSB and LNS groups was similar to that in the control group, a finding that others have documented from supplementary programmes[6]. However, a recent trial documented more episodes of vomiting and skin rash with LNS supplementation[15]. One reason for the difference might be because the current study was done in a less controlled setting such that some cases may not have been reported, unlike in the previous trial where the participants were visited weekly and encouraged to report to the hospital with any problem.

The current results did not show any protective effect of CSB nor LNS against morbidity.

The current findings, however, should be regarded as preliminary, given that the period of supplementation was relatively short and did not cover both seasons. Caution must be taken when extrapolating the results since the current study was not strictly operational in that the participants were recruited into the study rather than them coming through the health system by themselves. This might affect the generalizability of the results from the study. However, all the infants and children aged 6–15 months in the catchment area were screened and given a chance to participate in the study.

The participants' diet in the study area is dominated by foods of vegetable origin with very limited intake of animal-source foods, making the quality of the diet poor. Supplementation of LNS could therefore add value and improve the nutritional quality of the diet, contributing towards optimal nutrition and thereby preventing malnutrition from becoming worse.

Conclusion

LNS supplementation provided through the national health system during the lean season to underweight children, the majority of whom were only slightly wasted, was associated with a modest increase in weight gain compared with no supplementation. The effect size was however lower than previously reported in more controlled research settings. There is need to verify the findings through a study with longer supplementation duration that covers both seasons to determine the effects of supplement duration and season on the outcomes.

Acknowledgements

This work was supported by the Academy of Finland (grant 109796). C.M.T. was supported by a personal stipend from Nestlé Foundation and the St. Louis Nutrition Project. There are no conflicts to declare. All authors designed the trial; P.A. wrote the protocol and raised funds for the trial; C.M.T. and M.J. were responsible for data collection; Y.B.C. designed the details of the statistical analysis; C.M.T. and J.C.P. did the analysis; C.M.T. wrote the first draft of the manuscript under the supervision of K.M., P.A. and Y.B.C. All authors commented on the analysis and participated in revising the manuscript. K.M.M. had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The authors thank the study participants and the staff at Jalasi, Koche, Kukalanga and Katema health centres in Mangochi District for their positive attitude, support and help in all stages of the study; Andre Briend and Taneli Puumalainen for commenting on the analysis and participating in the writing of the manuscript; the DSMB (Kamija Phiri, Paul Ndebele, Tom Heikens) for monitoring the trial; and Laszlo Csonka for designing the data entry program.

References

1. Diop EH, Dossou NI, Ndour MM *et al.* (2003) Comparison of the efficacy of a solid ready to use food and a liquid milk-based diet for the rehabilitation of severely malnourished children: a randomized trial. *Am J Clin Nutr* **78**, 302–307.
2. Manary MJ, Ndekha M, Ashorn P *et al.* (2004) Home-based therapy for severe malnutrition with ready-to-use food. *Arch Dis Child* **89**, 557–561.
3. Ndekha MJ, Manary MJ, Ashorn P *et al.* (2005) Home-based therapy with ready-to-use therapeutic food is of benefit to malnourished, HIV infected Malawian children. *Acta Paediatr* **94**, 222–225.
4. Patel M, Sandige H, Ndekha M *et al.* (2005) Supplemental feeding with ready-to-use therapeutic food in Malawian children at risk of malnutrition. *J Health Popul Nutr* **23**, 351–357.
5. Briend A (2001) Highly nutrient-dense spreads: a new approach to delivering multiple micronutrients to high-risk groups. *Br J Nutr* **85**, S175–S179.
6. Ciliberto M, Sandige H, Ndekha M *et al.* (2005) Comparison of home based therapy with ready-to-use therapeutic food with standard therapy in the treatment of malnourished Malawian children: a controlled, clinical effectiveness trial. *Am J Clin Nutr* **81**, 864–870.
7. Adu-Afarwuah S, Lartey A, Brown KH *et al.* (2007) Randomized comparison of 3 types of micronutrient supplements for home fortification of complementary foods in Ghana: effects on growth and motor development. *Am J Clin Nutr* **86**, 412–420.
8. Phuka JC, Maleta K, Thakwalakwa C *et al.* (2008) Complementary feeding with fortified spread and incidence of severe stunting in 6- to 18-month-old rural Malawians. *Arch Pediatr Adolesc Med* **162**, 619–626.
9. Phuka JC, Thakwalakwa C, Maleta K *et al.* (2009) Post intervention growth of Malawian children who received 12-month dietary complementation with a lipid-based nutrient supplement or maize–soy flour. *Am J Clin Nutr* **89**, 382–390.
10. Beaton GH & Ghassemi H (1982) Supplementary feeding programs for young children in developing countries. *Am J Clin Nutr* **35**, 864–916.
11. Perez E & Klein B (2009) Impact of fortified blended food aid products on nutritional status of infants and young children in developing countries. *Nutr Rev* **67**, 706–718.
12. Navarro-Colorado C, Shoham J & Mason F (2008) *Measuring the Effectiveness of Supplementary Feeding Programmes in Emergencies. Humanitarian Practice Network Paper* no. 63. London: Overseas Development Institute.
13. Kuusipalo H, Maleta K, Briend A *et al.* (2006) Growth and change in blood haemoglobin concentration among underweight Malawian infants receiving supplementation with fortified spreads for 12 weeks. *J Pediatr Gastroenterol Nutr* **43**, 525–532.
14. Kuczmarski RJ, Ogden CL, Guo SS *et al.* (2000) 2000 CDC Growth Charts for the United States: methods and development. *Vital Health Stat 11* issue 246, 1–190.
15. Thakwalakwa C, Ashorn P, Phuka J *et al.* (2010) A lipid-based nutrient supplement but not corn–soy blend modestly increases weight gain among 6- to 18-month-old moderately underweight children in rural Malawi. *J Nutr* **140**, 2008–2013.
16. Flax VL, Phuka J, Cheung YB *et al.* (2010) Feeding patterns and behaviors during home supplementation of underweight Malawian children with lipid-based nutrient supplements or corn–soy blend. *Appetite* **54**, 504–511.
17. Adu-Afarwuah S, Lartey A, Zeilani M *et al.* (2011) Acceptability of lipid-based nutrient supplements (LNS) among Ghanaian infants and pregnant or lactating women. *Matern Child Nutr* **7**, 344–356.
18. Hess SY, Bado L, Aaron GJ *et al.* (2011) Acceptability of zinc-fortified lipid-based nutrient supplements (LNS) prepared for young children in Burkina Faso. *Matern Child Nutr* **7**, 357–367.
19. Phuka J, Ashorn U, Ashorn P *et al.* (2011) Acceptability of three novel lipid-based nutrient supplements among Malawian infants and their caregivers. *Matern Child Nutr* **7**, 368–377.
20. Maleta K, Kuittinen J, Duggan MB *et al.* (2004) Supplementary feeding of underweight, stunted Malawian children with ready-to-use food. *J Pediatr Gastroenterol Nutr* **38**, 143–145.
21. Maleta K, Virtanen S, Espo M *et al.* (2003) Seasonality of growth and the relationship between weight and height gain in children under three years of age in rural Malawi. *Acta Paediatr* **92**, 491–497.
22. Schroeder DG, Martorell R, Rivera JA *et al.* (1995) Age differences in the impact of nutritional supplementation on growth. *J Nutr* **125**, 4 Suppl., 1051S–1059S.
23. Simondon KB, Gartner A, Berger J *et al.* (1996) Effect of early, short-term supplementation on weight and linear growth of 4-7-mo-old infants in developing countries: a four-country randomized trial. *Am J Clin Nutr* **64**, 537–545.
24. Brabin BJ & Coulter JBS (2003) Nutrition-associated disease. In *Manson's Tropical Diseases*, pp. 561–580 [GC Cook and AI Zumla, editors]. London: Saunders.
25. Food and Agriculture Organization of the United Nations (2004) Undernourishment around the world. In *The State of Food Insecurity in the World 2004*, pp. 6–17. Rome: FAO.
26. WHO Multicentre Growth Reference Study Group (2006) *WHO Child Growth Standards: Length/height-for-age, Weight-for-age, Weight-for-length, Weight-for-height and Body mass index-for-age: Methods and Development.* Geneva: WHO.

Maternal & Child Nutrition

DOI: 10.1111/mcn.12105

Original Article

Impact of lipid-based nutrient supplements and corn–soy blend on energy and nutrient intake among moderately underweight 8–18-month-old children participating in a clinical trial

Chrissie M. Thakwalakwa*†, Per Ashorn*§, John C. Phuka†, Yin Bun Cheung‡, André Briend* and Kenneth M. Maleta†

*Department of International Health, University of Tampere School of Medicine, Tampere, Finland, †Department of Community Health, College of Medicine, University of Malawi, Blantyre, Malawi, ‡Centre for Quantitative Medicine, Duke-NUS Graduate Medical School, Singapore, and §Department of Paediatrics, Tampere University Hospital, Tampere, Finland

Abstract

Nutrition interventions have an effect on growth, energy and nutrient intake, and development, but there are mixed reports on the effect of supplementation of energy-dense foods on dietary intake. This substudy aimed at assessing the effect of supplementation with corn–soy blend (CSB) or lipid-based nutrient supplement (LNS) on energy and nutrient intake in moderately underweight children participating in a clinical trial. A total of 188 children aged 8–18 months participated and received daily either 284 kcal from CSB or 220 kcal from LNS and no supplements (control). An interactive 24-h recall method was used to estimate energy and nutrient intakes in the groups. Total mean energy intake was 548 kcal, 551 kcal and 692 kcal in the control, CSB and LNS groups, respectively ($P = 0.011$). The mean (95% confidence interval) intake of energy and protein were 144 (37–250; $P < 0.001$) and 46 (1.5–7.6; $P < 0.001$) larger, respectively, in the LNS group than among the controls. No significant differences were observed between the control and CSB groups. Energy intake from non-supplement foods was significantly lower in the CSB group compared with the control group, but not in the LNS group, suggesting a lower displacement of non-supplement foods with LNS. Both CSB and LNS supplementation resulted in higher intakes of calcium, iron, zinc and vitamin C compared with controls (all $P \leq 0.001$). This study indicates that LNS might be superior to CSB to supplement underweight children as it results in higher energy intake, but this requires confirmation in other settings.

Keywords: CSB, infant, interactive 24-h recall, LNS, Sub-Saharan Africa, undernutrition.

Correspondence: Ms. Chrissie M. Thakwalakwa, College of Medicine, University of Malawi, P/Bag 360, Chichiri, Blantyre 3, Malawi.
E-mail: cthakwalakwa@yahoo.com; cthakwalakwa@medcol.mw
Trial registration: Clinical trials.gov identifier: NCT00131209.

Introduction

Nutrition interventions during the complementary feeding period have shown to be effective in promoting child growth and development and in improving macronutrient and micronutrient intake (Dewey & Adu-Afarwuah 2008). Provision of all the necessary nutrients to rapidly growing or underweight infants during the complementary feeding period has proven difficult, especially where animal source foods are limited. To fill the nutrient gaps during this period, World Health Organization (WHO) recommended use of fortified products or nutritional supplements (PAHO/WHO 2003).

Supplementary foods are widely used in the treatment of severe or moderate malnutrition in children. While the supplementation is usually associated with improved weight gains when used in a hospital setting, the impact has often appeared smaller when used at home. One possible explanation has been that at home, in uncontrolled conditions, the supplement replaces other foods.

A previous trial by our study team showed increased weight gain among children supplemented with Lipid-based nutrient supplement (LNS), but not those supplemented with corn–soy blend (CSB) compared with a control group receiving no supplement (Thakwalakwa *et al*. 2010a). In this study, we wanted to test three hypotheses: (1) that both LNS and CSB are associated with increased micronutrient intakes (because both are fortified); (2) that LNS, but not CSB, is associated with increased total energy and macronutrient intakes; and (3) that CSB, but not LNS, supplementation is associated with reduced energy, macronutrients and micronutrients intakes from non-supplement foods.

Methods and materials

Study design

This study was part of a clinical intervention trial in moderately underweight 6–15-month-old children receiving either: (1) CSB; (2) LNS; or (3) no supplementation (control; Thakwalakwa *et al*. 2010a). Children received 71 g of CSB or 43 g of LNS corresponding to 284 kcal and 220 kcal, respectively. The composition of supplements is shown in Table 1. Underweight was defined as low weight-for-age [weight-for-age *z*-score (WAZ) <–2] relative to the National Center for Health Statistics reference median.

Trial setting

The study was conducted in the Lungwena area, Mangochi District, Malawi, South-Eastern Africa. In Lungwena, underweight (defined as WAZ <–2) and stunting [defined as length-for-age *z*-score (LAZ) <–2] are very common with a prevalence of 40% and almost 80% by 18 months of age, respectively (Maleta *et al*. 2003a). Farming and fishing form the main occupations. A significant proportion of households have poor food security, as cultivated land areas are usually small. The area has one rainy season between December and March during which maize, the staple food, and other crops are grown. During this season, food security in the area is typically at its lowest and weight and length gain of children are poorer than during the rest of the year (Maleta *et al*. 2003b). Maize is normally harvested from April to May. The energy and nutrient intake assessment was conducted between March and May 2007.

Table 1. Nutrient composition of daily dose of corn–soy blend (CSB) or lipid-based nutrient supplement (LNS)

	CSB	LNS
Weight, g	71	43
Energy, kJ*	1188	920
Protein, g	10.4	6.0
Carbohydrates, g	NA†	11.9
Fat, g	3.1	13.5
Retinol, µg RE	139	400
Folate, µg	43.2	160
Niacin, mg	3.5	6
Pantothenic acid, mg	NA†	2
Riboflavin, mg	0.3	0.5
Thiamin, mg	0.13	0.5
Vitamin B6, mg	0.3	0.5
Vitamin B12, µg	0.9	0.9
Vitamin C, mg	48	30
Cholecalciferol, µg	NA†	5
Calcium, mg	72	366
Copper, mg	NA†	0.4
Iodine, µg	NA†	135
Iron, mg	5.46	8
Magnesium, mg	NA†	60
Zinc, mg	3.6	8.4

*1 kcal = 4.184 kJ. †No information provided by the manufacturer. NA, not applicable; RE, retinol equivalent.

Key messages

- Lipid-based nutrient supplement (LNS) and corn-soy blend (CSB) supplementation results in increased micronutrient intakes.
- LNS and not CSB supplementation is associated with increased total energy and macronutrient intakes.
- CSB and not LNS supplementation is associated with reduced energy and macronutrient intakes.
- LNS appears to be superior to CSB to supplement underweight children, but this requires confirmation in other settings.

Eligibility

All 192 children who were enrolled in the clinical intervention trial were eligible for this substudy.

Data collection method

Data collection for the substudy occurred when the participants had been enrolled into the clinical trial for 9 weeks. A structured interactive 24-h dietary recall method (Ferguson *et al*. 1989, 1995) was used to assess food intake. This is a modified version of the 24-h recall and was used to quantify dietary intakes among pregnant women and 3–4-year-old children in Lungwena (Ndekha *et al*. 2000; Maleta *et al*. 2004). The validity of the method has been documented (Ferguson *et al*. 1995; Thakwalakwa *et al*. 2010b).

To help reduce memory lapses, the participant's mother was given a local food picture calendar. The mother was advised to tick on the calendar all foods the child would eat the following day starting from the very first food in the morning until the very last food on that day. The actual structured interactive 24-h recall was conducted 3 days after the calendars were delivered.

On the data collection day, the parent was asked to handover the marked food picture calendar to the enumerator. Then the parent was asked to recite all foods taken by the participant the preceding day. The enumerator compared oral information with what was marked on the calendar. The parent was then asked to describe in detail each of the foods or beverage consumed by the child. This included ingredients and methods used to prepare the food or beverage.

To help estimate the portions consumed, standard spoons, cups and plates were provided to measure servings of all different foods including nsima, the stiff maize-based porridge, dry fish, boiled cassava and sweet potatoes. All the collected information was recorded in specially developed structured interactive 24-h recall questionnaire.

Data were collected by research assistants (RA) in the local Chiyao language. These RAs went through a 5-day training in conducting dietary intake surveys using the structured interactive 24-h recall method (Ferguson *et al*. 1989, 1995)

Data management and analysis

All statistical analyses were conducted using Stata 9.0 (Stata Corp, College Station, TX, USA). The analysis compared mean intakes of energy, protein, calcium, iron, zinc, vitamin A and vitamin C between each of the intervention groups versus the control group. All children were analysed in the group where they were initially randomised, i.e. on an intention to treat basis. The Huber White robust standard error (Binder 1983) was used for statistical inference without making distributional assumption. To guard against inflated type 1 error because of multiple group comparisons, hypotheses for pairwise comparison would not be rejected unless the global null hypothesis of no difference among all groups is rejected. Hypothesis testing was not done for comparisons between the two intervention groups. Mean energy and nutrient intakes were compared between the intervention groups and the control group. Mean energy and nutrient intakes from non supplement foods in each of the two intervention groups were also compared with those from the control group.

Ethical approval and consent

The study was approved by the College of Medicine Research and Ethics Committee (COMREC), Malawi, 29.09.2004 (COMREC decision P.03/04/268R) and Pirkanmaa Health Care Area Ethics Committee, Finland, 14.09.2004 (PSHP EC decision 17, approval number R04111). Clinical Trials.gov Identifier: NCT00131209. An informed consent was sought from at least one parent before conducting this assessment.

Results

Out of the 192 children randomised into the clinical trial, 188 gave consent and were included in the dietary intake assessment study. The participant flow is shown in Fig. 1. Nutrient composition of daily dose of CSB or LNS is shown in Table 1. The control and

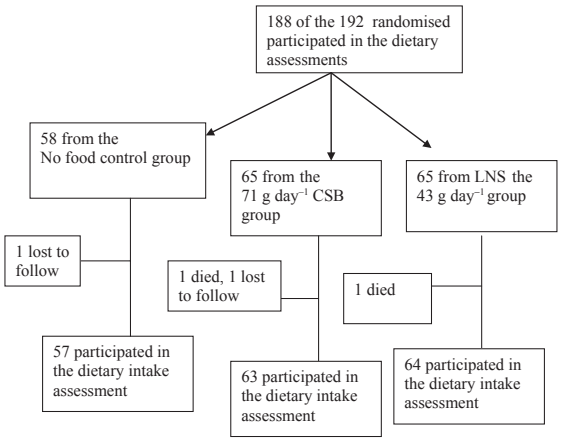


Fig. 1. Participant flow for the participants supplemented with lipid-based nutrient supplement (LNS), corn–soy blend (CSB) or nothing.

Table 2. Baseline information of study participants*

Variable	Control	CSB	LNS
Participants, *n*	58	65	65
Age, months	13.3 ± 2.58	13.3 ± 2.80	13.5 ± 2.54
Weight, kg	7.35 ± 0.79	7.23 ± 1.10	8.29 ± 5.75
Length, cm	67.4 ± 8.7	68.1 ± 4.3	69.0 ± 3.6
Mid-upper arm circumference, cm	13.6 ± 0.8	14.0 ± 4.3	13.9 ± 0.9
Head circumference, cm	44.8 ± 1.5	44.4 ± 1.6	44.6 ± 1.3
Weight-for-age *z*-score	−3.20 ± 0.84	−3.36 ± 1.16	−2.91 ± 0.85
Weight-for-length *z*-score	−1.14 ± 0.84	−1.17 ± 0.97	−0.90 ± 0.94
Length-for-age *z*-score	−2.63 ± 0.82	−2.75 ± 1.05	−2.47 ± 0.74

*Values are mean ± standard deviation. CSB, corn–soy blend; LNS, lipid-based nutrient supplement.

CSB groups had slightly lower baseline age, weight, length, LAZ, WAZ and weight-for-length *z*-score than the LNS group (Table 2).

Mean energy intake was 548 kcal, 551 kcal and 692 kcal in the control, CSB and LNS groups, respectively ($P = 0.01$). Mean protein intakes were 13.7 g, 15 g and 18.3 g ($P \leq 0.001$). Compared with the control group, children in the LNS group had on average [95% confidence interval (CI)] 144 kcal (37–250, $P \leq 0.001$) higher energy intake and 4.6 g (1.5–7.6, $P \leq 0.001$) higher protein intake. CSB group had slightly higher energy and protein intakes as compared with the control group (both $P \geq 0.05$). Both CSB and LNS groups had higher intake of calcium, iron, zinc and vitamin C compared with control (all $P \leq 0.001$). Comparable vitamin A intakes were observed between the control group and either of the intervention groups (Table 3).

When the food supplements were excluded from the analysis, the mean energy intake was 548 kcal in control group, 366 kcal in CSB group and 596 kcal in LNS group ($P \leq 0.001$). Mean protein intakes were 13.7 g, 11.1 g and 15.7 g in control, CSB and LNS groups, respectively ($P = 0.045$). Compared with the control group, infants in the LNS group had a higher energy intake from the non-supplement foods ($P \geq 0.05$). Infants in the CSB group had on average (95% CI) 182 kcal (−286 to 79, $P \leq 0.001$) lower energy intake from the non-supplement foods than the control group. Both CSB and LNS groups had comparable intakes from non-supplement foods of protein, calcium, iron, zinc, vitamin A and vitamin C with the control group (Table 4).

Discussion

In this trial, supplementation with CSB or LNS led to higher intakes of energy and proteins in moderately underweight 8–18-month-old children compared with control children. This increase, however, was significant only in children who received LNS. Children who received CSB reduced their intake of non-supplement foods in contrast to children receiving LNS. This is likely to have reduced the effect of CSB supplement on overall energy intake.

This result seems likely to reflect a true difference between the supplements, as the groups were randomised. The study was not blinded, however, and it cannot be excluded that some preference of the caretaker led to a biased estimation of intake in the one of the groups. It would be important to confirm these findings in other settings.

One weakness in this study is that during randomisation into the clinical trial (Thakwalakwa *et al.* 2010a), a participant was asked to pick an envelope from all the remaining reshuffled sealed envelopes. Some envelopes may not have been shuffled properly leading to unequal numbers in the groups. However, the groups were comparable at enrolment.

Table 3. Comparison of mean energy and nutrient intake in the three trial arms (Food supplements included)

Outcome	Results by study group				Comparisons between CSB and control		Comparisons between LNS and control	
	Control	CSB	LNS	*P**	Difference† (95% CI)	*P**	Difference† (95% CI)	*P**
Mean energy, kcal	548 (38)	551 (56)	692 (54)	0.011	3 (−107 to 113)	0.961	144 (37–250)	0.009
Mean protein, g	13.7 (1.1)	15.0 (1.8)	18.3 (1.6)	0.004	1.3 (−2.2 to 4.8)	0.469	4.6 (1.5–7.6)	0.004
Mean calcium, m	136 (21)	392 (53)	331 (38)	<0.001	256 (151–360)	<0.001	195 (119–270)	<0.001
Mean iron, mg	4.9 (0.3)	9.0 (0.8)	9.2 (0.7)	<0.001	4.1 (2.5–5.6)	<0.001	4.3 (3.0–5.6)	<0.001
Mean zinc, mg	4.7 (1.0)	9.6 (1.4)	10.2 (1.5)	<0.001	4.9 (2.2–7.6)	0.001	5.5 (2.5–8.5)	<0.001
Vitamin A, μg	357 (61)	350 (77)	408 (78)	0.660	−7 (−160 to 146)	0.930	51 (−103 to 205)	0.513
Vitamin C, mg	15.9 (1.9)	33.3 (3.7)	30.2 (4.0)	<0.001	17 (10–25)	<0.001	14 (6–22)	<0.001

*Huber–White Robust standard error. †Differences are mean values in intervention group – mean value in control group. CI, confidence interval; CSB, corn–soy blend; LNS, lipid-based nutrient supplement.

Table 4. Comparison of energy and nutrient intake in the three trial arms (food supplements not included)

Outcome	Results by study group				Comparisons between CSB and control		Comparisons between LNS and control	
	Control	CSB	LNS	*P**	Difference† (95% CI)	*P**	Difference† (95% CI)	*P**
Mean energy, kcal	548 (38)	366 (52)	596 (53)	<0.001	−182 (−286 to −79)	<0.001	48 (−58 to 158)	0.373
Mean protein, g	13.7 (1.0)	11.1 (1.7)	15.7 (1.5)	0.045	−2.6 (−6.0 to 0.8)	0.134	2.0 (−1.1 to 5.0)	0.206
Mean calcium, mg	136 (21)	155 (49)	172 (34)	0.580	18 (−78 to 115)	0.707	35 (−32 to 103)	0.301
Mean iron, mg	4.9 (0.3)	3.8 (0.6)	5.7 (0.6)	0.017	−1.1 (−2.3 to 0.1)	0.075	0.8 (−0.3 to 2.0)	0.138
Mean zinc, mg	4.7 (1.0)	4.2 (1.3)	6.5 (1.5)	0.228	−0.5 (−3.1 to 2.1)	0.689	1.8 (−1.1 to 4.7)	0.213
Vitamin A, μg	357 (61)	261 (75)	234 (74)	0.251	−96 (−245 to 52)	0.203	−123 (−270 to 0.24)	0.101
Vitamin C, mg	16 (2)	14 (3)	17 (4)	0.621	−2 (−7 to 3)	0.487	1.2 (−6 to 8)	0.733

*Huber–White Robust standard error. †Differences are mean values in intervention group – mean value in control group. CI, confidence interval; CSB, corn–soy blend; LNS, lipid-based nutrient supplement.

Our results are consistent with the findings of another study, also from Malawi, in underweight stunted children receiving either CSB or ready-to-use therapeutic food, another form of LNS (Maleta *et al*. 2004). This previous study reported a decrease of intake in non-supplement foods in children receiving CSB, but not in those receiving LNS resulting in a higher overall energy intake in the LNS group. This previous study, however, did not have a control group receiving no supplement, and our study shows that the groups supplemented with CSB reduces its energy intake from non-supplement foods compared with children receiving no supplement.

The selective effect of LNS on energy intake may be related to its energy density. All LNS have an energy density >500 kcal/100 g, which is considerably higher than for CSB, which is cooked with water and usually have an energy density of 100 kcal/100 g or less when given to the child. There is an abundant literature suggesting that high-energy density foods, and in particular fat foods, have a smaller suppressing effect on appetite than other foods (Rolls 2009; Rolls & Bell 1999).

Often, children in poor communities have low-energy intakes as a result of poor appetite, which has been attributed to insufficient intake of key nutrients such as zinc or potassium or magnesium (Golden 1991). The presence of such a mechanism cannot be ruled out in our sample, but it seems unlikely to explain the difference of energy intake between LNS and CSB, both supplements providing approximately the same amount of zinc, calcium, iron and vitamin

C. A difference of zinc absorption or a difference of intake in another nutrient cannot be ruled out, however.

While a recent study has shown that LNS has poor acceptability of LNS among malnourished children in South Asia (Ali *et al*. 2013), some studies in Africa have shown that LNS has an excellent acceptability by the children (Flax *et al*. 2009; Hess *et al*. 2011; Phuka *et al*. 2011;) and appears to have an appetising effect that could significantly induce higher energy intakes of the complementary (non-supplemented) food. With this, LNS would be able to deliver a high energy-dense diet to those in need of increased dietary energy intakes. However, as there are different cultural and behavioural factors that can affect the acceptability of an intervention in different settings, there is need to conduct some more studies in South Asia to determine acceptability of LNS in South Asia since it was the first acceptability trial to be conducted in that setting.

The higher energy intake in the LNS group suggests it should be preferred to CSB to supplement underweight children. The effect of LNS on recovery of underweight children compared with food supplements made from fortified flours is not clear, however (Patel *et al*. 2005; Phuka *et al*. 2009; Nackers *et al*. 2010). It is plausible that the increased energy intake observed in the LNS group is preferentially used for physical activity, and not for growth, which would minimise the impact on anthropometry of LNS compared with CSB.

In conclusion, our study suggests that both LNS and CSB are effective to increase intake of zinc calcium, iron and vitamin C, but that LNS seems superior to provide extra energy. While it is important to confirm these findings, LNS cannot be recommended compared with CSB in underweight children without clear evidence that it is superior to CSB in terms of anthropometric recovery or increased physical activity or other functional outcome.

Acknowledgements

We thank the study participants and the staff members of Lungwena Health Centre in Mangochi District for their positive attitude, support and help in all stages of the study; the data safety and monitoring board members (K Phiri, P Ndebele, T Heikens) for monitoring the trial.

Source of funding

Funding for our research came from the Academy of Finland (grant 109796). Chrissie Thakwalakwa was supported by a personal stipend from Nestlé Foundation and the St. Louis Nutrition Project. YBC was supported by the Singapore Ministry of Health's National Medical Research Council under its Clinician Scientist Award.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Contributions

All authors designed the trial, PA wrote the protocol and raised trial funding; CT was responsible for data collection; YBC designed the details of statistical analysis; and CT and JP did the analysis. CT wrote the first draft of the paper under the supervision of KM, PA and AB. All authors commented on the analysis and participated in writing of the paper. KM had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

Ali E., Zachariah R., Dahmane A., Van Den Boogaard W., Shams Z., Akter T. *et al*. (2013) Peanut-based ready-to-use therapeutic food: acceptability among malnourished children and community workers in Bangladesh. *Public Health Action* **3**, 128–135.

Binder D.A. (1983) On the variances of asymptotically normal estimators from complex surveys. *International Statistical Review* **51**, 279–292.

Dewey K.G. & Adu-Afarwuah S. (2008) Systemic review of the efficacy and effectiveness of complementary feeding interventions in developing countries. *Maternal and Child Nutrition* **4**, 24–85.

Ferguson E.L., Gibson R.S., Ounpuu S. & Sabry J.H. (1989) The validity of the 24-hour recall for estimating

the energy and selected nutrient intakes of a group of rural Malawian pre-school children. *Ecology of Food and Nutrition* **23**, 273–285.

Ferguson E.L., Gadowsky S.L., Huddle J.M., Cullinan T.R., Lehrfeld J. & Gibson R.S. (1995) An interactive 24 h recall technique for assessing the adequacy of trace mineral intakes of rural Malawian women, its advantages and limitations. *European Journal of Clinical Nutrition* **49**, 565–578.

Flax V.L., Thakwalakwa C., Phuka J., Ashorn U., Cheung Y.B., Maleta K. & Ashorn P. (2009) Malawian mothers' attitudes towards the use of two supplementary foods for moderately malnourished children. *Appetite* **53**, 195–202.

Golden M.H. (1991) The nature of nutritional deficiency in relation to growth failure and poverty. *Acta Paediatrica Scandinavica. Supplement* **374**, 95–110.

Hess S.Y., Bado L., Aaron G.J., Ouédraogo J.B., Zeilani M. & Brown K.H. (2011) Acceptability of zinc-fortified, lipid-based nutrient supplements (LNS) prepared for young children in Burkina Faso. *Maternal & Child Nutrition* **7**, 357–367.

Maleta K., Kuittinen J., Duggan M.B., Briend A., Manary M., Wales J. *et al*. (2004) Supplementary feeding of underweight, stunted Malawian children with ready-to-use food. *Journal of Pediatric Gastroenterology and Nutrition* **38**, 143–145.

Maleta K., Virtanen S.M., Espo M., Kulmala T. & Ashorn P. (2003a) Childhood malnutrition and its predictors in rural Malawi. *Paediatric and Perinatal Epidemiology* **17**, 384–390.

Maleta K., Virtanen S., Espo M., Kulmala T. & Ashorn P. (2003b) 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.

Nackers F., Broillet F., Oumarou D., Djibo A., Gaboulaufd V.B., Guerin P. *et al*. (2010) Effectiveness of ready-to-use therapeutic food compared to a corn/soy blend-based pre-mix for the treatment of childhood moderate acute malnutrition in Niger. *Journal of Tropical Pediatrics* **56**, 407–413.

Ndekha M., Kulmala T., Vaahtera M., Cullinan T., Salin M. & Ashorn P. (2000) Seasonal variation in the dietary sources of energy for pregnant women in Lungwena, Rural Malawi. *Ecology of Food and Nutrition* **38**, 605–622.

Pan American Health Organization/World Health Organization (PAHO/WHO) (2003) *Guiding Principles for Complementary Feeding of the Breastfed Child*. PAHO: Washington, DC.

Patel M.P., Sandige H.L., Ndekha M.J., Briend A., Ashorn P. & Manary M.J. (2005) Supplementary feeding with ready to use therapeutic food in Malawina children at risk of Malnutrition. *Journal of Health, Population, and Nutrition* **4**, 351–357.

Phuka J., Ashorn U., Ashorn P., Zeilani M., Cheung Y., Dewey K.G., Manary M. & Maleta K. (2011) Acceptability of three novel lipid-based nutrient supplements among Malawian infants and their caregivers. *Maternal and Child Nutrition* **7**, 368–377.

Phuka J., Thakwalakwa C., Maleta K., Cheung Y.B., Briend A., Manary M. & Ashorn P. (2009) Supplementary feeding with fortified spread among moderately underweight 6–18-month-old rural Malawian children. *Maternal and Child Nutrition* **2**, 159–170.

Rolls B.J. (2009) The relationship between dietary energy density and energy intake. *Physiology and Behavior* **97**, 609–615.

Rolls B.J. & Bell E.A. (1999) Intake of fat and carbohydrate: role of energy density. *European Journal of Clinical Nutrition* **53** (Suppl. 1), S166–S173.

Thakwalakwa C., Ashorn P., Phuka J., Cheung Y.B., Briend A., Puumalainen T. *et al*. (2010a) A lipid-based nutrient supplement but not corn–soy blend modestly increases weight gain among 6- to 18-month-old moderately underweight children in rural Malawi. *The Journal of Nutrition* **140**, 2008–2013.

Thakwalakwa C.M., Kuusipalo H.M., Maleta K.M., Phuka J.C., Ashorn P. & Cheung Y.B. (2010b) The validity of a structured interactive 24-hour recall in estimating energy and nutrient intakes in 15-month-old rural Malawian children. *Maternal and Child Nutrition* **8**, 380–389.