# 1 Introduction

*In this chapter the subject of the thesis is introduced and objectives are presented.*

Child malnutrition, more specifically undernutrition, results in considerable morbidity and, according to recent estimates, is responsible for 3.1 million child deaths annually (1). Furthermore, malnutrition can have long-term consequences on physical and mental development, which in turn affects school performance, income potential of the individual as well as productivity and economic development of countries (1).

Undernutrition can occur in the form of wasting (also referred to as acute malnutrition), stunting, micronutrient deficiencies and deficiency diseases. Nutrition programs in humanitarian emergencies usually focus on treatment of acute malnutrition, partly because it is associated with a high risk of mortality (2). Since different types of malnutrition can occur simultaneously, treatment of wasting may also have an impact on other types of malnutrition. Currently the moderate and severe form of acute malnutrition are treated separately, using different treatment products and protocols, in different programmes and by different organisations. While there is consensus regarding severe acute malnutrition (SAM) treatment, there are questions regarding the effectiveness of moderate acute malnutrition (MAM) programs in emergencies and which products with which composition should be used for treatment (3). In 2012 WHO published a proposed nutrient composition for supplementary foods for children with MAM but called for more research (4). While the body of evidence has grown in recent years, more high quality evidence is needed on the impact of different compositions of supplementary foods (4,5). Studies evaluating food supplements for management of MAM have mainly assessed anthropometric outcomes (6–14). Even though MAM is defined using anthropometric measurements and children are considered to have recovered from acute malnutrition once they reach a weight-for-height z-score (WHZ) $\geq$-2 or a mid-upper-arm circumference (MUAC) $\geq$125mm (15), they are then not necessarily well-nourished since micronutrient deficiencies and deficiency diseases, such as iron deficiency and resulting anaemia, may co-exist and persist after anthropometric recovery. It is therefore important to understand whether supplements provided for treatment of MAM also address these deficiencies and related diseases.

Anaemia, affects an estimated 71% of young children in west and central Africa (16) and has previously been shown to be common in children with MAM (17). Causes of anaemia include infectious diseases such as malaria, hemoglobinopathies and deficiencies of folate, vitamin $B_{12}$ or vitamin A or iron (18,19), where the latter is believed to be responsible for approximately 50% of anaemia cases (20). When evaluating the impact of interventions on MAM and anaemia, causes of anaemia, particularly the most common ones namely, iron deficiency (ID) and infection, should therefore also be investigated. Diagnosis of ID is however a challenge because biomarkers of iron status are affected by inflammation (18,21). In order to interpret biomarkers of iron status in the presence of inflammation it has been suggested to adjust measured concentrations for inflammation using correction factors or regression models (22,23). While the former approach has been used in a number of studies (17,23–29) the latter requires further investigation.

An understanding of the prevalence of infection and inflammation in children with MAM before and after treatment is important not only because it is a cause of anaemia or affects biomarkers of iron status, but also because it may affect response to treatment and because there are concerns about the safety of iron and micronutrient supplements (30–33). Yet, despite the important role infection plays in development and recovery from malnutrition only few studies have reported on morbidity in children with MAM (7–9,11,12,17,34) and most based only on symptom-recall. Recall data however is affected by reporting and recall bias (35,36) and it is unclear how this data relates to acute phase protein (APP) concentrations which are objective markers of inflammation. Furthermore, even asymptomatic children can have elevated levels of APPs (37,38) indicating the presence of subclinical inflammation, due to conditions that are not captured by patient history or even physical examination and which may affect nutrient absorption.

## 1.1 Objectives

The objectives of this PhD thesis were to:

- Describe morbidity and inflammation in children with MAM and to assess to what extent morbidity by maternal recall and physical examination explains the variation in markers of inflammation (Paper I)

- Explore the use of regression models to adjust biomarkers of iron status for the effect of inflammation in young children with MAM (Paper II)
- Investigate the impact of key factors in supplementary foods used for the treatment of MAM on anaemia, iron status and inflammation (Paper III)