Evidence Report/Technology Assessment
Number 72

Criteria for Determining Disability in Infants and Children: Failure to Thrive

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
2101 East Jefferson Street
Rockville, MD 20852
www.ahrq.gov

Contract No. 290-97-0019

Prepared by:
Tufts-New England Medical Center EPC, Boston, MA

Investigators
Ellen C. Perrin, MD, MA
Cynthia H. Cole, MD, MPH
Deborah A. Frank, MD
Stephan R. Glicken, MD
Nicholas Guerina, MD
Kevin Petit, MD
Robert Sege, MD, PhD
MaryAnn V. Volpe, MD

EPC Staff
Joseph Lau, MD, Director
Caroline A. McFadden, MD, /Priscilla Chew MPH, Project Leaders
Deirdre DeVine, M Litt, Project Manager
Kimberly Miller, BA, Research Assistant

AHRQ Publication No. 03-E020
March 2003

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Suggested Citation:
Perrin E, Frank D, Cole C, et al. Criteria for Determining Disability in Infants and Children: Failure to Thrive. Evidence Report/Technology Assessment No. 72 (Prepared by Tufts-New England Medical Center Evidence-based Practice Center under Contract No. 290-97-0019). AHRQ Publication No. 03-E020. Rockville, MD: Agency for Healthcare Research and Quality. March 2003.

Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome written comments on this evidence report. They may be sent to: Director, Center for Practice and Technology Assessment, Agency for Healthcare Research and Quality, 6010 Executive Blvd., Suite 300, Rockville, MD 20852.

Carolyn M. Clancy, M.D.
Director
Agency for Healthcare Research and Quality

Jean Slutsky, P.A., M.S.P.H.
Acting Director, Center for Practice and Technology Assessment
Agency for Healthcare Research and Quality

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Structured Abstract

Objectives. The evidence report provides a systematic review of the scientific evidence to answer the question of whether children, defined by investigators as failing to thrive or grow adequately, have a concurrent 'disability', or will have one within 6 months. The population of interest includes children age 18 years or younger, both male and female, of all racial, ethnic and socioeconomic groupings.

Search Strategy. Systematic searches were performed for relevant articles in MEDLINE® from 1966 through December 2000, with updates through September 2001. Additional studies were identified from other databases, reference lists of review and primary articles, and from domain experts**.** Since disability is not a specific medical condition that can readily be searched for, many studies with related concepts (i.e. medically definable impairments that are related to disability) were reviewed to identify potentially relevant studies. Search terms were textwords: failure to thrive, failure to grow, growth retardation, childhood malnutrition, protein-calorie malnutrition, starvation and psychosocial dwarfism

Selection Criteria. Eligibility criteria for study inclusion included: 1) published articles including at least one disability related outcome; 2) cross-sectional or longitudinal studies; 3) studies with at least two arms, one of which had a non-failure to thrive or healthy control group [added to control for potential confounders for any particular statistically significant outcome or covariate]; 4) studies conducted in either developed or developing countries. Studies of sample size of less than 10 subjects per arm, or those concerned primarily with particular diagnoses and conditions were excluded, as were studies published only as abstracts. Investigators' own definitions of failure to thrive were retained despite their resulting variability in inclusion criteria across studies.

Main Results. Including studies found from other sources, a total of 10,966 English language citations were identified. A total of 275 original studies were retrieved for careful evaluation. Detailed examination of these articles identified 52 publications comprising 43 studies that met inclusion criteria. Detailed data extraction was performed on these 43 studies.

Persistent disorders of growth. Overall these studies comparing children who were thriving with those who were undernourished in both developed and developing countries show that children with FTT have poorer growth in weight, height, and head growth, and that this poorer growth is often long-standing despite appropriate interventions. Earlier intervention leads to potentially better long-term outcome.

Associations of FTT with immunologic/infectious outcomes. The evidence that children with FTT have significantly greater susceptibility to infection is strong, with significant immunologic dysfunction and clinical infectious complications seen consistently across a variety of conditions. The laboratory markers of immunologic dysfunction were apparent in children with moderate severity. Only one study demonstrated improvement following immunologic intervention. Severe complications were most prevalent among the most severely malnourished children.

Disabilities related to child behavior associated with Failure to Thrive. The evidence identified by the search showed that children with failure to thrive concurrently exhibited a variety of behavioral disorders as well as at follow-up. The behavioral problems ranged from eating disorders, increased negative and decreased positive affective expression, to lower scores in communication and mood.

Developmental disorders associated with Failure to Thrive. FTT is associated consistently with depressed developmental test scores. In both clinical and epidemiological samples, FTT is associated on average with roughly 2/3 of a standard deviation decrease in developmental test scores. As a result, a greater proportion of children who are failing to thrive than children in a reference population will score in the supplemental security income (SSI) qualifying range for developmental delay.

Evidence that Failure to Thrive (FTT) is associated with other psychosocial and family factors. Compared to well-nourished peers, children with FTT were more likely to have had neonatal problems (jaundice, possible sepsis, and poor feeding, and family problems). There were no differences however in the incidence of prematurity, LBW, or maternal pregnancy complications.

Conclusions. The findings emphasize the importance of early and intensive intervention for children with poor growth velocity (FTT) so as to prevent permanent growth retardation. The evidence also supports the value of identification of children with growth failure as a marker for chronic and multiple acute infections. Children with a history of FTT were found to have clinically and statistically significant behavioral deficits and consistently depressed scores in cognitive, neurological, and psychomotor development. The increased risks for secondary disability generally persist in spite of intervention.

In summary, there is persuasive evidence that failure to thrive is associated with a range of organic and psychosocial difficulties and significant disability. Primary categories of associations include the child's age, socioeconomic factors (lower income, lower maternal education, less enriched family environment/interactions); neonatal morbidity; acute illnesses and hospitalizations; and neurological/anatomical abnormalities.

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Summary

Overview

The Social Security Administration (SSA) requested that the Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Center (EPC) program, provide a systematic review of the scientific evidence on whether children, defined by investigators as failing to thrive or grow adequately, have a concurrent disability, or will have one within 6 months. The population of interest includes children age 18 years or younger, both male and female, of all racial, ethnic, and socioeconomic groupings.

The evidence report was prepared to assist SSA in updating its *Listing of Impairments* and revising its disability policy, as may be appropriate.

Causes of Failure to Thrive

The underlying cause of failure to thrive (FTT) is always insufficient usable nutrition. This may occur when sufficient nutrients are not available to the child as a result of social or environmental causes that prevent parents from obtaining, preparing, or offering age-appropriate foods to the child. This growth failure often includes concurrent and potentially persistent disability. This syndrome of under-nutrition, previously termed "non-organic FTT" is recognized as a multifaceted disease. Because of this, the world's literature on the disabilities of poorly nourished children in developing as well as developed countries becomes relevant to the discussion of disability arising from FTT even in the United States.

In addition, almost any serious pediatric illness can result in FTT. There are three basic mechanisms for this phenomenon:
1) insufficient nutrition is available to the child because of the child's inability to feed properly, e.g., severe neurological dysfunction, gastroesophageal reflux, cleft palate; 2) nutrition is adequate but inadequately absorbed and/or utilized (malabsorption syndromes); or 3) the disease process creates added metabolic requirements, e.g., asthma, cardiac failure, thyroiditis. It is not uncommon for FTT to be the first clue to an active disease process which has not yet manifested itself in specific symptomatology.

Whatever its multidimensional causes, FTT affects growing children in many important ways. Severe malnutrition has been shown to cause permanent damage to various parts of the brain and central nervous system, leading to a range of disabilities manifested by aberrant behavioral, cognitive, language, and motor development. In addition, FTT is closely linked with infectious disease. Children who are undernourished (of which FTT is an indicator) consistently have been found to have significant and profound changes in cell-mediated immunity, complement levels, and opsonization that lead to susceptibility to various infections. FTT is also associated with disabilities in cardiac functioning, gastrointestinal conditions, persistently small stature, and other physiological derangements.

Reporting the Evidence

The key question posed by SSA was refined by the EPC Evidence Review Team and technical experts to review the association of five categories of disability with failure to thrive.

Key Question: Among children defined by investigators as failing to thrive or grow adequately, what evidence exists that they have, or will have within 6 months, a concurrent disability?

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The following associations between FTT and disability were investigated:

- Persistent disorders of growth following FTT
- Association of FTT with immunologic/infectious outcomes
- Child behavior associated with FTT
- Developmental disorders associated with FFT
- Association of FTT with other psychosocial and family factors

Methodology

Definition of Failure to Thrive

Most clinicians make a diagnosis of FTT when a child's growth in weight and/or in height fails to increase as expected for his or her age. Operationally this is frequently defined as a crossing of two or more standard percentile lines in a standard growth chart. Other clinicians use a definition of FTT that can be assessed without access to growth charts, or that can be assessed at a single point in time. These definitions include children who are persistently at or below the third or fifth percentile for weight, or less than the 80th percentile of median weight-for-height.

Other definitions used commonly in the professional literature include height-for-weight <3rd percentile; weight-for-age less than 3rd or 5th percentile or less than 80 percent of mean for age; weight-for-height <10th percentile; and weight-for-age less than 2 standard deviations below the mean for age. Because of inconsistent definitions it is hard to make comparisons among the various investigative approaches to this syndrome.

Current SSA guidelines consider FTT to be present when there is a fall in weight to below the 3rd percentile or to less than 75 percent of median weight-for-height or age in children under 2-years old. There must be no underlying medical disorder, and growth failure should last, or be expected to last, for at least 12 months.

Earlier research attempted to distinguish FTT that resulted from a known organic disease process from the more common circumstance in which the specific cause for the growth failure is unknown. This distinction is no longer considered useful. Instead, current data suggest that organic and non-organic causes and effects are intertwined in most affected children. This review therefore will not use the terms *organic* or *non-organic* FTT.

Literature Search

Disability is not a specific medical condition that can readily be searched for. Thus, we had to look at many studies with related concepts (i.e., medically definable impairments that are related to disability) to identify potentially relevant studies.

The main search consisted of a MEDLINE® search from 1966 through December 2000. A broadly sensitive, rather than specific, search strategy was employed to identify relevant studies. The search strategy used the following textwords: failure to thrive, failure to grow, growth retardation, childhood malnutrition, protein-calorie malnutrition, starvation and psychosocial dwarfism. Development of the search strategies was an iterative process that included input from domain experts. Keywords from known relevant studies were used to refine and focus the final search strategies used. Results were limited to studies in age-group under 18 and English language only. Various investigators defined the population of interest differently. We accepted whatever definition the investigator had used to identify children who were not growing as expected. We also inspected references from retrieved primary studies and relevant reviews, and consulted with technical experts and colleagues in order to identify additional studies.

Study Selection

Including studies found from other sources, a total of 10,486 English-language citations were identified in the initial search. An updated MEDLINE® search using the same search strategy was conducted in September 2001 which resulted in additional 480 abstracts.

Titles and abstracts were manually screened by physician members of the EPC and pediatricians to identify potentially relevant articles. Inclusion criteria for article selection were as follows: 1) published articles including at least one disability-related outcome; 2) cross-sectional or longitudinal studies; 3) studies with at least two arms, one of which had a non-FTT or healthy control group; and 4) studies conducted in either developed or developing countries. The third inclusion criteria was added to control for potential confounders for any particular statistically significant outcome or covariate. Studies of sample size of less than 10 subjects per arm, or those concerned primarily with particular diagnoses and conditions were excluded, as were studies published only as abstracts.

The mechanisms of undernutrition have been well-studied in developing countries. In addition, the associations of undernutrition and various outcomes such as cognitive and neurological development and infections are clearly delineated in these conditions. Because undernutrition as applied to developed countries may not be understood or studied as extensively, studies in developing countries were included to help correlate associations made.

Summarizing the Literature

A total of 275 original studies were retrieved for careful evaluation. Detailed examination of these articles identified 52 publications comprising 43 studies that met the inclusion criteria. Detailed data extraction was performed on these 43 studies. Their overall methodologic quality will be described individually below.

Findings

Persistent Disorders of Growth Following Failure to Thrive

Findings From Industrialized Nations. Seven studies compared anthropometric data of FTT patients with healthy comparison groups in developed countries. Most studies were performed in the United States or the United Kingdom, with one study from Israel. The majority of the studies were prospective-longitudinal, and two of the studies were ambidirectional blinded studies. Six out of seven of these studies show a statistically significant association between FTT and sub-optimal weight-for-height and weight-for-age. This growth retardation for the most part persists despite adequate correction of malnutrition. The clinical significance of this degree of growth retardation is not clear.

Findings From the Developing World. Seven studies compared anthropometric data of FTT patients with well-nourished control groups in developing countries. The studies in developing countries mainly compared children with marasmus and kwashiokor to healthy controls, mostly from outpatient settings, and six of the seven studies found similar associations. One study looked primarily at the effect of home visits on Jamaican children with FTT and found that height for age remained low in the FTT group, even with the intervention. The addition of more adequate nutritional supplementation to such children would be anticipated to aid in these improvements in outcome. Two other studies also showed significant differences in body fat and arm muscle composition in the FTT groups compared to controls; in one of the studies, the decreased body fat and muscle mass had a negative impact on physical performance.

Overall these studies comparing children who were thriving with those who were undernourished in both developed and developing countries show that children with FTT have poorer weight, height, and head growth, and that this poorer growth is often long-standing despite appropriate interventions. Earlier intervention leads to potentially better long-term outcomes. The fact that children who fail to thrive have poorer head growth is not surprising considering that human brain growth is tremendous in the early childhood years and insults during this time may impact permanently on developmental and intellectual outcome. These findings emphasize the importance of early and intensive intervention for children with, or at risk for, FTT so as to prevent permanent growth retardation.

Association of Failure to Thrive With Immunologic/Infectious Outcomes

A total of eight controlled studies were identified for review; four of these focused primarily upon aspects of immune function while four examined clinical infections among FTT children. Studies carried out in developing countries have variable generalizability for outcomes and policies in the United States.

Of the studies, seven were prospective cross-sectional studies and one study was retrospective. Only two studies were longitudinal; all others were cross-sectional. The principal source of potential bias involved the selection of controls. One study included adults as well as children in the controls; additionally, there were only controls (no FTT patients) entered from the children in an urban study center. The FTT and control groups in one study were from different hospitals serving different social-economic status (SES) populations; in another study controls included children with "nutritional growth retardation," likely comparable to the United States FTT population.

Studies comparing children who were thriving with those who were undernourished in both developed and developing countries show that children with FTT have such factors as significantly decreased chemotactic response to bacterial endotoxin as well as phagocytosis of zymogen particles; significantly lower percentages of rosette forming cells (a sensitive marker of cellular immune function); and reduced Candida killing ability. Studies comparing the same cohort of children also show that children with FTT have significantly greater evidence both clinically and in the laboratory of susceptibility to infection. These findings emphasize the importance of identifying children who are failing to grow normally since their growth failure may be a marker for a variety of chronic and multiple acute infections that would otherwise be hard to identify. In addition, treatment of FTT provides an opportunity to prevent the far more destructive consequences and costs associated with chronic infectious conditions in children.

Child Behavior Associated With Failure to Thrive

Fifteen studies examined the relationship between FTT and behavioral disorders. Evidence will be presented in three areas.

Evidence of Concurrent Feeding-Related Behavior Problems Associated With Failure to Thrive. Four studies noted concurrent feeding disorders in children diagnosed with FTT. Behavior problems were more common in children with FTT, even beyond those children who were known to be failing to grow on the basis of neurological or other organic damage or disease. Children had such factors as increased negative affect and decreased positive affect during feeding compared to controls, with no difference in non-feeding situations. Severity of malnutrition, but not presence of organic disease, was associated with affective outcomes. Also, parents reported more feeding problems during infancy for the FTT cases, and described their children as uninterested or poor eaters.

Evidence Suggesting Other Concurrent Behavioral Problems. Four studies examined behavior problems that were either diagnosed concurrently with diagnosis or within the ensuing weeks or months. These behavior problems were

related to evidence of insecure attachment, and problems with communication and with mood/affect. The FTT groups scored significantly lower than controls on reports describing affect and communication skills, matched for such factors as age, sex, and race.

Evidence Regarding Behavior Problems Detected in Followup After a Diagnosis of Failure to Thrive. Seven studies evaluated children with FTT for behavioral disorders. When compared to the controls, the index groups had significantly more family problems, poor psychological development, or behavioral deficits as measured by a variety of behavioral screening questionnaires or checklists used in the studies.

Developmental Disorders Associated With Failure to Thrive

FTT is consistently associated with evidence of neurologic disabilities. Insufficient intake of both macro- and micronutrients exerts diverse functional and structural effects on the nervous system, with effects particularly likely to persist if they occur during the vulnerable periods of most rapid development. Since FTT most often occurs in early life, during the period of most rapid postnatal brain development, developmental concomitants and lasting sequelae are to be expected. In addition, FTT appears to heighten developmental vulnerability to other adverse environmental factors. In addition, subtle neurologic deficits may interfere with the normal progression of feeding skills, even in the absence of clinically evident palsies. They contribute to FTT by interfering with the child's ability to take in adequate nutrients. We present data from three domains.

Oral Motor and Other Neurologic Findings

Five prospective, epidemiologic, and observational studies consistently noted increased rates of feeding difficulties in children with FTT with some investigators also noting clinically poorly specified "neurologic" findings other than in feeding skills. Since these studies are often based on parental report, it is difficult to disaggregate true subtle neurologic (either oral motor or sensory) deficits in feeding from parental perceptions and from learned behaviors. However, delays in acquisition of mature feeding skills are a consistent finding in every study where they have been assessed.

Developmental/Cognitive Impairments Concurrent With the Identification of Failure to Thrive

Historically, developmental delay was considered by some authors as one of the criteria necessary for a diagnosis of FTT in addition to growth failure. It is only in recent decades that children have been labeled as FTT on the basis of weight gain alone. Thus many older studies do not include children who are failing to thrive but developing normally. In addition it is difficult to mask testers to the differences in size between acutely underweight FTT children and normally growing comparison children of the same age. Therefore some experimenter effect cannot be ruled out in the studies summarized below.

There are three United States studies, two based on hospitalized children and the other on a sample not hospitalized but drawn from an outpatient inner city clinic (Mackner, Starr, Jr., and Black, 1997). In all three studies, the average Bayley Mental Development Index (MDI) scores were strikingly and significantly lower in children who had been identified with FTT compared to the control groups.

Two studies from the United Kingdom reported similar findings. Infants with FTT had scores that were significantly lower than controls on both the Bayley MDI (98.2 vs.108.5) and Psychomotor Development Index (PDI) (96.7 vs. 103.6). At 36 months, the Stanford Binet IQ scores were lower for children with FTT, 84.7 vs. 89.9 for non-FTT, $p < 0.007$.

Developmental/Cognitive Function in Later Childhood Among Survivors of Early Failure to Thrive

Four studies evaluated developmental/cognitive function in later childhood among survivors of early FTT. Three of the four were United Kingdom studies and one was a United States study. Two were ambidirectional longitudinal studies, one prospective longitudinal, and the fourth, an ambidirectional cross-sectional study. Two were of high quality, and two of low quality. In one study, children with a history of FTT were found to have clinically and statistically significant cognitive deficits. The remaining three studies found that FTT was associated with decreased cognitive, motor, or neurological measures compared to controls.

Summary

At the time of identification, FTT is associated with lower than expected developmental test scores, especially in clinically identified hospitalized children. However, even in samples identified epidemiologically rather than by clinicians, FTT is associated on average with roughly two-thirds of a standard deviation decrease in developmental test scores, so that many more FTT children will score in the Supplemental Security Income qualifying range of developmental delay than children in a reference population.

Association of Failure to Thrive With Other Psychosocial and Family Factors

Thirteen studies assessed diverse risks associated with FTT. These studies were from developed countries (eight from the United States, four from the United Kingdom, and one from Israel) and populations were highly comparable. Five studies were prospective longitudinal, three were prospective cross-sectional, two each were retrospective longitudinal or ambidirectional cross-sectional, and one, ambidirectional longitudinal.

There is persuasive evidence that FTT is associated with a variety of other difficulties that may themselves secondarily predict or cause significant disability. Categories of associations include socioeconomic factors (lower income, lower maternal education, less enriched family environment/interactions); neonatal morbidity; acute illnesses and hospitalizations; neurological/anatomical abnormalities; family dysfunction; and abuse/neglect. Clearly these factors may precede the infant's FTT and/or occur subsequent to it. These variables are almost certainly multiply interrelated and the directions of causation impossible to describe in a linear fashion (for example, poverty may be one factor that leads to malnutrition, which increases the risk of illness/disability, which leads to increased poverty).

Future Research

The studies comprising this report, though insufficient in number and variable in their methodologic quality and their potential biases, were of sufficient validity to provide significant information regarding the association of FTT with disability. The variety and long-term nature of the disabilities associated with FTT have major impact on the child, the family, and society.

Notwithstanding this, it may well be that the most significant finding of this review was the paucity of information available on the subject. Much remains to be learned regarding the extent and specifics of these associations and disabilities. Even more remains to be determined as to the optimal management of these patients.

The following recommendations for future research address specific problematic issues and limitations identified from review of existing research:

- One of the central problems in interpreting these studies was the heterogeneity of definitions of FTT. This variability in case definition makes it unclear how well the population at risk is being identified at present. Future research should apply a uniform definition of FTT. This would serve to facilitate comparison and perhaps even allow a meta-analysis of studies. It would also define more clearly the true prevalence of FTT.
- Within the definition of FTT, provisions should be made for categorization based upon 1) severity and 2) longevity or duration of growth failure. The data currently available indicate that both of these factors are strong predictors not only for the risk of associated disabilities but for potential response to therapy as well. Refining the classification of the FTT population in this way would facilitate identification of the relative risk of disability for an individual FTT child. It would also help in the evaluation of intervention studies.
- Although it is clear that the degree of disability increases with increasing severity of growth failure, this is an imprecise correlation especially in children with mild to moderate FTT. Since the majority of FTT that is seen in the United States tends not to be the most severe forms of marasmus and kwashiorkor, future research should specifically target those children with mild to moderate growth failure.
- Similarly, more research needs to be conducted in the United States or in developed countries with comparable social-economic structures and health care systems.
- Special emphasis should be given to outcomes focusing on neurodevelopmental and cognitive disorders. The data presented in this report indicate that this is likely one of the areas of strongest impact of FTT and certainly one with the greatest relevance for long-term disability. Specifically, very few studies have focused on the issue of FTT and brain growth during the immediate post-neonatal period and early infancy. This is one of the most critical periods for dendritic arborization, axonal myelination, and the development of cognitive functions. More studies are needed in this area.
- Further study is also needed on the association of FTT with general health outcomes because of their potential impact on the health care system. Beyond the risk to the individual child, the data linking FTT to increased risk of infections and poorer general health may have important implications at a broader level. Such data may help us understand the true "cost" of FTT and prove useful in evaluating intervention strategies.
- In order to better define the true nature and extent of the disabilities associated with FTT, more studies are needed that prospectively follow children for a sufficient duration to capture the more complex disabilities that may result from FTT.

A consistent finding among the studies reviewed was the ineffectiveness of existing intervention programs. Although strictly beyond the focus of this report, much work still needs to be done on developing effective treatment programs for children with FTT. Unfortunately, the optimal intervention will yet require better definition of the complex physical, medical, cognitive, and psychosocial problems associated with FTT.

Availability of the Full Report

The full evidence report from which this summary was taken was prepared for AHRQ by Tufts-New England Medical Center Evidence-based Practice Center under Contract No. 290-97-0019. It is expected to be available in spring 2003. At that time, printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling 800-358-9295. Requesters should ask for Evidence Report/Technology Assessment No. 72, *Criteria for Determining Disability in Infants and Children: Failure to Thrive.* Internet users will be able to access the report online through AHRQ's Web site at www.ahrq.gov.

AHRQ Pub. No. 03-E019
March 2003

ISSN 1530-440X

Evidence Report

Chapter 1. Introduction

The Social Security Administration (SSA) of the Department of Health and Human Services requested that the Agency for Healthcare Research and Quality, through its Evidence-based Practice Center (EPC) program produce an evidence report on the failure to thrive (FTT) syndrome. The purpose of this initiative is to assess evidence relating to the relationship between FTT and disability.

This is one of three reports requested by SSA in the broader topic of "Criteria for Determining Disability in Infants and Children." The evidence reports are prepared to assist the SSA in updating its *Listing of Impairments*, and revising its disability policy, as may be appropriate.

The syndrome of failure to thrive (FTT) is variously defined but in general terms it describes children who fail to maintain normal age and sex-adjusted growth parameters. FTT is not a diagnosis, but a syndrome that results from many different medical, social, or environmental processes. Children may fail to grow because they receive insufficient nutrients to sustain their caloric needs; because they fail to absorb and/or utilize the nutrients they take in; or because their caloric needs are excessive and thus the usual amount of nutrition is still insufficient for them to grow normally.

FTT sometimes reflects a systemic health condition or it may be a marker for some undiagnosed physiological derangement. In addition, FTT may itself exacerbate other unrelated conditions; and it can cause a variety of new health problems. We will address these various ramifications of growth failure in turn.

Definitions

Current SSA guidelines consider FTT to be present when there is a fall in weight to below the 3rd percentile or to less than 75% of median weight-for-height or age in children under two years old. There must be no underlying medical disorder, and growth failure should last, or be expected to last, for at least twelve months. These guidelines are to be updated and the purpose of this review of the literature was to generate an evidence base to assist the SSA in revising its disability policy with regard to children who are failing to thrive.

Most clinicians make a diagnosis of FTT when children's growth in weight and/or in height fails to increase as expected for their age. Operationally this is frequently defined as a crossing of two or more standard percentile lines in a standard growth chart. Other clinicians use a definition of FTT that can be assessed without access to growth charts, or that can be assessed at a single point in time. These definitions include children who are persistently at or below the third or fifth percentile for weight, or less than 80 percent of median weight-for-height or weight-for-age.

Other definitions are used commonly in the professional literature such as height-for-weight <3rd percentile; weight-for-age less than 3rd or 5th percentile or less than 80 percent of median for age; weight-for-height <10th percentile; and weight-for-age more than 2 standard deviations below the mean for age. Because of inconsistent definitions it is hard to make comparisons among the various investigative approaches to this syndrome.

Earlier research attempted to distinguish FTT that resulted from a known organic disease process from the more common circumstance in which the specific cause for the growth failure is unknown. This distinction is no longer considered useful. Instead, current data suggest that organic and non-organic

causes and effects are intertwined in most affected children. Therefore, this review will not use the terms *organic* or *non-organic* FTT. Parenthetically, the SSA definition is a reflection of an outdated conceptual model and should be reconsidered. It does not reflect the current thinking, which is that failure to thrive is a complex interaction of medical, nutritional developmental, and social factors which all can contribute to disability.

Depending on the definition used and demographics of the population sampled, the reported prevalence of FTT ranges from 1.3% to 20. 9% (Reilly and Skuse, 1994). Previous reports have estimated its prevalence among hospitalized children to be from 1 to 5% (Zenel, Jr., 1997). It is difficult to estimate the true prevalence of FTT due to the variety of diagnostic criteria used to identify it, and because most children are not hospitalized.

Cross sectional data from the developing world suggest that weight for age is a potent predictor of mortality, while height for age, which reflects duration of insult, correlates with developmental outcome (Wright, Ashenburg, and Whitaker, 1994). Further research is needed to define which criteria are the best predictors of medical and cognitive sequelae of FTT in the United States.

Causes and Effects of FTT

The underlying cause of FTT is always insufficient usable nutrition. This may occur when sufficient nutrients are not available to the child as a result of social or environmental causes that prevent parents from obtaining, preparing, or offering age-appropriate foods to the child. This growth failure often includes concurrent and potentially persistent disability. This syndrome of under-nutrition, previously termed "non-organic FTT" is recognized as a multifaceted disease. Because of this, the world's literature on the disabilities of poorly nourished children in developing as well as developed countries becomes relevant to the discussion of disability arising from FTT even in the USA.

In addition, almost any serious pediatric illness can result in FTT. There are three basic mechanisms for this phenomenon: (1) insufficient nutrition is available to the child because of the child's inability to feed properly, e.g. severe neurological dysfunction, gastroesophageal reflux; cleft palate; (2) nutrition is adequate but inadequately absorbed and/or utilized (malabsorption syndromes); or (3) the disease process creates added metabolic requirements, e.g. asthma, cardiac failure, thyroiditis. It is not uncommon for FTT to be the first clue to an active disease process, which has not yet manifested itself in specific symptomatology.

Whatever its multidimensional causes, FTT affects growing children in many important ways. Severe malnutrition has been shown to cause permanent structural aberrations in the central nervous system. Even mild malnutrition not sufficient to cause dramatic growth failure has been associated with aberrations in neural transmitters and CNS functions with the detectable impairments reflected in a range of disabilities. In addition, FTT is closely linked with infectious disease. Children who are undernourished (of which FTT is an indicator) consistently have been found to have significant and profound changes in cell-mediated immunity, complement levels, and opsonization (vi) that lead to susceptibility to various infections. FTT is associated with persistently small stature. Severe FTT are associated with multiple physiological derangement in cardiovascular and gastrointestinal functioning.

The review that follows attempts to determine the value of the symptom complex of FTT as a marker for basic physiological derangements that might otherwise be either undetectable or non-

existent. That is, we are interested in how often a child's failure to grow occurs prior to or coincident with another potentially disabling childhood condition. We do not consider the co-occurrence of FTT with known chronic health conditions that are already regarded as disabling e.g. cystic fibrosis, congenital heart disease, or celiac disease, although undernutrition is known to exacerbate the severity and course of these and other pediatric health conditions. The question that directed this review is: Among children defined by investigators as failing to thrive or to grow adequately, what evidence exists that they have a concurrent disability, or will have one within six months. The definition of disability used for this investigation is an operational one; "the presence of a medically determinable physical or mental impairment that causes marked and severe functional limitations and that is expected to last for 12 months or more".

Association of FTT with Immunological Functioning

Malnutrition severe enough to produce growth failure also impairs immuno-competence, particularly cell-mediated immunity, and diminishes production of complement and secretory IgA. Recurring otitis media, gastrointestinal and respiratory infections are more common among children who fail to thrive than among well-nourished children of the same age.

Children who are not thriving are often trapped in an infection-malnutrition cycle. With each illness, the child's appetite and nutrient intake decrease while nutrient requirements increase as a result of fever, diarrhea, and vomiting. In settings in which nutrient intake is already marginal, even when the child is well, cumulative nutritional deficits occur, leaving the child increasingly vulnerable to more severe and prolonged infections and even less adequate growth. Even in developed countries, malnourished children succumb more often than thriving children to fulminating infections. The more common syndrome of recurrent low-grade infections interferes with both physiologic and psychological processes of childhood.

Association of FTT with Neurological Functioning

Insufficient nutrition is associated with perturbations of neurotransmitters and impaired exploration and learning, even before growth is affected. By the time a child has experienced under-nutrition for a long enough period to be identified as "failing to thrive" there have been many "silent" episodes of impaired learning and interaction which cumulatively produces lasting disabilities in cognition and social behavior. Evidence from developing countries of the dire effects of protein-calorie malnutrition on intelligence and social behavior have shed light on the mechanisms that result in impairments at even far less extreme levels of malnutrition, such as those found in the US with alarmingly high prevalence.

These mechanisms account for the most significant persistent physiological derangement that is associated with FTT, namely that of central nervous system function. The majority of available data documents both delayed development and disordered behavior and affect in children at the time of diagnosis of FTT/malnutrition. This is particularly true of children who come to medical attention because of their growth failure, but also to a lesser extent of children identified only in epidemiologic surveys. The majority of studies of clinically diagnosed cases of FTT show reproducible developmental impairments. Various aspects of school achievement, memory, and attentional functions seem to suffer

lasting impairment. The effects on the CNS are both structural with impaired myelinization and dendritic arborization, and functional in terms of altered neurotransmitter synthesis.

Growth Abnormalities

Growth failure is the most obvious and persistent symptom and sequelae of FTT. Depending on the age of the child when growth failure occurred and the length of time it existed before it was corrected, short stature almost always persists even after the child is once again adequately nourished.

Other Associated Health Problems

Elevated lead levels correlate with impaired growth, even in the 5 to 35 mg/dl range. Here too, a negative cycle develops. Nutritional deficiencies of iron and calcium enhance the absorption of lead and other heavy metals. As lead levels rise, constipation, abdominal pain, and anorexia occur, leading to even less adequate dietary intake. In a recent study, 16% of children with FTT had lead levels high enough to warrant chelation.

Summary

Some of the disabilities created and/or maintained by malnutrition/FTT are restored with nutritional rehabilitation, such as immune, gastrointestinal, and cardiac function, and weight for height. On the other hand, other disabilities are permanent; there are persistent impairments in stature, cognition, attention, and behavior.

Chapter 2. Methodology

This evidence report is based on a systematic review of the literature. Several teleconferences were held with the science partner representatives from the Social Security Administration (SSA), the American Academy of Pediatrics (AAP), the internal technical experts from the EPC, and a representative of the Disability Law Center to refine and address the key question formulated by SSA. A comprehensive search of the medical literature was conducted to identify the evidence available to address the questions.

Detailed information about each study used in the systematic review was abstracted. The results are presented as detailed evidence tables. Information directly pertinent to answer each aspect of the key question is presented in summary tables with the Results chapter (Chapter 3).

Key Question Addressed in the Evidence Report

Current SSA guidelines consider FTT to be present when there is a fall in weight to below the 3rd percentile or to less than 75% of median weight-for-height or age in children under two years old. There must be no underlying medical disorder, and growth failure should last, or be expected to last, for at least twelve months. Disability is defined as the presence of a 'medically determinable physical or mental impairment' that causes 'marked and severe functional limitations' and that is expected to last for twelve months or more. In turn, a 'medically determinable impairment' is 'an impairment that results from anatomical, physiological, or psychological abnormalities which can be demonstrated by medical evidence consisting of signs, symptoms and laboratory findings' (Disability evaluation under Social Security. Social Security Administration, 1999)

SSA Functional limitations may occur in any of six areas of functioning: 1) acquiring and using information; 2) Attending and completing tasks; 3) Interaction with others; 4) Moving about and manipulating objects; 5) caring for oneself; and 6) health and physical well-being. Marked limitation in two areas or extreme limitation in one suffices to establish disability. These guidelines are to be updated and the purpose of this study question was to generate an evidence base to assist the SSA in revising its disability policy.

Following a series of teleconferences, science partners and EPC technical experts arrived at a consensus on the main study question as outlined below:

- *Among children defined by investigators as failing to thrive or grow adequately, what evidence exists that they have a concurrent disability (or will have one within six months)?*

For the purposes of this question, the SSA definition of disability was applied; however, the definition of FTT was expanded to include growth failure in children older than two years, with failure to grow at the expected rate, without reference to specific percentile height and weight cutoffs or underlying medical conditions. Duration of disability was to be at least six months.

Search Strategies

Disability is not a specific medical condition that can readily be searched for. Thus, we had to look at many studies with related concepts (i.e. medically definable impairments that are related to disability) to identify potentially relevant studies.

The main search consisted of a MEDLINE® search from 1966 through December 2000. A broadly sensitive, rather than specific search strategy was employed to identify relevant studies. The search strategy used the following textwords: failure to thrive, failure to grow, growth retardation, childhood malnutrition, protein-calorie malnutrition, starvation and psychosocial dwarfism. Results were limited to studies in age group under 18 and English language only. We also inspected references from retrieved primary studies, relevant reviews, and consulted with technical experts and colleagues in order to identify additional studies.

A total of 10,486 abstracts were identified in the initial search. An updated MEDLINE® search using the same search strategy was conducted in September 2001, which resulted in additional 480 abstracts.

Study Selection

Physician members of the EPC and pediatricians manually screened titles and abstracts to identify potentially relevant articles. Inclusion criteria for article selection were as follows: 1) published articles including at least one disability-related outcome; 2) cross-sectional or longitudinal studies; 3) studies with at least two arms, one of which had a non-failure to thrive or healthy control group; 4) studies conducted in either developed or developing countries. Studies of sample size of less than 10 subjects per arm or those concerned primarily with particular diagnoses and conditions were excluded, as were studies published only as abstracts. The third inclusion criterion was added to control for potential confounders for any particular statistically significant outcome or covariate.

The mechanisms of undernutrition have been well studied in developing countries. In addition, the associations of undernutrition and various outcomes such as cognitive and neurological development, and infections are clearly delineated in these conditions. Because undernutrition as applied to developed countries may not be understood or studied as extensively, studies in developing countries were included to help correlate associations made.

Covariates / Outcomes Considered

Disability-related concepts include mental or physical impairment that results from anatomical, physiological, or psychological abnormalities that can be shown by medically acceptable clinical and laboratory diagnostic techniques. A physical or mental impairment must be established by medical evidence consisting of signs, symptoms, and laboratory findings. The rational is to relate FTT with physical or mental impairment. There are factors that in turn may cause or modify the severity of the impairments. Listed below are factors or correlates explored in this evidence report.

Table 1. Outcomes and covariates studied

Outcomes	
Social/behavioral functioning	Neurological development
Infectious illnesses	Anthropometric, measurements
Cognitive development	
Covariates	
Perinatal –	Organic illness –
Tobacco	Congenital defects
Alcohol	Pulmonary
Cocaine	Cardiovascular
Infection	Gastrointestinal
Prematurity	Kidney
LBW	Neurological
Demographic –	Immunologic
Education	Infectious
Income	Endocrine
Health coverage	
Maternal IQ	
Quality of HOME Environment	
Age	
Gender	

Data Abstraction

The data abstraction form was developed as part of an iterative process involving the methodologic and domain experts. The form was designed to capture data from primary articles including study setting, demographic data on the study subjects as well as data on the family social-economic status (SES), inclusion/exclusion criteria, number of subjects, study design, funding source, relevant measurements and outcomes evaluated, statistical methodology, results, potential biases, and study quality.

As part of the data abstraction form development, domain experts performed data abstraction after a training period. Each pediatrician tested the form with two different articles and each article was extracted at least twice by different pediatricians. Because of the variation of data reporting by the primary articles, this process also served to validate the forms.

Data abstraction of each study was performed in duplicate, once by the pediatrician and once by an EPC methodologic staff. Discrepancies were resolved in a conference or by a third reviewer.

Reporting the Evidence

The evidence we found for the FTT is summarized in two complementary forms. The evidence tables provide detailed information about the feature of study design and results of all the studies reviewed. A narrative and tabular summary of the strength and quality of the evidence of each study are provided for each main outcome. In addition, the country in which the study was conducted was divided between two sets of tables categorized by developed and developing

countries. This is for the purpose of generalizability as conditions are more severe in developing countries and may not apply to the FTT populations in the United States. However, the outcomes can provide a parallel comparison to measure the strength of association.

Evidence Tables

Evidence tables were constructed for five different categories and grouped between developed and developing countries. The categories include cognitive & neurological development, behavioral problems, immunologic response or infectious diseases, anthropometrics, and other correlates/outcomes. They are presented under the Evidence Tables section of this evidence report:

Evidence Tables in the Report

Table Number	Table Content
Evidence Table 1	Studies associating anthropometrics with Failure to Thrive patients compared to healthy control subjects in developed countries
Evidence Table 2	Studies associating anthropometrics with malnourished patients compared to well-nourished control subjects in developing countries
Evidence Table 3	Studies associating immunologic response or infectious diseases with Failure to Thrive patients compared to healthy control subjects in developed countries
Evidence Table 4	Studies associating immunologic response or infectious diseases with malnourished patients compared to well-nourished control subjects in developing countries
Evidence Table 5	Studies associating behavioral problems with Failure to Thrive patients compared to healthy control subjects in developed countries
Evidence Table 6	Studies associating behavioral problems with malnourished patients compared to healthy control subjects in developing countries
Evidence Table 7	Studies associating cognitive & neurological development with Failure to Thrive patients compared to healthy control subjects in developed countries
Evidence Table 8	Studies associating cognitive & neurological development with malnourished patients compared to well-nourished control subjects in developing countries
Evidence Table 9	Studies associating other correlates / outcomes with Failure to Thrive patients compared to healthy control subjects in developed countries (miscellaneous)
Evidence Table 10	Studies associating other correlates / outcomes with malnourished patients compared to well-nourished control subjects in developing countries (miscellaneous)

Summary Tables

Summary tables were created to describe studies reviewed for each main topic. The tables describe the strength of the evidence according to six dimensions: study size, age at follow-up, duration of follow-up, study sample applicability, strength of association, and methodological quality. The study data on follow-up duration and age at enrollment were presented in a heterogeneous manner that required reporting of follow-up data to be approximated in some cases. When possible, follow-up time was calculated from the age of diagnoses of FTT or malnutrition. The summary tables are presented in Chapter 3 of this evidence report.

Summarizing the Evidence of Individual Studies

In order to answer the key questions, it was necessary to assess the strength of the available evidence. There is no current standard approach to assess the methodological quality and the reliability of these studies. In this report, we used the evidence-grading scheme described below.

Study Quality

Methodological quality (or internal validity) refers to the design, conduct, and reporting of the clinical study. Because studies with a variety of design types were evaluated, a three-level classification of study quality, used in previous reports, was modified:

- ● Least bias: Results are valid. A study that mostly adheres to the commonly held concepts of high quality, including the following: a formal study; prospective design, clear description of the population and setting; proper measurement techniques; appropriate statistical and analytic methods; no reporting errors; no obvious bias.

- ◉ Susceptible to some bias, but not sufficient to invalidate the results. A study that does not meet all the criteria of category A. It has some deficiencies but none likely to cause major bias.

- ○ Significant bias that may invalidate the results. A study with serious errors in design or reporting. These studies may have large amounts of missing information or discrepancies in reporting.

Applicability

Applicability (also known as generalizability or external validity) addresses the issue of whether the study population is sufficiently broad so that the results can be generalized to the population of interest at large. The study population is typically defined by the inclusion and exclusion criteria. The target population was defined to include patients with non-organic failure to thrive, except for studies that included a small subset of FTT deriving from possible or definite organic etiology. A designation for applicability was assigned to each article, according to a three-level scale.


Patients enrolled in the trial represent a broad spectrum of the population (high degree of applicability). Typically this would be a large study, although a large study in itself does not guarantee a high degree of generalizability.


The study included only a narrow/restricted study population, but the result is relevant to similar types of patient population (restricted applicability). Typically this would be a small study, but may also be a large study of a very homogeneous population.


Studied outlier population that is not immediately relevant to the study question (very limited direct applicability or not applicable), or where the study reported only limited information.

Results

Results are represented by proportions (percents), categorical variables, mean levels for continuous variables, and associations between study measures and children with FTT compared to children without FTT. Symbols indicate the type and significance of associations between study measures.

 or  Statistically significant association, ($p < .05$)

 Positive association

 No association

 Negative association or inverse relationship

Study Size

The study size is used as a measure of the weight of the evidence. Some studies have a high drop out rate due to lost to follow-up; we provide both the enrolled and evaluable number of patients, when these data are reported. A large study provides a more precise estimation of the treatment effect but does not automatically confer broad applicability unless the study included a broad spectrum of patients. Very small studies, taken individually, cannot achieve broad applicability. But several small studies that enrolled diverse populations, taken together, may have broad applicability. The study size is included as a separate dimension used to assist the assessment of applicability. For summarizing all studies, this would be the number of studies and the total number of patients in these studies.

Chapter 3. Results

A total of 275 original articles were reviewed, of which 52 publications comprising 43 studies met the criteria outlined in Chapter 2 and were assembled to provide the summary of results that follows. For the purposes of this summary, we will present the findings in categories of disability that were identified. Thus some articles will appear in more than one section if the investigators identified more than one type of disability in their sample. Categories of disability presented include (1) growth; (2) infectious/immunologic disorders; (3) behavioral disorders; (4) disorders of development; and (5) miscellaneous conditions.

Persistent disorders of growth following diagnosis of Failure to Thrive

Findings from Industrialized Nations

Most studies were performed in the United States, the United Kingdom, with one study from Israel. Six out of seven of these studies show a statistically significant association between failure to thrive and a risk of continued sub-optimal weight-for-height and weight-for-age. Of particular concern is the finding, in the majority of these studies, that this growth retardation persists despite adequate correction of malnutrition (Black and Krishnakumar, 1999; Corbett, Drewett, and Wright, 1996; Drewett, Corbett, and Wright, 1999; Kelleher, Casey, Bradley, et al., 1993; Mitchell, Gorrell, and Greenberg, 1980; Reif, Beler, Villa, et al., 1995).

Mitchell, Gorrell, and Greenberg (1980) showed that weight and head circumference were lower in children with FTT than in healthy controls at least until age 4-5 years (FTT 10-15% below controls for weight, $p<0.001$) and 10% below controls for head circumference ($p<0.05$). This was a longitudinal study on a US population in an outpatient clinical setting. The authors found no differences between controls and FTT groups for age, sex, mother's age/marital status, household composition, or maternal employment. Neonatal problems were more common in the FTT group, including evaluations for sepsis, poor sucking ability, mild neonatal jaundice but they were not thought to be a medically significant etiology for the FTT.

In an ambidirectional blinded study from the United Kingdom by Drewett, Corbett, and Wright (1999), children who failed to thrive from 1 to 5 years of age were smaller and had smaller head circumferences than their non-FTT counterparts at school age (median weight for FTT of 23.8 kg, IR 21.5 to 26.8 vs. controls 27.9 kg, IR 15.3 to 17.8). Black and Krishnakumar (1999), in a prospective, longitudinal study in the outpatient setting, demonstrated that despite catch up growth, weight and height for age were of significantly slower velocity in the FTT group compared to non-FTT controls. In another ambidirectional-longitudinal outpatient study by Reif, Beler, Villa, et al. (1995), mother's education level and family issues/living conditions were significant ($p<0.05$) covariants for long term recovery of weight and height in the FTT group.

Similar findings were shown in the prospective, longitudinal study by Haynes, Cutler, Gray, et al. (1984), where weight, head circumference and length were significantly lower in the FTT group, both on initial evaluation and at 6 month follow-up, despite an outpatient treatment program that included a case worker, visiting nurse, pediatrician and infant stimulation program, with 29/37 children not showing catch up growth in 6 months. Significantly, children diagnosed

and treated within the first 6 months of life were more likely to have improved growth outcomes. In their conclusion, the authors emphasized the need for more aggressive identification and more intensive intervention to reverse the altered growth patterns in these children.

Corbett, Drewett, and Wright (1996) extended the association of FTT with poor weight, height and developmental outcome one step further. This study was also an outpatient-based longitudinal 5-year follow up study. They identified a significant difference within the failure to thrive group with the severity of poor growth (weight and height) correlating with poorer developmental outcome.

Table 2. Studies of persistent anthropometric abnormalities following diagnosis of Failure to Thrive in developed countries

Author, Year, UI	Sample N	Age (mo) at assessment	Follow-up duration (mo)	Applicability	Internal validity	Correlates	Association
Mitchell, 1980 80166667	FTT 30 Ctrl 282	36-60	12-36	🚹 🚹	●	Weight(%) Height(%) Head circumference(%)	⬇ ⇔ ⬇
Haynes, 1984 84233543	FTT 50 [a] Ctrl 25	ND	6	🚹 🚹 🚹	O	Weight	⇩
Kelleher, 1993 93234174	FTT 180 Ctrl 591	12 & 24	12 & 24	🚹 🚹	O	Weight / age Height / length Head circumference	⬇
Reif, 1995 95362505	FTT 61 Ctrl 65	74.4 81.6	61.5	🚹 🚹 🚹	O	Weight(%) Height(%) Ideal weight(%)	⬇
Corbett, 1996 97113595	FTT 48 Ctrl 46	72-84	> 36[d]	🚹 🚹 🚹	●	Weight(SDS) Height(SDS)	⬇
Black, 1999 10064327	FTT 127 Ctrl 98	ND	> 60[d]	🚹 🚹 🚹	O	Weight Height	⬇
Drewett, 1999 99284054	FTT 107[b] Ctrl 117	84-96[c]	> 60[d]	🚹 🚹	O	Weight Height Head circumference	⬇

Ctrl, control; FTT, failure-to-thrive; MO, month; ND, no data; SDS, standard deviation score; UI, MEDLINE® unique identifier.
[a] 25 FTT had Lay Health Visitor intervention.
[b] 2 FTT and 9 Ctrl with definite medical condition affecting growth; 1 FTT and 2 Ctrl with possible medical condition affecting growth.
[c] Five were age 9 y, ND whether cases or controls.
[d] See Chapter 2 – Methods.

⬇ FTT associated with decreased anthropometric measures compared to controls, (statistically significant, $p < .05$).
⇩ FTT associated with decreased anthropometric measures compared to controls.
⇔ FTT *not* associated with difference in anthropometric measures compared to controls.

Findings from the Developing World

In addition to these findings from industrial nations, seven pertinent studies were identified in developing countries. The studies in developing countries mainly compared children with marasmus and kwashiokor to healthy controls, mostly from outpatient settings, (Branko 1979; Evans et al. 1980, Galler et al. 1985). Using ambidirectional/longitudinal and prospective longitudinal research design, the majority of the studies found similar associations between the diagnosis of FTT and long-term disorders of growth (Branko 1997; Galler et al. 1985; Alvear et al. 1986; Grantham-McGregor et al. 1982, 1987; Benefice 1992; Walker et al. 1996). Specifically, in the studies by Grantham-McGregor, Schofield, and Powell (1987) looked primarily at the effect of home visits on Jamaican children with FTT and found that height for age remained low in the FTT group, even with the intervention ($p<0.001$ for Height/Age 88% FTT, 101% control; Head Circumference/Age 91% FTT, 99% control). The addition of more adequate nutritional supplementation to such children would be anticipated to aid in these improvements in outcome. This is further supported in the study by Evans and colleagues (1980), where height and weight improvements ($p<0.01$ in treatment vs. control group) seen two years post nutritional intervention did not persist six to seven years after intervention. Two other studies also showed significant differences in body fat and arm muscle composition in the FTT groups compared to controls ($p<0.05$) (Alvear, Artaza, Vial, et al., 1986, arm fat area 73.5+/-15.3 and 64.5 +/-16.5 in FTT groups and 91+/-24.7 and 95.7 +/-28.5 in control groups) (Benefice, 1992, % body fat of arm muscle area 18.7+/-0.33 in FTT and 21.8 +/-0.47 in controls). In the study by Benefice (1992), the decreased body fat and muscle mass had a negative impact on physical performance.

Table 3. Studies of persistent anthropometrics abnormalities in malnourished cases in developing countries

Author, Year, UI	Sample N	Age (y) at assessment	Follow-up duration (y)	Applicability	Internal validity	Correlates	Association
Branko, 1979 79228898	Gp[a] 87 Ctrl 559	(5.5-14) (5-14)	7.5(2.5)	🧍	○	Height Weight Head circumference	⇩
Evans, 1980 81008912	Gp1 14 Gp2 14 Ctrl 26[b]	8.9(0.5) 13(1.9) 10.7, 12	2 & 6-7	🧍	●	Height Weight	⇧[f] ⇔[g]
Galler, 1985a 85241832	Gp[c] 108 Ctrl 107	9-15	6-12	🧍 🧍	○	Height Weight	⇩
Alvear, 1986 86185605	Gp 40[d] Ctrl 38	4-6	4[h]	🧍 🧍	○	Birth height Birth weight Arm fat area	⇓
						Bone age	⇔
Grantham-McGregor, 1987, 1982 82236679 87117313	Gp[e] 34 Ctrl 20	~7[i]	6	🧍 🧍	●	Height for age	⇓
						Weight for height	⇔

Author, Year, UI	Sample N	Age (y) at assessment	Follow-up duration (y)	Applicability	Internal validity	Correlates	Association
Bénéfice, 1992 92296639	Gp 64 Ctrl 34	9-14	NA[i]			Body fat Arm muscle	⬇
Walker, 1996 97154651	Gp[k] 122 Ctrl 32	7.7(0.4)	4			Height Weight Head circumference	⬇

Ctrl, control; Gp1, Marasmus; Gp2, Kwashiorkor; NA, Not applicable; UI, MEDLINE® unique identifier; Y, year.
[a] 2 groups collapsed into 1: 44 with marasmus, 43 with kwashiorkor.
[b] 3 control arms collapsed into 1: controls consist of 30 siblings, 30 yardmates of index cases, 90 High SES Whites.
[c] PEM Grade II – III.
[d] Cases hospitalized for PEM.
[e] 2 groups with severe PEM collapsed into 1: 18 had intervention, 16 had standard care.
[f] Assessment at 2 yr post-intervention for height & weight.
[g] Assessment at 6-7 year post-intervention for height & weight.
[h] After discharge.
[i] See Chapter 2 – Methods.
[j] Cross-sectional study.
[k] 5 study arms collapsed into 2: index group consists of 31 stunted cases with supplement intervention, 29 stunted cases with psychosocial intervention, 30 stunted cases with both interventions; control group – nonstunted.

⬆ Index cases associated with increased anthropometric measures compared to controls, (statistically significant, $p < .05$).
⬇ Index cases associated with decreased anthropometric measures compared to controls, (statistically significant, $p < .05$).
⇩ Index cases associated with decreased anthropometric measures compared to controls.
⇔ Index cases *not* associated with difference in anthropometric measures compared to controls.

Summary

Overall these studies comparing children who were thriving with those who were undernourished in both developed and developing countries show that children with FTT are at substantial risk for continued poor growth in weight, height, and head circumference, and that this growth disturbance is difficult to reverse despite appropriate interventions. The data also suggest that earlier diagnosis and intervention lead to potentially better long-term outcome. The fact that children who fail to thrive have poorer head growth is not surprising considering that human brain growth is tremendous in the early childhood years and insults during this time may impact permanently on developmental and intellectual outcome. These findings emphasize the importance of early and intensive intervention for children with or at risk for FTT so as to prevent permanent growth retardation.

Associations of FTT with Immunologic/Infectious Outcomes

Eight controlled studies were identified for review; four of these focused primarily upon aspects of immune function while four examined clinical infections among FTT children. Studies carried out in developing countries have variable generalizability for outcomes and policies in the United States. The studies conducted by Sherrod, O'Connor, Vietze, et al. (1984) in Tennessee, and by Carvalho Neves Forte, Martins Campos, and Carneiro Leao (1984) in Brazil involved infants and children with moderate degrees of malnutrition, similar to the patient

population in the USA. Studies by Ferguson, Lawlor, Jr., Neumann, et al. (1974) (Ghana) and Friedland (1992) (South Africa) included only cases of severe malnutrition, i.e., marasmus and kwashiorkor. The studies of Tuck, Burke, Gracey, et al. (1979), Neumann, Lawlor, Jr., Stiehm, et al. (1975), and Pandey and Chakraborty (1996) included more than one group of FTT children, graded by severity. Patients in the moderate malnutrition categories likely represent a reasonable comparison to the US population of FTT patients.

Seven studies were prospective and one study was retrospective. Only three studies (Ballard and Neumann, 1995; Pandey and Chakraborty, 1996; Sherrod, O'Connor, Vietze, et al. 1984) were longitudinal; all others were cross-sectional. The principal source of potential bias involved the selection of controls. Tuck, Burke, Gracey, et al. (1979) included adults as well as children in his controls; additionally, there were only controls (no FTT patients) entered from the children in the urban study center. The FTT and control groups in the study by Carvalho Neves Forte, Martins Campos, and Carneiro Leao (1984) were from different hospitals serving different SES populations. Friedland's (1992) controls included children with "nutritional growth retardation", likely comparable to the US FTT population; further specifics are not provided.

Evidence of Immunologic Dysfunction in Failure to Thrive

Multiple indicators of immunologic function and dysfunction have been used to try to understand the effects of malnutrition on children's response to infectious insults.

Carvalho Neves Forte, Martins Campos, and Carneiro Leao (1984) examined monocyte chemotaxis and phagocytosis in Brazilian children (6 months to 5 years) with moderate protein calorie malnutrition (PCM). Because these investigators were interested in immunologic functioning of children with moderate PCM rather than severe malnutrition, they recruited a sample of children whose weight for age was between the 25^{th} and 40^{th} percentile of standards for age. Compared to well nourished controls, patients with moderate PCM demonstrated significant decreases in chemotactic response to bacterial endotoxin, as well as phagocytosis of zymogen particles ($p < .001$). Serum complement levels were not different between groups, and the differences in chemotaxis and phagocytosis persisted whether cells were incubated with simple media, patient serum or pooled normal serum suggesting that the defect existed at the level of the cell receptor.

Ferguson, Lawlor, Jr., Neumann, et al. (1974), studied in vivo cell mediated immunity in 10 infants (ages 12-42 months) with severe PCM in Ghana (3 with marasmus, 7 with kwahiorkor) compared to 10 age matched controls. Although total lymphocyte counts were similar in the two groups, PCM infants had significantly lower percentages of rosette forming cells (RFC), a sensitive marker of cellular immune function; 16.6 percent $\pm$ 2.7 vs. 64.5 percent $\pm$ 1.0 ($p<0.001$). PCM infants also manifested a higher incidence of negative skin hypersensitivity responses to monilia and SK/SD; no analysis is provided regarding the significance of this trend. Repeat studies on five of the malnourished infants following nutritional therapy with high protein diet showed reversion to normal for both the skin delayed hypersensitivity response and the percentage of RFC's.

Tuck, Burke, Gracey, et al. (1979) studied candidacidal activity of leukocytes in three groups of children in Indonesia as well as both urban and rural Australia: Controls (>80 percent standard weight for age (SWFA)); moderate under-nutrition (60-80 percent SWFA); and marasmus (<60 percent SWFA). Both under-nourished and marasmic children demonstrated reduced Candida killing ability (17.6 percent and 13.7 percent respectively) compared to controls (44.5 percent;

p< .001 for comparison of each malnourished group to controls). The candidacidal activity of leukocytes was not improved by addition of normal serum, suggesting, as does the study by Carvalho Neves Forte, Martins Campos, and Carneiro Leao (1984), that there is a primary cellular defect in leukocyte function. No population demographics are provided, including the age of patients and controls, which makes for some difficulty in interpretation and concern about potential bias. Controls included both adults and children; the authors note that candidacidal activity is known not to be age-related, with no difference between healthy, well nourished children and adults.

Neumann, Lawlor, Jr., Stiehm, et al. (1975), examined markers of immunologic dysfunction along with clinical correlates of infection in children ages 6 months to 6 years in Ghana. Three groups of children were compared: Group I, severe malnutrition (50-60 percent weight for age with low serum albumin); Group 2, moderate malnutrition (61-80 percent weight for age with normal serum albumin); and Group 3, well nourished controls (>81 percent weight for age with normal serum albumin). Delayed hypersensitivity skin test response to PHA, monilia and SK-SD were significantly decreased in both malnourished groups compared to controls. Forty-four percent of children with severe malnutrition and 29 percent of those with moderate malnutrition were non-responders to PHA, compared to only 5 percent for controls. In addition, malnourished responders manifested significantly smaller areas of induration. Lymphocyte response to PHA tested in vitro was significantly less in both malnourished groups and absolute lymphocyte counts were significantly lower in the severely malnourished group (all significance at p<.05). Immunoglobulin and complement levels, as well as antibody response to KLH (keyhole limpit hemocyanin) and PPS (pneumococcal polysaccharide) were similar among all three groups.

Tonsil size was reduced in Group 1 compared to Group 2 and Group 3; with 36 percent demonstrating trace or absent tonsil tissue compared with 5 percent of group 2 and none of the control group 3. Clinical infections, particularly pneumonia and fungal skin infections were more frequent in severely malnourished children.

Clinical Infections in Failure to Thrive

Friedland (1992) conducted a large prospective study of FTT infants (median 11 months, range 2-84 months) in South Africa. One thousand five hundred eighty two FTT children (792 with kwashiorkor, 513 with marasmus, and 277 with marasmic kwashiorkor), all of whom were hospitalized specifically for their malnutrition, were compared to 7282 controls hospitalized for other reasons. Controls included both well nourished and "nutritionally growth retarded"; no specifics are provided regarding the percentage of the controls with nutritional growth retardation or the degree of growth retardation present.

Bacteremia, whether compared as total cases, or by subsets of community acquired and hospital acquired cases, was consistently more common among the FTT population. The overall incidence of bacteremia was 9.9 percent for the FTT children vs. 6.0 percent of controls (p<0.001). Furthermore, the mortality among bacteremic patients was also significantly greater among FTT cases (FTT 31 percent vs. controls 13 percent; p<0.001). Therefore, both the risk of bacteremia and subsequent mortality from bacteremia are significantly associated with FTT.

Sherrod, O'Connor, Vietze, et al. (1984) found a 4-fold increase in "bacterial or viral infections such as URI or mumps" among American infants aged 0 to 3 months with non-organic failure to thrive compared to controls (p<.05, Evidence Table 3). FTT was defined as weight gain falling below two-thirds of the Harvard fiftieth percentile growth curve.

Ballard and Neumann (1995) conducted a prospective cohort study of 200 children in Kenya, age 14-25 months. Children were followed for development of acute lower respiratory infections (ALRI) for up to 12 months. Symptom checklists were completed based on parental report at weekly visits. FTT, either low weight for age or low height for age, was a strong predictor of development of ALRI. Height for age < 90 percent of the median had the strongest correlation, with a relative risk of 4.5 vs. non-FTT (95 percent CI 1.1-17.4). The fact that height for age was a stronger predictor than weight for age suggests that chronicity of malnutrition has a greater impact upon immune function and risk of infection than does acute malnutrition.

Pandey and Chakraborty (1996) followed a cohort of 200 Indian children, documenting episodes of acute respiratory infections (ARI). Malnutrition was graded based on weight for age. The number of ARI episodes per child was significantly greater in FTT children than controls (6.6 episodes/year vs. 4.8 episodes /year; $p<0.05$). Furthermore, there was a stepwise increase from grade I (mild malnutrition; 5.6 episodes/year) to grade IV (severe malnutrition (7.7 episodes/year; $p<.05$, chi-square) (Evidence Table 4).

In summary, studies comparing children who are thriving with those who were undernourished in both developed and developing countries show that children with FTT have significant pertubrations in immunologic function, and a corresponding increased susceptibility to clinical infection. These findings emphasize the importance of identifying children who are failing to grow normally since their growth failure may put them at additional risk for a variety of acute and chronic infections that might not necessarily be appreciated. In addition, treatment of FTT provides an opportunity to prevent the additional consequences and costs associated with chronic infectious conditions in children.

Table 4. Studies with associations of immunologic dysfunction or infectious diseases to Failure to Thrive & healthy comparison groups in developed countries

Author, Year, UI	Sample N	Age (mo) at assessment	Follow-up duration (mo)	Applicability	Internal validity	Correlates / outcomes	Association
Carvalho, 1984 85145406	FTT 20[a] Ctrl 40	6-60	NA[b]			Immune function • Phagocytic responses • Chemotactic function • Complement levels	⬇ ⬇ ⇔
Sherrod, 1984 85026403	FTT 31 Ctrl 24	ND	36			Infections	⬆

Ctrl, control; FTT, failure-to-thrive; Mo, month; NA, not applicable; UI, Medline® unique identifier.
[a] Cases diagnosed with moderate & chronic primary protein-calorie malnutrition.
[b] Cross-sectional study.

⬆ FTT associated with increased incidence of infectious diseases compared to controls, (statistically significant, $p < .05$).
⇔ FTT *not* associated with increased incidence of immunologic response or infectious diseases.
⬇ FTT associated with decreased immunologic response.

Table 5. Studies with associations of immunologic dysfunction or infectious diseases and malnourished cases compared to well-nourished controls in developing countries

Author, Year, UI	Sample N	Age (y) at assessment	Follow-up duration (y)	Applicability	Internal validity	Correlates	Association
Ferguson, 1974 75022280	Gp[a] 10 Ctrl 10	28.9 38.8	NA[b]	🧍	⭕	Rosette forming cells	⬇
Neumann, 1975 75106463	Gp1[c] 34 Gp2 42 Ctrl 41	6 m – 6 y	NA[b]	🧍🧍	⭕	Clinical infections	⇧
						Parasites	⇔
						Delayed hypersensitivity response	⬇
Tuck, 1979 79254720	Gp1[d] 21 Gp2 23 Ctrl 25	ND	NA[b]	🧍🧍	○	Candida killing Capacity	⬇
Friedland, 1992 93159117	Gp[e] 11 Ctrl 12	11 m 12 m	NA[b]	🧍	●	Bacteremia Nosocomial Bacteremia	⬆
Ballard, 1995 95239862	Gp1[f] 27 Gp2 51 Ctrl 31	2.5 - 3	1	🧍🧍	●	Acute lower respiratory infections	⬆
Pandey, 1996 97246349	Grl-IV 115 Ctrl 85	1 - 6	1	🧍	⭕	Acute respiratory Infections	⬆

Ctrl, control; Gp, group; M, month(s); NA, Not applicable; UI, Medline® unique identifier; Y, year.
[a] Severe protein-calorie malnutrition.
[b] Cross-sectional study.
[c] Gp1 - Severely malnourished: kwashiorkor (23) & marasmus (11); Gp2 – moderately malnourished.
d Gp1 - marasmus; Gp2 – "underweight".
[e] Kwashiorkor, maramus, marasmic kwashiorkor.
[f] Gp1 – Moderate & severe kwashiorkor Gp2 – Mild malnutrition.

⬆ Index cases associated with increased incidence of infectious diseases compared to controls, (statistically significant, $p < .05$).
⇧ Index cases associated with increased incidence of infectious diseases compared to controls
⇔ Index cases *not* associated with increased incidence of immunologic or infectious disease response.
⬇ Index cases associated with decreased immunologic response, (statistically significant, $p < .05$).

Child Behavior Problems Associated with Failure to Thrive

Systematic assessment of children's behavior (usually by parent report) was a part of about one-third of the studies reviewed. The specific aspects of behavior assessed, and the instruments used to quantify these difficulties, are disparate and not easily comparable. Therefore we will present descriptive information summarizing the conclusions of the sixteen investigators who addressed behavioral difficulties as a part of their analyses. Evidence will be presented in three areas:

- concurrent feeding-related behavior problems associated with FTT
- other concurrent behavioral problems
- behavior problems detected in follow-up subsequent to the diagnosis of FTT.

Evidence of Concurrent Feeding-Related Behavior Problems Associated with FTT

Feeding is a critical self help skill that develops during infancy and toddlerhood. Inability to self-feed in toddlers or inability to be cooperative with caretaker feeding during infancy is a functional impairment in caring for oneself and in maintaining health and physical well-being. Depending on degree, disorders of feeding may result in either marked or severe functional limitation, thus contributing to or establishing disability.

Four controlled studies noted concurrent feeding disorders in children diagnosed with FTT. These studies varied in their definitions of eating disorders, and will be reviewed individually. One study grouped feeding behaviors with other behavior disorders, one study observed infant affect during feeding, one observed feeding behavior directly, and the fourth used maternal recall of feeding behavior. Regardless of methodology used, significant feeding-related issues were more frequently in infants with failure-to-thrive than in control infants.

In the first relevant study, 19 FTT children and age/sex-matched controls were evaluated over several weeks to determine incidence of feeding, autoerotic and self-harming behaviors by Pollitt and Eichler (1976). Children with mean age of 33 months were enrolled in an outpatient clinic. Controls were matched for age, sex, and race. Children with already-identified birth complications, physical disability, brain damage or "organic growth retardation" were excluded. Thus the group called “FTT” were those for whom no medical cause for the FTT had been identified. Behavior was assessed by interview and direct observations at home. Of particular interest/attention were the child’s response to food, mood while eating, and the presence of polydipsia, pica, and hiding food. Eating behavior was rated by observers on a 4-point scale created by the investigators. Information was collected also about autoerotic and self-harming behaviors. Overall, 10 children with FTT exhibited abnormal eating behavior determined over weekly interviews conducted for 7-11 weeks, compared to matched controls. These data demonstrate that eating behavior is more problematic in children with FTT, than in children growing normally.

Polan, Leon, Kaplan, et al. (1991) reported a small masked study of affective expression in 6-36 month old children born appropriate for gestational age (AGA) at 35 weeks or older in US with (28) and without (14) FTT in feeding and non-feeding situation. The Kiddie Affect Inventory and Assessment, which reports four channels of emotion - facial display pattern, vocalization, gesture, body position and movement was used. FTT was associated with increased negative affect and decreased positive affect during feeding compared to controls, with no difference in non-feeding situations. Severity of malnutrition, but not presence of organic disease, was associated with affective outcomes.

A community-based cohort of children at 15 months of age was identified through medical records from two Israeli communities by Wilensky, Ginsberg, Altman, et al. (1996). A subgroup of 50 diagnosed cases of FTT was assessed along with 50 matched controls. A maternal questionnaire was developed to assess feeding behavior. Feeding problems included both behavioral (e.g. turned head from food, spits out food) and affective items (e.g. shows pleasure at

meals). The results demonstrated significantly more feeding problems among FTT children compared with controls.

A population-based study in Newcastle, England utilized a screening program to identify one hundred twenty cases of FTT during the two-year enrollment period. Wright and Birks (2000) reported on ninety-seven FTT cases who had complete data and 28 controls identified from 3 general practices. FTT cases were reported to start solid foods later than controls, 3.89 months versus 3.04 months ($p = .003$), as well as being delayed in starting finger foods, at 7.15 months versus 6.14 months ($p = .005$). The clinical importance of these small differences is unclear. However, there were more parent-reported feeding problems during infancy for the FTT cases, 28 percent versus 2 percent for the controls ($p = .022$). Parents of FTT children more often described their children as uninterested or poor eaters (FTT 11 vs. Controls 0, $p = .003$).

Evidence Suggesting Concurrent Behavioral Problems Associated with FTT

This section reviews concurrent or nearly-concurrent behavioral problems associated with failure-to thrive. Four controlled studies examined behavior problems that were either diagnosed concurrently with diagnosis or within six months. Because each study established its own definition of behavioral disorder, the studies are reviewed individually rather than combined. Three of the four studies found an increase in attachment disorders or other early childhood behavior disorders in infants and toddlers with diagnosed FTT. These disorders all comprise functional limitations in interacting or relating to others, which may be marked or severe in individual cases, and would contribute to or establish disability.

Hutcheson, Black, and Starr, Jr. (1993) observed the behaviors of thirty-four children with FTT and matched comparison children with their mothers during feeding. The children were divided into two age groups, infants (age 8 – 13.4 months), and toddlers (age 13.5 – 24 months). Controls were matched based on age, sex and race. Parenting functioning, child functioning, and contextual sources of stress and support were assessed, using the Infant Characteristics Questionnaire. Mothers of younger children reported a greater level of difficulty in caretaking. No other age or group differences were found on parenting stress, informal support, life events, and negative affectivity.

Chatoor, Ganiban, Colin, et al. (1998) studied three groups of toddlers from various ethnic and economic classes based on diagnosis of infant anorexia (n=33), picky eaters (n=34), and healthy eaters (n=34). The study examined attachment and security level in the three groups, using the Ainsworth and Cassidy & Marvin attachment classification systems. Most of the children were evaluated as 'secure', but the frequency of insecure attachments was significantly related to diagnostic group, $\chi^2 = 8.0$, $p < .05$. There was a greater frequency of insecure attachments in infants with anorexia compared to picky eaters, or compared to healthy eaters $\chi^2 = 6.7$, $p < .0$ and $\chi^2 = 3.9$, $p < .05$, respectively. A nine point Likert scale was used to assess the degree of attachment security. The infants with anorexia obtained the lowest score of 4.9 while picky eaters and healthy eaters scored 6.0 and 6.1 respectively. There was a main effect for the group, $F = 5.8$, $p < .01$, and a positive correlation between ideal weight and attachment security, $r = 0.31$, $p < 01$ (Evidence Table 5).

Steward, Moser, and Ryan-Wenger (2001) evaluated 14 children with FTT compared to 14 controls matched for age, sex and race. They evaluated behavioral responsiveness of the infant using the Parent-Child Early Relational Assessment Scale. The FTT group scored significantly

lower on the communication subscale (FTT 3.19 vs. Control 4.07). During interactions with their mothers, they had less visual contact, more gaze aversion, and vocalized less than controls. They also scored lower than controls on the mood subscale, as they were more irritable and apathetic (FTT 3.65 vs. Control 4.26).

Skuse, Pickles, Wolke, et al. (1994) is a population study in south London of low SES infants. Forty-seven FTT cases identified and matched forty-seven controls were assessed at approximately 15 months of age. Using the Tester's Rating of Infant Behavior instrument, no significant differences were found between the groups for expression of positive affect, task directed behavior, and task persistence.

Evidence Regarding Behavior Problems Detected in Follow-up

Galler, Ramsey, Solimano, et al. (1983b) compared 129 Barbadian children with FTT prior to 1 year old with matched controls. Assessments were conducted at age 60-132 months. Behavioral disorders and the presence of ADD were measured using study-specific instruments. Classroom behavior problems were noted more frequently in children with a history of FTT during infancy.

Mitchell, Gorrell, and Greenberg (1980) reviewed the medical records and prospectively followed a cohort of three hundred and twelve children ages two to five years from three rural primary care centers. A majority of families received government insurance; 70 percent were black. Thirty children were defined as FTT based on weight below 80 percent of normal recorded during first 24 months of age. Compared to the remaining controls, the index group had significantly more family problems and neonatal abnormalities such as poor suckling, jaundice, and suspected sepsis, $p < .01$ and $p < .05$, respectively. Behavioral evaluation was conducted at a follow-up visit conducted at age 3-6 years, using a behavioral problems questionnaire and the McCarthy Scale of Children's abilities. Children with FTT had more behavioral problems reported and scored lower on intelligence tests (Evidence Table 5).

Drotar and Sturm (1992) evaluated preschool American children with FTT in a comparison trial of three different interventions involving varying degrees of psychosocial support. The scores of the three FTT groups (N= 48) were pooled and compared to healthy controls (N-47). Children were enrolled at age 3 and assessed at age 5. Comparisons were based on use of the California Child Q-set to assess their personality development, the Lock Box to measure organization in problem-solving, and the Child Behavior Checklist (CBCL) to assess problem behaviors. Results showed poor psychosocial development in the five-year-olds who had a history of FTT as infants. Scores in ego resiliency and behavioral organization were lower for the FTT group compared to controls; 376.06 versus 397.37, $p < .05$, and .95 versus 8.45, $p < .01$, respectively. The incidence of behavioral problems on the CBCL was also significantly higher for the index group compared to the controls, 58.5 versus 53.2, $p < .05$. There was no difference in ego control.

A cohort of inner city British white children who were born in 1980 were identified from medical records. Puckering, Pickles, Skuse, et al. (1995) reported on those diagnosed with FTT based on height and weight below 10th percentile compared with control children who were matched on the basis of sex, birth weight, and ethnic origin. Children with a history of FTT were found to have clinically and statistically significant behavioral deficits using the Behaviour Screening Questionnaire, 8.7 versus 6.9 for controls. These observed deficits did not appear to result from parenting practices or other environmental influences.

The study by Kerr, Black, and Krishnakumar (2000) is a follow-up of children 6 years of age from an earlier study (Mackner, Starr, Jr., and Black, 1997) consisting of two initial samples, FTT and adequately nourished children. History of maltreatment was based on at least one report to the Child Protective Services and was not part of the initial recruitment criteria. There was no effort to discern maltreatment in children not reported. Though it was reported that "most children had recovered" from FTT, there were no specific data provided. Three percent of the FTT sample persisted with weight for height below the 5th percentile. The one hundred ninety three, mainly poor, mostly African American inner-city children were divided into four risk factor groups; FTT (n=64), FTT with history of maltreatment (n=28), history of maltreatment alone (n=21), and neither risk factor (n=80). Behavior problems were documented by teacher reports of adaptive functioning at school and the Teacher Report Form; children's behavior at home was measured by the Child Behavior Checklist. Analyses of covariance showed main effects for risk status for all behavioral outcomes, $p < 0.01$. Analyses revealed statistical significance between the FTT and maltreatment versus the neither risk factor groups for adaptive functioning and school behavior, $p < 0.05$ (Evidence Table 5).

Corbett, Drewett, and Wright (1996) identified from records from a clinic serving a predominant low income, white population of Newcastle, 52 cases and 52 controls. The five-year follow-up for 48 FTT children and 46 controls found a trend towards behavior problems as measured by Child Behavior Checklist, $p < 0.296$ (Evidence Table 5).

The Kelleher, Casey, Bradley, et al. (1993) study, which followed a large cohort of low birth weight infants, assessed 180 who developed FTT. Though there were no significant differences between the 180 FTT cases and 591 nonFTT as measured by the Bates Temperamental Scale at 12 months, there was a trend for more behavior problems as measured by the Child Behavior Checklist at 24 months.

Table 6. Studies with association of behavioral correlates to Failure to Thrive compared to healthy comparison groups in developed and developing countries

Author, Year, UI	Sample N	Age (mo) at assessment	Follow-up duration (mo)	Applicability	Internal validity	Correlates / outcomes	Association
Pollitt, 1976 76109110	FTT 19 Ctrl 19	> 33[a] > 34	7-11 wk	🚹 🚹	⭘	Eating disorder; Autoerotic & self-harm	⬆
Mitchell, 1980 80166667	FTT 30 Ctrl 282	36-60	12-36	🚹 🚹 🚹	●	Behavior problems	⇧
Galler, 1983b 83136863	Gp 129 Ctrl 129	60-132	48-120	🚹 🚹	⭘	Classroom behavior	⬆
Polan, 1991 92098539	FTT 28 Ctrl 14	16.7[b] 18.9	NA[c]	🚹 🚹	⭘	Positive affect during feeding Negative affect during feeding	⬇ ⬆
Drotar, 1992 92372721	FTT 48 Ctrl 47	36	> 24[a]	🚹 🚹 🚹	⭘	Personality development Behavioral organization Behavioral problems	⬆

Author, Year, UI	Sample N	Age (mo) at assessment	Follow-up duration (mo)	Applicability	Internal validity	Correlates / outcomes	Association
Hutcheson, 1993 94015754	FTT 34 Ctrl 34	15.0[b] 14.9	NA[c]	🧍 🧍 🧍	⭘	Child temperament	⬆
Kelleher, 1993 93234174	FTT 180 Ctrl 591	12 & 24	12 & 24	🧍 🧍	⭘	Behavioral disorder	⇧
Skuse, 1994 94253258	FTT 47 Ctrl 47	14.6[b] 14.2	ND	🧍 🧍 🧍	●	Behavior Assessment	⇔
Puckering, 1995 95378341	FTT 23 Ctrl 23	48	> 12[a]	🧍 🧍 🧍	●	Behavior score	⇔
Corbett, 1996 97113595	FTT 48 Ctrl 46	72-84	> 36[a]	🧍 🧍 🧍	●	Behavioral disorder Teacher's report Parent's report	 ⇧ ⇔
Wilensky, 1996 97022837	FTT 50 Ctrl 50	20[b]	NA[c]	🧍 🧍	●	Feeding problems	⬆
Chatoor, 1998 99026462	Gp1 33[d] Gp2 34 Ctrl 34	12-37	NA[c]	🧍 🧍	○	Attachment classification Attachment security scale rating	⬆
Wright, 2000 20161504	FTT 97 Ctrl 28	15.1[g] (7-28) (16-18)	NA[c]	🧍 🧍	⭘	Behavior & temperament	⬆
Kerr, 2000 20277217	FTT 92[h] Ctrl 101	~73.8 ~73.3	48	🧍 🧍 🧍	⭘	Adaptive functioning at school School behavior Home behavior	 ⇧
Steward, 2001 21291243	FTT 14 Ctrl 14	9.2 8.6	NA[c]	🧍 🧍 🧍	⭘	Communication Mood effect	⬆

Ctrl, control; FTT, failure-to-thrive; Gp, group; Mo, month(s); NA, not applicable; ND, no data; UI, Medline® unique identifier; Wk, week(s).

[a] See Chapter 2 – Methods.

[b] Mean age.

[c] Cross-sectional study.

[d] Gp1 Infantile anorexia, Gp2 "Picky eaters", Ctrl "Healthy eaters".

[e] 2 FTT and 9 Ctrl with definite medical condition affecting growth; 1 FTT and 2 Ctrl with possible medical condition affecting growth.

[f] Five were age 9 y, ND whether cases or controls.

[g] Median age.

[h] 4 Study arms collapsed to 2: FTT group includes 64 diagnosed FTT and 28 diagnosed FTT & Maltreatment; Ctrl group includes 80 with neither diagnosis and 21 diagnosed with Maltreatment.

⬆ FTT associated with increased behavioral disorders or variables compared to controls, (statistically significant, $p < .05$).

⬇ FTT associated with decreased behavioral variables compared to controls, (statistically significant, $p < .05$).

⇧ FTT associated with behavioral disorders compared to controls.

⇔ FTT *not* associated with behavioral disorders compared to controls.

Developmental Disorders Associated with Failure to Thrive

FTT is consistently associated with evidence of neurodevelopmental disabilities. Insufficient intake of both macro and micronutrients exerts diverse functional and structural effects on the nervous system, with effects particularly likely to persist if they occur during the vulnerable periods of rapid neural development. Since FTT most often occurs in early life, during the period of most rapid postnatal brain development, developmental concomitants and lasting sequelae are to be expected. Subtle neurological deficits may interfere with the normal progression of feeding skills even in the absence of clinically evident palsies. They contribute to FTT by interfering with the child's ability to take in adequate nutrients. FTT also appears to heighten developmental vulnerability to other adverse environmental factors (Barrett & Frank, 1987).

For the purposes of this review we reported whatever indicators were chosen by particular investigators as indicative of developmental deviations. These heterogeneous indicators range in specificity and in severity. They include, for example, sucking/swallowing difficulties, delays in age of tolerating solid foods, pica, motor delays, and global developmental delays. We attempted to summarize comparisons made by diverse investigators between children failing to thrive and children growing normally. It is important to note that in spite of the highly variable developmental outcomes assessed, the presence of impairment in children who are not growing normally is found consistently across studies and circumstances.

The following discussion is divided by source of subject population (developed versus developing country) and within each category by 3 domains 1) oral motor and other neurological findings; 2) developmental/cognitive functioning concurrent with the identification of FTT; and 3) developmental/cognitive function in later childhood among survivors of early FTT.

Developed Countries

Oral Motor and other Neurological Findings

Prospective, epidemiological, and observational studies consistently note increased rates of feeding difficulties in children with FTT, with some investigators also noting clinically poorly specified "neurological" findings other than in feeding skills. Since these studies are often based on parental report, it is hard to distinguish true subtle neurological (either oral motor or sensory) deficits in feeding from parental perception and from learned behaviors. However, slow feeding and delayed acquisition of age-appropriate feeding skills are a consistent finding in every study where they have been assessed.

Prospectively, in the newborn period, Kelleher, Casey, Bradley, et al. (1993) noted increased rates of abnormal or suspect neurological exams among infants who later failed to thrive, compared to those who did not. Mitchell, Gorrell, and Greenberg (1980) found "suckling difficulties" were more likely to be noted in the newborn records of children who later failed to thrive. Hack, Merkatz, Gordon, et al. (1982) found increased rates of "neurological" abnormalities at 8 months among infants who failed to thrive compared to those who grew well. In a large epidemiological study, Wright and Birks (2000) in Newcastle, England utilized a screening program that identified 120 cases of FTT during the two-year enrollment period. Twenty-eight of the forty controls identified from three general practices that agreed to participate were compared to the 97 FTT cases who had completed data. FTT cases were reported to start solid foods later than controls, 3.89 months versus 3.04 months, $p = .003$,

respectively, as well as starting finger foods later, 7.15 months versus 6.14 months, p = .005. Also reported were more feeding problems during infancy for the FTT cases, 28 percent versus two percent for the controls, p = .022. FTT parents were more likely to describe their children as variable, uninterested, or poor eaters, 11 instances reported for FTT versus none by the control parents, p = .003. In a detailed observational study in the United States, (Pollitt and Eichler, 1976) 19 FTT children and age/sex-matched controls were evaluated over several weeks in open trial. FTT children were found to differ from controls in feeding behaviors as well as in other domains of development.

Developmental/Cognitive Impairments Concurrent with Identification of FTT

From developed countries there are relatively few controlled papers that document the developmental status of children with FTT at the time the condition is diagnosed either clinically or epidemiologically. The focus has been on follow-up studies, which are therefore described below. The issue is complicated further because developmental delay historically was considered by some authors (Coleman and Provence, 1957) as one of the criteria of FTT in addition to growth failure. It is only in recent decades that children have been labeled as FTT on the basis of weight alone. Moreover, except as noted, most of the studies of FTT children at the time of identification do not use masked testers (and indeed it is difficult to mask testers to the differences in size between acutely underweight FTT children and normally growing comparison children of the same age). Therefore an experimenter effect cannot be ruled out in the studies summarized below. Most, although not all, of the samples in these studies also contribute to long term outcome studies.

There are three US studies, two based on hospitalized samples (Haynes, Cutler, Gray, et al., 1984; Singer and Fagan, III, 1984) and the other on a sample not hospitalized but drawn from an outpatient inner city clinic (Mackner, Starr, Jr., and Black, 1997). In the Singer and Fagan, III (1984) study, 8 month old infants with FTT showed on average a large deficit (30-40 points) on the Bayley Mental Development Index compared to controls, and among some FTT children, a difference also in visual recognition memory. As a baseline for an intervention study, Haynes, Cutler, Gray, et al. (1984) compared 50 FTT children with 25 "thriving" children on the Bayley Scales of Infant Development and found that 62 percent of the FTT sample were either delayed or retarded (22 percent with an MDI less than 70) compared to only 19 percent of controls who were delayed, with none retarded.

Mackner, Starr, Jr., and Black (1997) performed a cross sectional study controlled for maternal IQ and child age on a large sample of 177 inner city toddlers, 3-30 months old who were predominantly African American. Ninety-seven children had FTT defined as weight for age less than 5^{th} percent before age 2. Of these, 27 were also characterized as "neglected," defined as the lowest tercile on a Home Observation for Measurement of the Environment (HOME) score obtained by a masked examiner. It is not clear if the psychometrician who performed the Bayley tests was masked to FTT status. Children with both FTT and low HOME scores attained Bayley Mental Development Index scores one standard deviation lower than children with neither. Children with FTT with HOME scores above the lowest tercile scored on average 3 points lower than children with neither on Bayley MDI.

Skuse, Pickles, Wolke, et al. (1994) reports on a population survey of low SES infants in south London born in the year 1986. Forty-seven infants with FTT and matched forty-seven controls were identified. They were assessed at approximately 15 months of age, using the

Bayley MDI and PDI scores. Infants with FTT had scores which were significantly lower than controls on both the MDI (98.2 vs.108.5) and the PDI (96.7 vs. 103.6). In addition, there was a negative correlation between the FTT children's oral motor skills and their MDI scores ($r = -0.38$, $p = .008$). Modeling predicted a correlation between the standardized weight falling during the first 6 months to a 10-point loss in mental and psychomotor development during the second postnatal year. The prediction included weight loss commencing after the first 4 months would have a 3 point loss in development whereas a weight loss after 8 months which would have no effect on development.

Kelleher, Casey, Bradley, et al. (1993) followed a large cohort of babies who had been born with low birth weight of 2500 grams or less and with gestational age up to 37 weeks. Of the 4,551 infants born at the eight Infant Health and Development Program sites, 842 met the inclusion criteria for this study and of those, 180 developed FTT. At 12 and 24 months, Bayley Mental and Psychomotor Development Indexes were lower for children with FTT than children without FTT ($p < 0.005$) (Evidence Table 7). At 36 months, the Stanford-Binet IQ scores were lower for children with FTT, 84.7 vs. 89.9 for non-FTT, $p < 0.007$.

Corbett, Drewett, and Wright (1996) reviewed records from the "most economically deprived wards in Newcastle" to identify children with FTT. Diagnosis of FTT required at least 6 recorded weights during their first 18 months. The controls were also from the same clinic serving a predominant low income, white population of Newcastle. The children were assessed at school entry using the CBCL and the Wechsler Pre-School and Primary Scale of Intelligence - Revised. The severity of FTT was significantly associated with full-scale IQ, though no overall group differences were noted between children with a history of FTT and normal controls.

Drewett, Corbett, and Wright (1999) enrolled 136 children with a thrive index < 5 percent, and 136 controls, matched for age and residential area. Follow-up occurred at ages 5.5 to 7.5 years. Assessment was conducted by interviews and testing using the WISC-III and WORD tests. Lower IQ scores were noted in children with a history of FTT compared to controls (mean IQ, FTT 87.6 vs. 90.6).

A cohort of inner city British white children who were born in 1980 were identified from medical records. Puckering, Pickles, Skuse, et al. (1995) reported on those diagnosed with FTT based on height and weight below 10 percentile compared with control children who were matched on the basis of sex, birth weight, and ethnic origin. Using the McCarthy Scales of Children's Abilities, children with a history of FTT were found to have clinically and statistically significant cognitive deficits (FTT 77.1 vs. Control 97.7).

Kerr, Black, and Krishnakumar (2000) followed children 6 years of age from an earlier study (Mackner, Starr, Jr., and Black, 1997). Children with FTT and adequately nourished children were compared. Developmental assessment included cognitive performance measured by Wechsler Preschool and Primary Scale of Intelligence-Revised Edition, and showed that children with FTT consistently had lower cognitive test scores than nutritionally adequate children (FTT 81.98/FTT with maltreatment 77.98 vs. Controls 83.95).

In summary, at the time of identification, FTT is associated with depressed developmental test scores, with most profound depression seen in clinically identified hospitalized children. However, even in samples identified epidemiologically rather than by clinicians, FTT is associated on average with roughly two-thirds of a standard deviation decrease in developmental test scores, so that many more FTT children will score in the SSI qualifying range of developmental delay than children in a reference population.

Developmental/Cognitive Functions in Childhood Among Survivors of FTT in Early Childhood

Duration of follow-up of children with FTT varies widely between studies, as does the setting in which FTT was initially identified (hospital, outpatient clinic, or epidemiological survey). There is often ambiguity in these studies as to whether the deficits identified are attributable to FTT in early life or to concurrent undernutrition and environmental stressors at the time the outcome is measured. Nevertheless, there is a consistent trend for children with a history of FTT to score lower than their social class peers on developmental/cognitive test scores. In contrast to the studies of developmental status of children with FTT at the time of diagnosis, many of the follow-up studies (Corbett, Drewett, and Wright, 1996; Drewett, Corbett, and Wright, 1999; Mitchell, Gorrell, and Greenberg, 1980; Puckering, Pickles, Skuse, et al., 1995; Wilensky, Ginsberg, Altman, et al., 1996) specify that psychometric examiners were masked to the children's early growth history.

The Haynes, Cutler, Gray, et al. (1984) and Singer and Fagan, III (1984) studies which followed small cohorts of hospitalized children for six months after diagnosis and up to age 3 years respectively found persistent and profound decrements in scores on the Bayley Scales of Infant Development compared to the scores of controls. In contrast, Drotar and Sturm (1992) reported in passing that previously hospitalized FTT and not hospitalized comparison children retained until age 4 for a behavioral outcome study did not differ at age 3 in their Stanford-Binet Scores, which were roughly one standard deviation below the mean in both groups (86 vs. 88).

Among samples selected from outpatient clinics the trend is similar across diverse settings Mitchell, Gorrell, and Greenberg (1980) in rural North Carolina measured McCarthy Scores between 3 and 6 years among 12/30 children who had failed to thrive in earlier life and 16/282 comparison cases. On average the children with FTT scored 5 points lower than the comparisons (87.5 vs. 92.5) but the difference was not significant in the sample overall, although girls with a history of FTT scored significantly lower than those without.

Kerr, Black, and Krishnakumar (2000) conducted a follow-up of children at 6 years of age from an earlier study (Mackner, Starr, Jr., and Black, 1997) of one hundred ninety-three, mainly poor, predominantly African American inner-city children divided into four risk factor groups; FTT (n=64), FTT with history of "maltreatment" (n=28), history of "maltreatment" alone (n=21), and neither risk factors (n=80). History of "maltreatment" was based on at least one report to the Child Protective Services (primarily for neglect, but some also for suspected physical or sexual abuse) and was not part of the initial recruitment criteria. There was no effort to discern maltreatment in children not reported. Developmental assessment measured by an abbreviated version of the Wechsler Preschool and Primary Scale of Intelligence-Revised Edition revealed statistically significance differences (78 vs. 84) between the FTT and maltreatment versus the neither risk factor group, with a non-significant trend toward depressed scores among children with FTT but without "maltreatment" (82 vs. 84). There are two urban Israeli studies, one from Jerusalem (Wilensky, Ginsberg, Altman, et al., 1996) and one from Tel Aviv (Reif, Beler, Villa, et al., 1995). Wilensky, Ginsberg, Altman, et al. (1996) found statistically significant differences in average Bayley Mental Development Scores (99.7 vs. 107) and a higher incidence of MDI below 80 (11.5 vs. 4.6%) in 50 children with a history of FTT compared to 50 matched controls. Reif, Beler, Villa, et al. (1995) in a five year follow-up study found almost identical statistically significant rates of developmental delay (not precisely defined) (11.5% vs. 0%) and "learning difficulties" (18% vs. 3%) among 61 children with a history of FTT compared to 65 controls.

The epidemiological studies fall into two main categories -- American studies which follow prospectively low birthweight cohorts and English studies which evaluate term birth cohorts in defined urban neighborhoods. Hack, Merkatz, Gordon, et al. (1982), examined very low birth weight infants' mental, in relation to catch-up growth, at 8 months. One hundred and ninety two infants less than 1,500 grams were divided into two groups, thirty-eight SGA and one hundred fifty-four AGA. At eight months, eight tertiary subgroups were created and measurements were taken again along with the Bayley performance assessment. The developmental scores at eight months for all five normal weight subgroups were above 100, significantly different from those of the subnormal weight groups; SGA (n=19) at 99, AGA (n=30) at 93, and AGA at eight months only (n=13) at 89, $p < .005$.

The more recent Kelleher, Casey, Bradley, et al. (1993) study incorporates the Infant Health and Development Program which follows a large cohort of low birth weight of 2500 grams or less and with gestation age up to 37 weeks. One hundred eighty of 842 children in the cohort developed FTT. Bayley Mental and Psychomotor Development Indexes were lower for children with FTT than children without FTT for assessments at 12 and 24 months, $p < 0.005$. At 36 months, the Stanford-Binet IQ scores were lower for children with FTT, 84.7 vs. 89.9 for non-FTT, $p < 0.007$.

In contrast, the English epidemiologic studies are restricted to infants born at term. Puckering, Pickles, Skuse, et al. (1995) identified from medical records, a cohort of inner city British white children born in 1980. The twenty-three diagnosed with FTT compared to demographically matched controls were found to have strikingly lower developmental quotients on average (77 vs. 97) with deficits of similar magnitude in all the sub-scales of the McCarthy Scales of Children's Abilities. When FTT is defined by slower weight gain, but not by attained weight percentile at any given age, two studies (Corbett, Drewett, and Wright, 1996; Drewett, Corbett, and Wright, 1999) from the same Newcastle research group, but with independent cohorts, at age 6-7 years found on average a three point decrement in WPPSI full scale IQ (84 vs. 87) in one (Corbett, Drewett, and Wright, 1996) and on the Wechsler Intelligence Scale for Children (WISC)-III at 7-9 years (88 vs. 91), but the differences were not statistically significant.

In summary, there is a consistent association between FTT in early life and depressed developmental test scores in the pre and primary school years. While the studies are methodologically disparate and therefore difficult to compare, the direction of the effect is consistent across multiple study designs with samples of diverse ethnicities and gestational age. The magnitude of these effects is quite variable, ranging from 3 to 20 point deficits on standardized cognitive test scores compared to controls. From the perspective of the SSA, the research literature from developed countries suggests that FTT is associated with persistent deficits in cognitive development both at presentation and in follow-up, even if the child's growth has improved. The precise degree of developmental delay that would constitute "disability" from the perspective of the SSA cannot be determined. Most investigators describe developmental scores that are ≥ 1 standard deviation lower than the standard mean score for the test.

Table 7. Studies with association of cognitive & neurological development to Failure to Thrive compared to healthy comparison groups in developed countries

Author, Year, UI	Sample N	Age (mo) at assessment	Follow-up duration (mo)	Applicability	Internal validity	Instrument	Association
Mitchell, 1980 80166667	FTT 30 Ctrl 282	36-60	12-36	🧍🧍🧍	●	McCarthy-GCI	⇩
Hack, 1982 82227864	Gp1 38 [a] Gp2 154	8[i]	~ 5-7[g]	🧍🧍	●	Bayley Neurological exam	⬇
Singer, 1984 85057547	FTT 11 Ctrl 11	20.6[h]	~ 12[g]	🧍🧍🧍	○	Bayley MDI-Kent Scoring Adaptation	⇩
Haynes, 1984 84233543	FTT 50 [b] Ctrl 25	ND	6	🧍🧍🧍	○	Bayley MDI & PDI	⇩
Drotar, 1992 92372721	FTT 48 Ctrl 47	36	> 24	🧍🧍🧍	○	Stanford-Binet	⇩
Kelleher, 1993 93234174	FTT 180 Ctrl 591	12 & 24	12 & 24	🧍🧍	○	Bayley MDI & PDI	⬇
Skuse, 1994 94253258	FTT 47 Ctrl 47	14.6[h] 14.2	NA[j]	🧍🧍🧍	●	Bayley MDI & PDI	⬇
Reif, 1995 95362505	FTT 61 Ctrl 65	74.4[h] 81.6	61.5	🧍🧍🧍	○	Developmental delay / academic performance	⬇
Puckering, 1995 95378341	FTT 23 Ctrl 23	48	> 12	🧍🧍🧍	●	McCarthy-GCI	⬇
Corbett, 1996 97113595	FTT 48 Ctrl 46	72-84	> 36[g]	🧍🧍🧍	●	Bayley MDI	⇩
Wilensky, 1996 97022837	FTT 50 Ctrl 50	20[h]	NA[j]	🧍🧍	●	Bayley MDI	⬇
Mackner, 1997 97381196	FTT 97[c] Ctrl 80	~14 ~17.7	NA[j]	🧍🧍🧍	○	Bayley MDI	⬇
Drewett, 1999 99284054	FTT 107[d] Ctrl 117	97.4[h] 97.2	> 60[g]	🧍🧍	○	WISC-III	⇩
Kerr,[e] 2000 20277217	FTT 92[f] Ctrl 101	~73.8 ~73.3	> 46	🧍🧍🧍	○	WPPSI-R	⇩

Ctrl, control; FTT, failure-to-thrive; GCI, general cognitive index; Gp, group; IQ, intelligence quotient; MDI, mental development index; Mo, month; NA, not applicable; ND, no data; UI, Medline® unique identifier; WISC, Wechsler Intelligence Scale for Children; WPPSI-R, Wechsler Pre-school and Primary Scale of Intelligence.

[a] Gp1 (n=38) = small for gestational age, Gp2 (n=154) = appropriate for gestational age.

[b] 25 FTT had Lay Health Visitor intervention.

[c] 4 Study arms collapsed to 2: FTT group includes 70 diagnosed FTT and 27 diagnosed FTT & Neglect; Ctrl group includes 57 with neither diagnosis and 23 diagnosed with Neglect.

[d] 2 FTT and 9 Ctrl with definite medical condition affecting growth; 1 FTT and 2 Ctrl with possible medical condition affecting growth.
[e] Sample overlaps with Mackner, 1997.
[f] 4 Study arms collapsed to 2: FTT group includes 64 diagnosed FTT and 28 diagnosed FTT & Maltreatment; Ctrl group includes 80 with neither diagnosis and 21 diagnosed with Maltreatment.
[g] See Chapter 2 – Methods.
[h] Mean age.
[i] Corrected age.
[j] Cross-sectional study.

⬇ FTT associated with decreased cognitive, motor, or neurological measures compared to controls, (statistically significant, $p < .05$).
⇩ FTT associated with decreased cognitive, motor, or neurological measures compared to controls.

Developing Countries

Oral, Motor, and Other Neurologic Findings

In contrast to the data from developed countries which look at neurological findings preceding or concurrent with FTT, studies from the developing world focus on neurological outcomes months to years after the initial diagnosis. Bartel, Griesel, Burnett, et al. (1978) studied the long-term effects of kwashiorkor in 6-12 year old black African children, five to ten years after their hospitalization during infancy. The thirty-one in the index group were compared to siblings and yardmates in the area of psychomotor development. The Lincoln-Oseretsky motor development scale, Smedley hand dynamometer, Reitan Indiana and Halstead neuropsychological test batteries measured motor development, grip strength, and finger-tapping/fine motor speed, but showed no group effects. Two of the ninety-three items involving tapping with feet and fingers were lower for the index group and yardmates compared to the sibling group by Scheffé's multiple comparison, $p < 0.10$ (Evidence Table 10). In contrast, Galler, Ramsey, and Solimano (1985) reported that children who had been hospitalized for malnutrition in the first year of life showed more neurologic soft signs at ages 5-11 years and impaired scores on the Purdue Pegboard Test between 8 and 15 years, although the latter effect seems to be mediated by IQ. Evans, Hansen, Moodie, et al. (1980) found no impact of early nutritional growth failure on Bender-Gestalt scores between 8 and 9 using sibling controls of children with kwashiokhor.

Bartel, Griesel, Freiman, et al. (1979) in the cohort described above also examined the effect of kwashiorkor on the electroencephalogram using the same study design and comparison groups, but also adding a large control of ninety white children of a higher SES. EEG frequency results were significant for group effect for both hemispheres. There was group effect for the incidence of alpha and delta bands in the right and alpha, delta, and omega in the left hemisphere, $p < 0.01$. The kwashiorkor consistently scored higher in the delta and lower in the alpha bands compared to the other groups (Evidence Table 10).

Developmental/Cognitive Functions Concurrent with Identification of FTT

A hospitalized Jamaican cohort (Grantham-McGregor, Stewart, and Schofield, 1980; Grantham-McGregor, Stewart, and Desai, 1978) and an epidemiologic out patient cohort from India (Agarwal, Awasthy, Upadhyay, et al., 1992) provide some information about the

developmental function of children from developing countries concurrent with acute malnutrition. Grantham-McGregor, Stewart, and Desai (1978, 1980) compared two cohorts of children with third degree malnutrition (one of which later received developmental intervention) with a hospitalized control group at the time of admission and found that the two malnourished groups scored nearly 20 points lower than controls on the Griffith's Mean Development Quotient (61,64, vs. 86), with similar differences in each of the sub-scales of the Griffith's Test. Agarwal, Awasthy, Upadhyay, et al. (1992) looked at Gesell Developmental quotient scores concurrent with the severity of malnutrition at 18,24, and 30 months. At every age there was an inverse relationship between the mean scores on the Gesell and degree of malnutrition. At 3 years of age, the Binet Kulshrestha Intelligence Scale, an Indian adaptation of the Stanford-Binet test, was administered to assess IQ. For overall cognitive development, or IQ, there was a main effect by group; normal group 95.5, Grade I 91.9, Grade II/III 86.8, $F = 13.27$, $p < 001$. This result was parallel for measures of motor development, language, and reasoning, $p < 001$, and concept formation at the level of $p < .01$. None of the normally nourished children, 23 % of the Grade I malnourished children, and 51% of the Grade II-III children attained scores at age 36 months below 85 (more than 1 std. below the mean).

Developmental/Cognitive Functions in Childhood Among Survivors of FTT in Childhood and Early Adolescence

Two investigators, Evans, Hansen, Moodie, et al. (1980) and Drewett, Wolke, Asefa, et al. (2001) reported on South African and Ethiopian cohorts respectively. To account for possible genetic influences on outcome, Evans, Hansen, Moodie, et al. (1980) performed a longitudinal study in South Africa looking at the long-term effects of early infant food supplements on the development of a group of newborns from fourteen families with older children with a history of undernutrition. The siblings constituted one control group. Fourteen children with kwashiorkor, who at one time were hospitalized, and their closest in age siblings, formed two more comparison groups. Height and weight data was taken at 4 years of age, 2 years after supplementation for the intervention group. The children who had food supplements during infancy were statistically greater in weight than the other groups at age 4 years, indicating less malnutrition. At 7 years post intervention, height and weight data was collected again, at which time, all children were tested with the New South African Individual Intelligence scale. At testing time the advantage in height and weight by the intervention group were gone. Results of the intelligence scale for full scale score showed an overall significance for the intervention group 82.0 over the other 3 groups; 71.9, 70.0, 72.0, $p < 0.05$. For verbal, the trend was higher for the intervention group, with significant difference over their siblings, 81.3 vs. 70.6, $p < 0.05$. Their performance score for the intervention group was also higher, 86.3 vs. 71.3 for the kwashiorkor, $p < 0.01$, and 74.4 for the kwashiorkor's siblings, $p < 0.05$. In a group of normal birthweight Ethiopian children, Drewett, Wolke, Asefa, et al. (2001) compared children with nutritional growth faltering to weight below the third percentile before 4 months of age to those whose growth faltered between 10 and 12 months of age and those who maintained weights above the third percentile throughout the first year. When evaluated by masked assessors at 24 months of age on an Ethiopian adaptation of the Bayley Scales of Infant Development, both groups of growth falterers scored below the controls, and those who faltered early scored below those who faltered late. Mean PDI scores were 6.6 for the early falterers, 8.5 for the late, and 10.2 for controls. Similarly for the MDI mean scores were 22.6 for the early falterers, 26.6 for

the late and 28.9 for controls. All differences were significant at $p < .001$. However, in this cohort malnutrition was untreated and enduring, and the effects were not attributable to early growth faltering after weight at time of testing was controlled statistically.

There are multiple reports from two prospectively followed West Indian cohorts -- one from Jamaica (Grantham-McGregor, Schofield, and Harris, 1983; Grantham-McGregor, Schofield, and Powell, 1987; Grantham-McGregor, Stewart, and Schofield, 1980; Grantham-McGregor, Powell, Stewart, et al., 1982; Grantham-McGregor, Stewart, and Desai, 1978) and the other from Barbados (Galler, Ramsey, Solimano, et al., 1983a; Galler, Ramsey, Solimano, et al., 1983b). Grantham-McGregor, Schofield, and Harris (1983), Grantham-McGregor, Schofield, and Powell (1987), Grantham-McGregor, Stewart, and Schofield (1980), Grantham-McGregor, Powell, Stewart, et al. (1982), and Grantham-McGregor, Stewart, and Desai (1978) studied the short- and long-term effects of a psychosocial intervention on the mental development of Jamaican children hospitalized with severe malnutrition. The study consisted of three arms: the intervention FTT group, a nonintervention FTT group, and a comparison group hospitalized for reasons unrelated to malnutrition. The later two groups received standard care. Intervention consisted of structured daily play during hospitalization. After discharge the sessions were weekly over 2 years and once every 2 weeks for the third year. Using the Griffith's Mental Development Scales, the Development Quotient (DQ) scores were determined for the three groups at various intervals. When scores at admission were compared with those 6 months later, there were increases for all groups; the intervention group's DQs increased from 86 to 96 compared to 98 to 105 for the control group, $p < 0.1$ at both intervals. The nonintervention group was statistically behind compared to both intervention and control groups. At 60 months after discharge, the relative positions remained unchanged, with the nonintervention group's DQ score less than the intervention group's DQ score, which was lower than the control group's, 78 vs. 86 vs. 93, respectively, $p < 0.01$. All groups improved over time with respect to anthropomorphic measures. Samples sizes were small for the intervention, nonintervention, and control groups, 18, 16, and 20, respectively.

Galler, Ramsey, Solimano, et al. (1983a, 1983b) examined the intellectual and behavioral development of 5 to 11 year old Barbadian children hospitalized in their first year of life with Grades II and III malnutrition. The Wechsler Intelligence Scale for Children was administered to 119 index children who had a mean IQ score 12 points lower than the 127 controls, with 50 percent of the index group scoring below 90 compared to 14 percent for the later group. One percent of the comparison and nine percent of the index groups had scores below 70. The sex, age, or socioeconomic status of the child had no significant effect on the Full IQ scores.

In summary, while cohorts in the developing world tend to contain a higher proportion of more severely malnourished children than those in the developed world, there is considerable overlap between the distribution of anthropometric measurements in the two settings. Malnutrition with edema (kwashiokhor) is rare in developed countries, but appears to have similar sequelae to malnutrition without edema which is widely prevalent in both settings.

The evidence from developing countries is mixed with regard to persistent non-cognitive neurological findings after early undernutrition. However, in the developing world children malnourished in the first three years of life, who in developed countries would be diagnosed as "FTT," consistently show concurrent and persistent developmental/cognitive delay compared to their ethnic and SES peers, with an apparent dose response such that children with the most severe degree and the earliest onset of malnutrition show the greatest magnitude of effect. While controlled follow-up data from the developed world do not extend beyond age 9 years, data from

the developing world provide evidence of the persistence of effect into later elementary school and early adolescent age groups.

Table 8. Studies with association cognitive & neurological development and malnourished cases compared to well-nourished controls in developing countries

Author, Year, UI	Sample N	Age (y) at assessment	Follow-up duration (y)	Applicability	Internal validity	Correlates	Association
Bartel, 1978, 1979 78180773 79162492	Gp2 30 Ctrl 150[a]	6-12	4-12	🧍	○	LOMDS Smedley hand dynamometer Reitan Indiana & Halstead neuropsychological test batteries	⇔
Evans, 1980 81008912	Gp1 14 Gp2 14 Ctrl 26[b]	8.9(0.5) 13(1.9) 10.7, 12	6-7	🧍	●	New S. African Individual Intelligence scale	⇓[h]
						Bender-Gestalt test/Koppitz scoring	⇔
Galler, 1983a, 83136873	Gp[c] 108 Ctrl 107	5-11	4-10	🧍 🧍	◎	WISC Perdue Pegboard Tasks	⇓
Grantham-McGregor, 1987, 1978, 1980, 1982, 1983 87117313 79086701 81051042 82236679 83246270	Gp[d] 34 Ctrl 20	5	5	🧍 🧍	●	Griffith's Mental Development Scale	⇓
						Stanford-Binet Test	⇩
Agarwal, 1992 92372206	Gp1[e] 245 Gp2[e] 324 Ctrl 64	3	3	🧍 🧍	◎	Binet Kulshrestha Intelligence Scale	⇓[i]
Drewett, 2001 21174599	Gp1[f] 25 Gp2[f] 66 Ctrl 100	2	= 1[g]	🧍 🧍	◎	Bayley PDI & MDI	⇓[j]

Ctrl, control; Gp1, undernourished, Gp2, Kwashiorkor; LOMDS, Lincoln-Oseretsky motor development scale; MDI, mental development index; PDI, psychomotor development index; UI, MEDLINE® unique identifier; WISC, Wechsler Intelligence Scale for Children; Y, year.

[a] 3 control arms collapsed into 1: controls consist of 30 siblings, 30 yardmates of index cases, 90 High SES Whites.

[b] 2 control arms collapsed into 1: controls consist of 13 siblings with hx of undernourishment, 13 siblings of kwashiorkor cases with no hx of kwashiorkor but underweight.

[c] PEM Grade II – III.

[d] 2 groups with severe PEM collapsed into 1: 18 had intervention, 16 had standard care.

[e] Gp1 = Grade I, Gp2 = Grade II-III based on NCHS.

[f] Gp1 = early growth faltering, Gp2 = late growth faltering.

[g] See Chapter 2 – Methods.

[h] Undernourished vs. Kwashiorkor & Control groups (Gp1 vs. Gp2 & Ctrl).

[i] Grade I & Grade II/III vs. Control groups; Grade I vs. Grade II/III (Gp1 & Gp2 vs. Ctrl; Gp1 vs. Gp2).

[j] Early growth faltering & late growth faltering vs. Control groups; early growth faltering vs. late growth faltering (Gp1 & Gp2 vs. Ctrl; Gp1 vs. Gp2).

⬇ Index cases associated with decreased cognitive, motor, or neurological measures compared to controls, (statistically significant, $p < .05$).

⇩ Index cases associated with decreased cognitive, motor, or neurological measures compared to controls.

⇔ Index cases *not* associated with difference in cognitive, motor, or neurological measures compared to controls.

Evidence that Failure to Thrive (FTT) is Associated with Other Clinical, Psychosocial and Family Factors

Fourteen studies assessed diverse risks associated with FTT. These studies were from developed countries (9 from the US, 4 from the UK and 1 from Israel) and were highly comparable to the FTT population in the US. Some of the associated factors are assumed to precede the development of the clinical syndrome of FTT while others are likely to have followed. We make no attempt to discern direction of causality but describe the associations that have been found to be correlated with the development of FTT.

Among studies from the United States, Pollitt and Eichler (1976) reported that children with FTT demonstrated lower maternal education level ($p< .05$) and per capita income ($p<.01$) than their matched controls (N=19). Mitchell, Gorrell, and Greenberg (1980) examined a cohort of children from a rural US health center, of whom 30 (9.6 percent) met criteria for FTT (weight for age <80 percent of the Harvard 50 percentile). Compared to their well-nourished controls (282 cases; 90.4 percent of cohort), FTT cases demonstrated a higher incidence of neonatal problems (jaundice, possible sepsis, and poor feeding, 15% vs. 30%, $p<.05$). There were no differences in the incidence of prematurity, LBW, or maternal pregnancy complications. Family problems, assessed by Coddington scale, were more common for the FTT group (FTT 36.7% vs. Controls 11%, $p< .01$). The fact that the diagnosis of FTT generated increased inquiry into home situations presents a potential bias. No SES differences were noted, although the clinic population was 70 percent black and of low SES overall (49-53 percent Medicaid). Evidence of concurrent disability was not sought or described.

Hack, Merkatz, Gordon, et al. (1982) reported on the development of FTT in a population of VLBW infants, both SGA infants who failed to catch up and AGA infants who subsequently fell off in growth. FTT was defined as weight for age more than 2 SD below the mean. Assessment of FTT was at term and again at 8 months corrected age. The diagnosis of FTT at 8 month corrected age correlated with neonatal risk score, an index of severity of the neonatal course, as well as the duration of initial hospitalization ($r= 0.28, 0.30, 0.32$, $p< .005$). The incidence of rehospitalization after the neonatal period was also significantly greater in children who failed to thrive ($p< .001$, Evidence Table 9).

Sherrod, O'Connor, Vietze, et al. (1984) reported on 31 cases of FTT within a study examining abused, neglected, and FTT children with a comparison group. FTT was defined as weight for age less than 2/3 of Harvard 50 percentile weight for age. FTT cases revealed more "anatomical abnormalities" (chi-square=5.44, $p< .025$) and more family dysfunction (chi square 5.32, $p< .025$) accounting for or identified at clinic visits over the first three years of life compared to controls (N=24) (Evidence Table 9).

Casey, Bradley, and Wortham (1984) compared 23 FTT cases (<3 percentile weight for age or > 3 SD fall off over time) to 23 appropriate weight controls, all of whom had been referred to

a Growth and Development Clinic. Despite close matching for SES, the FTT cases scored lower on the HOME inventory for both total score ($p < .04$) as well as subsets for maternal responsivity (7.7 vs. 8.9, $p < .03$), maternal acceptance (5.1 vs. 6.2, $p < .01$), and organization of home environment (4.7 vs. 5.3, $p < .02$).

Hutcheson, Black, and Starr, Jr. (1993) presented findings of an observational study examining maternal-infant interactions during feedings in 31 FTT cases (weight <5 percent NCHS) and 39 well nourished controls. No differences were found between FTT and controls for parenting stress, "informal supports", negative "life events" or negative affect. Age-related differences were found--i.e., maternal affect was rated less positive towards FTT toddlers than FTT infants ($p < .05$). They noted that as all study subjects were drawn from similar low SES, this may account for the lack of distinction between children with FTT and controls; i.e., poverty may prove a stronger marker for negative maternal interactions than FTT (Evidence Table 9).

Kelleher, Casey, Bradley, et al. (1993) reported on 180 FTT cases, all of whom were preterm/LBW. In comparison to 591 well-nourished preterm/LBW controls, the FTT group manifested a significantly higher incidence of SGA ($p < .05$) and more suspect or abnormal neurological exams (4.6 vs. 8.9, respectively, $p < .005$). These children also scored lower on the Rand General Health Rating ($p < .05$), but not the Stein Total Health Scores. FTT also scored lower on the HOME inventory (32.6 vs. 33.9, $p < .03$).

Drotar, Pallotta, and Eckerle (1994) studying 31 FTT infants (weight < 5th percentile), found them to have lower composite Family Relationship Index (FRI) scores than 39 controls ($p < .01$), both at intake (1-9 mos of age) as well as at follow-up at 4 years of age, despite the fact that total scores did show improvement over time (Evidence Table 9).

Four studies were from the United Kingdom (Evidence Table 9). Skuse, Gill, Reilly, et al. (1995) found a four-fold increase in the risk of abuse or neglect among 47 FTT cases (weight for age <3rd percentile) compared to 47 non-FTT controls (RR 4.43; $p < .01$).

Puckering, Pickles, Skuse, et al. (1995) described fewer positive maternal interactions and a higher incidence of negative interactions among FTT cases (weight <10 percent for age; N=23) compared to controls (N=23; $p = .01$). In a matched paired comparison (136 FTT; 136 Control), Drewett, Corbett, and Wright (1999) reported that for those infants noted as failing to thrive during the first 18 months of life (at least 2 weights <5 percent), subsequent follow-up at approximately 8 years of age revealed a significantly greater likelihood for hospital admission, or visit to hospital outpatient clinic compared to controls ($p = .033$).

Wright and Birks (2000) using a definition of FTT related to fall off in weight gain rather than absolute weight percentiles, found a higher incidence of abuse, neglect, or involvement with social services, although it did not prove statistically significant. FTT infants were found to experience a later onset for solid food feedings ($p < .03$).

Wilensky, Ginsberg, Altman, et al. (1996) reported that Israeli children with FTT (weight <3 percent for age) were twice as likely to be admitted to hospital in the first year compared to controls (N=50 each group; $p < .05$). They were also noted to have less stimulating home environments (0.84 vs. 0.92, $p < .05$).

Studies from developing countries again presented much more severe cases of protein energy malnutrition (PEM), and are therefore less directly comparable to the US FTT population. These studies noted a variety of outcomes associated with FTT. Ghosh, Vaid, Mohan, et al. (1979), in a study from India, compared two groups of children with FTT; mild-moderate PEM (weight 71-80 percent of Harvard 50th percentile for age; N=28) and severe PEM (weight for age <60 percent of Harvard 50 percentile; N=39) to well nourished controls (N=60). Lower nerve

conduction was observed in severe PEM cases compared to controls ($p < .001$); no difference was found between controls and the mild-moderate PEM group. Further significant difference was found between those cases whose PEM had its onset before 12 months compared to those with onset after 12 months ($p<.001$) (Evidence Table 10).

Bartel, Griesel, Burnett, et al. (1978) published two studies from South Africa; the first study examined psychomotor development among 31 patients identified by hospitalization for kwashiorkor during the first 27 months of life. These cases were studied 5-10 years after identification and treatment to consider the potential long-term effects of early severe PEM. Comparison was made to two control groups; well nourished siblings (N=31) and age matched "yardmates"(N=31). There were no significant differences noted between groups for a variety of psychomotor tasks. Subsequently, these same three groups, with an additional control group of age-matched, well-nourished white children (N=90) were studied by EEG monitoring. Findings included significantly lower mean frequency for both hemispheres in kwashiorkor cases compared to white and sibling controls ($p<.05$). No difference was found among groups for mean EEG amplitude. There was a higher incidence of delta and theta waves, as well as a lower incidence of alpha waves for kwashiorkor cases than for either sibling or white controls ($p<.05$). The differences between groups, however, fell within range normal variation and thus the biologic significance of these findings is not clear (Evidence Table 10).

Kothari, Patel, Shetalwad, et al. (1992) studied cardiac mass and function by doppler ultrasound in 25 cases of FTT in India, all of whom had severe marasmus or marasmic kwashiorkor. Left ventricular mass was less in FTT cases than controls (N=26; $p<.05$), but the LV mass/body weight ratio was higher ($p<.001$); this represents a poor prognostic factor. Ejection fraction was not different between the groups, but cardiac index was higher ($p<.05$) in FTT cases. The severity of these cases of malnutrition is underscored by the fact that 2 of the 25 FTT cases died within 3 weeks of study.

Benefice (1992) found that Senegalese children with moderate chronic FTT (N=64) scored lower in physical activity ($p<.05$); lower work capacity and pulmonary function (FVC) than controls (N=34; $p<.001$).

In summary, there is persuasive evidence that failure to thrive is associated with a range of organic and psychosocial difficulties that may in themselves secondarily predict or cause significant disability. Categories of associations include socioeconomic factors (lower income, lower maternal education, less enriched family environment/interactions); neonatal morbidity; acute illnesses and hospitalizations; neurological/anatomical abnormalities; family dysfunction; and abuse/neglect.

Chapter 4. Conclusions

Overview

This research has produced an evidence base that the SSA can use to help update its disability guidelines and to revise its disability policy. The review was designed to address the following question: Among children defined by investigators as failing to thrive (FTT) or grow adequately, what evidence exists that they have a concurrent disability (or will have one within six months)?

We reviewed 275 articles and used 52 articles encompassing 43 studies to produce this evidence report. It should be stressed that the single most common reason for exclusion was the lack of a non-FTT comparison group, as we thought that no valid associations could be drawn from descriptive reports or interventional studies that lacked an appropriate control. The quality of the studies we were able to use was variable. While the study question regarding FTT is clear, most of the studies were not designed to specifically address issues relating to disability as defined by the U.S. Congress and interpreted by SSA. Despite this, the evidence extracted from the articles we reviewed clearly suggests a relationship between FTT and concurrent disability, disability within 6 months, and disability beyond 6 months. We described this evidence with respect to specific disabilities in Chapter 3, and in this section we review the implications of those findings as well as some limitations of the studies.

There are a number of potential confounders that need to be considered. The studies from developed countries looked at FTT mainly in lower social-economic status (SES) groups. Several potential risk factors for developing FTT are prevalent among lower SES populations, such as lower family income and maternal level of education, higher incidence of abuse or neglect, family dysfunction and negative maternal interaction. Such factors may exert independent and potentially stronger negative influences on childhood health, well-being and development than those of growth failure, thereby masking the specific deleterious impact of the failure to thrive. Alternatively, the diagnosis of FTT may inherently create bias by increasing clinicians' suspicion and subsequent investigation for potential covariates such as disturbances in family dynamics, or maternal interaction, abuse and neglect.

Studies from developing countries were generally examining the effects of severe malnutrition, often marasmus or kwashiorkor. The extrapolation of their results to the FTT population in the US must be approached with some caution. Lastly, even within developed countries, where the population of FTT children was generally well matched to those in the US, the available studies still demonstrated significant variation, both in specific FTT inclusion criteria, and exclusion criteria (e.g., LBW/SGA).

Persistent Disorders of Growth

There is substantial evidence that long term growth in all parameters (weight, height, and head circumference) of children with FTT compares unfavorably with thriving children and that this disparity persists even with appropriate attempts at intervention. This pattern of a persistent growth deficit is seen in both developed and developing countries and across a wide spectrum of severity of FTT.

The effect on head growth is especially concerning, since increasing head circumference reflects brain growth, and therefore any impairment in head growth impacts neurodevelopmental outcomes. There is also evidence that the longer the growth failure continues, the less likely it becomes that treatment will be effective in reversing the negative long-term outcomes. These findings highlight the importance of early identification and intensive nutritional intervention for children with FTT syndrome to improve efficacy of the therapy and to minimize long-term damage.

Associations of FTT With Immunologic/infectious Outcomes

The evidence that children with FTT have significantly greater susceptibility to infection is strong, and includes both markers of immunologic dysfunction at the cellular level and clinical correlates seen consistently across a variety of conditions. The laboratory indices of cellular immunologic dysfunction were apparent in children with moderate severity and, at least in such moderate cases, may be amenable to nutritional intervention. As expected, the more severe complications were most prevalent among the most severely malnourished children. The evidence is supportive of identifying children with growth failure as being at risk for multiple acute and chronic infections, especially as this may be an area where intervention may effectively reverse the associated risk.

Behavior Difficulties Associated With Failure to Thrive

The evidence identified by the search showed that children with FTT exhibited a variety of behavioral disorders, both concurrently at diagnosis as well as at follow-up. All except one of the relevant studies were conducted in developed countries, on a population of children with moderate degrees of FTT, representing a strong match to the case mix of FTT children in the US.

Studies involving concurrent behavioral abnormalities in FTT cases examined children up to 3 years of age. The behavioral problems exhibited by the children diagnosed with FTT included various eating disorders, such as delayed introduction of solid foods, spitting, disinterest, and food aversions. Other behavioral disorders that were noted involve increased negative and decreased positive affective expressiveness, and lower scores on measures of communication and mood. These behavioral difficulties do not in themselves constitute disabilities using the SSA definition, but may contribute to functional deficits noted in neurologic and cognitive/social development.

Studies examining behavior problems in children diagnosed with FTT at follow-up focused on social situations such as classroom behavior. School-related behavioral problems such as attention deficit disorder (ADD) were found in one study to be more common among FTT children than controls. In addition, one investigator found interference with problem-solving skills more often in FTT children than in well-nourished controls.

Developmental Disorders Associated With Failure to Thrive

The evidence identified by the search showed that children with FTT exhibited consistently poorer scores in a variety of tests of cognitive, neurological, and psychomotor development. Indeed, the deleterious effect of growth failure and malnutrition on neurodevelopment is among

the strongest and most important associations found. This trend toward poor neurodevelopmental performance was consistent for all fourteen of the studies conducted in developed countries, and five of the six studies conducted in the developing countries.

Despite exclusion of children with overt neurodevelopmental abnormalities from the case definition of FTT, at the time of identification, FTT is still strongly associated with poorer developmental test scores. Again, not unexpectedly, the most severe developmental delays are found among the most severely malnourished, often hospitalized children. However, even in larger epidemiological studies, the effect of FTT on neurodevelopmental outcome is apparent. Such studies indicate that the diagnosis of FTT is associated with an average decrease in developmental test scores of roughly two-thirds of a standard deviation. This means that children with failure to thrive are also more likely to meet criteria for the SSA qualifying range of developmental delay than are children in the general population. Adding to the concern of such cases is the fact that these lower neurodevelopmental testing scores persisted regardless of intervention.

Evidence that Failure to Thrive is Associated With Other Clinical, Psychosocial and Family Factors

There is persuasive evidence that FTT is associated with a range of organic and psychosocial difficulties. Some of these associations may be potential causal factors for the growth failure, such as low socioeconomic status and maternal education level, family dysfunction and the presence of neonatal morbidities. Others, such as the frequency of hospitalization, general health status, and specific neurologic abnormalities are more likely the result of the malnutrition. Furthermore, several of these factors may also independently predict or place a child at risk for significant disability. The possible interrelation of such factors complicates the delineation of the true nature of their association with FTT; nonetheless, they provide further insight into the complexities of the risks inherent in the diagnosis of growth failure.

Overall, the results are generally consistent across a broad spectrum of growth failure severity, and the majority of the studies are readily and creditably generalizable to the population of children with FTT as defined by SSA. Additionally, the study results further highlight the severity and potential long-term impact of these associations in their consistent finding that these psychosocial and family difficulties are not readily amenable to current interventions.

The implications of FTT on long-term morbidity and disability can vary depending upon the severity of FTT, its cause, and most importantly the chronological age at which FTT occurred. Thus, in spite of an appropriate review of literature, we may still be not be able to assess the full magnitude of FTT on developing children because of the wide age range of subjects in the reported studies. One thing we can certainly conclude is that a major FTT event in a child's life occurring particularly at a critical phase of the growth curve (which varies among body systems; brain, skeleton etc.) has a high likelihood of causing major disability. The age of the child and the magnitude of FTT thus may have differing effects on different body systems. This is an important area in which to target intervention programs as well as further probe molecular and genetic bases for such impairments.

Chapter 5. Future Research

The studies comprising this report, though insufficient in number and variable in their methodologic quality and their potential biases, were of sufficient validity to provide significant information regarding the association of FTT with disability. The variety and long-term nature of the disabilities associated with FTT have major impact on the child, the family, and society.

Notwithstanding this, it may well be that the most significant finding of this review was the paucity of information available on the subject. Much remains to be learned regarding the extent and specifics of these associations and disabilities. Even more remains to be determined as to the optimal management of these patients.

Similarly, whatever limitations may have been found in these studies, they have also served to better define relevant outcomes for further study. With this in mind, we offer the following recommendations for future research addressing specific problematic issues and limitations identified from review of existing research.

- One of the central problems in interpreting these studies was the heterogeneity of definitions of FTT. This variability in case definition makes it unclear how well the population at risk is being identified at present. Future research should apply a uniform definition of FTT. This would serve to facilitate comparison and perhaps even allow a meta-analysis of studies. It would also define more clearly the true prevalence of FTT.

- Within the definition of FTT, provisions should be made for categorization based upon 1) severity and 2) longevity or duration of growth failure. The data currently available indicate that both of these factors are strong predictors not only for the risk of associated disabilities but for potential response to therapy as well. Refining the classification of the FTT population in this way would facilitate identification of the relative risk of disability for an individual FTT child. It would also help in the evaluation of intervention studies.

- Although it is clear that the degree of disability increases with increasing severity of growth failure, this is an imprecise correlation especially in regards to children with mild to moderate FTT. Since the majority of FTT that is seen in the US tends not to be the most severe forms of marasmus and kwashiorkor, future research should specifically target those children with mild to moderate growth failure.

- Similarly, more research needs to be conducted in the US, or in developed countries with comparable social-economic structures and health care systems.

- Special emphasis should be given to outcomes focusing on neurodevelopmental and cognitive disorders. The data presented in this report indicate that this is likely one of the areas of strongest impact of FTT and certainly one with the greatest relevance for long term disability. Specifically, very few studies have focused on the issue of FTT and brain growth during the immediate post-neonatal period and early infancy. This is one of the most critical periods for dendritic arborization, axonal myelination, and the development of cognitive functions. More studies are needed in this area.

- Further study is also needed on the association of FTT with general health outcomes because of their potential impact on the healthcare system. Beyond the risk to the individual child, the data linking FTT to increased risk of infections and poorer general health may have important implications at a broader level. Such data may help us understand the true "cost" of FTT and prove useful in evaluating intervention strategies.

- In order to better define the true nature and extent of the disabilities associated with FTT, more studies are needed that prospectively follow children for a sufficient duration to capture the more complex disabilities that may result from FTT.

- A consistent finding among these studies reviewed was the ineffectiveness of existing intervention programs. Although strictly beyond the focus of this report, much work still needs to be done on developing effective treatment programs for children with FTT. Unfortunately, the optimal intervention will yet require better definition of the complex physical, medical, cognitive, and psychosocial problems associated with failure to thrive.

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Evidence Table 1. Studies associating anthropometrics to Failure to Thrive cases compared to healthy control roup in developed countries
Part I

Author, Year, UI	Demographics	Maternal / household demographics	Inclusion criteria	Exclusion criteria	Definition of FTT	Study design
Mitchell, 1980 80166667	Country: US Setting: Outpatient clinic FTT Ctrl Age(y) 2-5 2-5 Wt/age ND ND Ht/length ND ND Enrolled : cohort of 312(323)* Evaluated 30 282 % Male 36.7 51.8 % Black 70 70 * See Potential biases column	Maternal educ: ND Income: ND Health insur: FTT-53% Medicaid Ctrl-49% Medicaid	See Definition of FTT Controls - wt = 80% of nl, matched for age, sex, mother's age/ marital status & family problems	Organic cause of FTT, single anomalous low wt recorded, clinic registration by age 6 mo, < 3 visits	Wt for age < 80% of nl up to age 24 mo	Ambidirectional longitudinal 1 fwup at age 3 – 6 y
Haynes, 1984 84233543	Country: US Setting: Inpatient & Outpatient Age: ND Wt/age: ND Ht/length: ND FTT1* FTT2† Ctrl Enrolled/Eval 25 25 25 % Race Sp-Am? 44 44 44 Sp-Am? 40 52 52 White? 36 44 36 White? 36 24 28 Black? 20 12 20 Black? 24 24 20 % Male: ND * std care & lay health visitor intervention, † std care only	Maternal Educ Income* Gp1 10 379(0-750) Gp2 11 372(0-950) Ctrl 10 362(0-1100) Health insur: ND * @ mo	Consecutive admissions for NOFTT Controls - thriving non-hospitalized patients matched for age, sex, birth wt, & mother's age, ethnicity, number of living children	ND	< 5 percentile or significant decline from birth wt percentiles	Prospective longitudinal 1 assessment 6 mo after intake

Evidence Table 1. Studies associating anthropometrics to Failure to Thrive cases compared to healthy control roup in developed countries
Part I

Author, Year, UI	Demographics	Maternal / household demographics	Inclusion criteria	Exclusion criteria	Definition of FTT	Study design
Kelleher, 1993 93234174	Country: US Setting: Primary care clinic FTT Ctrl GA(wk)* 33.0 33.1 Wt(g)* 1679 1845 Enrolled: 842* Evaluated 180 591 % Male 52.2 47.9 Race: % Black 50 53.8 * At birth	FTT Ctrl Maternal educ(%) <HS 40.6 38.1 HS 30.0 29.3 Some col 14.4 20.8 ≥col grad 15.0 11.8 Income <10K 38.6 34.5 10-20K 19.9 23.9 >20K 38.1 37.4 Health insur: ND	Gestation age ≤ 37 wks, birth wt ≤ 2500 g, FTT Controls matched for – birth wt +/- 250 g, maternal education, maternal race, & infant sex	Live outside catchment area, discharged outside recruitment period, discharge or died within 48 hr, hospitalized > 60 d, oxygen support > 90 d, twin, triplet or quadruplet of ineligible child, maternal drug/alcohol abuse, insufficient Eng skills, psychiatric hosp	< 5th percentile for gestation corrected age based on NCHS, growth status on "wt curve below that recorded at last regular assessment visit."	Prospective longitudinal Fwup at ages 12, 24, 36 mo
Reif, 1995 95362505	Country: Israel Setting: Outpatient FTT Ctrl Mean age(y) 6.2 6.8 Wt/age* 18.05 36.15 Ht/length* 21 33.55 Enrolled 86 65 Evaluated 61 65 % Male 52.5 54 Race: Sephardic 38 36 Ashkenazi 23 29	FTT Ctrl Maternal educ* 12.27 (0.29) 12.14 (0.24) Income: ND Health insur: Socialized medicine * Mean (SD)	FTT, < 2 y, term infants > 2500g birth wt Controls matched for age, sex, social class, & ethnic affiliation; admitted or evaluated in ER for intercurrent & nonsign disease	Organic cause of FTT, malnutrition, serious perinatal morbidity	Ht & wt < 5% in ≥ 2 measurements within 6 mo on Hamill PVV, Drizd TA growth chart,	Ambidirectional longitudinal Re-evaluation at mean 5.12 yr

Evidence Table 1. Studies associating anthropometrics to Failure to Thrive cases compared to healthy control roup in developed countries
Part I

Author, Year, UI	Demographics	Maternal / household demographics	Inclusion criteria	Exclusion criteria	Definition of FTT	Study design
Corbett, 1996 97113595	Country: UK Setting: Clinic Age: 6-7 yr FTT Ctrl Wt/age ND ND Ht/length ND ND Enrolled 52 52 Evaluated 48 46 % Male: ND Race: 100% White	Maternal educ: ND Income: "…most economically deprived wards in Newcastle" Health insur: National healthcare	Full term singleton with records of 6 or more weights over first 18 months age Consecutive controls matched for age & sex	Non-Caucasian, "poor growth resulting from major organic disease"	Weight deviated downward from maximal centile achieved at 4-8 wks, across ≥ 2 centile lines, & stayed at level ≥ 2 measurements (1 mo (Tanner & Whitehouse)	Ambidirectional longitudinal 5 year follow-up of cases
Black, 1999 99162090	Country: US Setting: Outpatient FTT Ctrl Age: ND ND Wt/age <5% >5% Ht/length <5% >5% Enrolled/Eval 127 98 Male: ND Race: 92% African American	FTT Ctrl Maternal educ* 11.4 (1.62) 10.76 (1.44) Income: AFDC 76% Health insur: ND * Mean (SD)	< 25 mo, full-term, AGA, no congenital or handicapping conditions	ND	< 5% for wt for age or wt vs. ht by NCHS growth charts	Prospective longitudinal FTT: three 6 mo followed by annual visits from ages 3-6 Control: annual visits ages 3-6

Evidence Table 1. Studies associating anthropometrics to Failure to Thrive cases compared to healthy control roup in developed countries
Part I

Author, Year, UI	Demographics	Maternal / household demographics	Inclusion criteria	Exclusion criteria	Definition of FTT	Study design
Drewett, 1999 9928405 4	Country: UK Setting: Clinic / home visits FTT Ctrl Age(y) 8.12(0.62) 8.10(0.57) Wt(kg)* 23.8 27.9 BMI* 14.9 16.3 Enrolled 136 136 Eval† 107/111 117/122 % Male‡ 40 38 % White‡ 91 91 * Median, † Psychological / anthropometric evaluation, ‡ FTT = 107, Ctrl = 117	FTT Ctrl Maternal 72 66 educ* Income: NA Health insur: National healthcare * % left school at 16 y	At least 1 wt at age 0-2 mo & 2 subsequent wts, thrive index < 5th centile = 2 occasions between 3 & 18 mo Controls with at least 1 wt at age 0–2 mo & 2 subsequent wts, no thrive index < 10th centile, age ± 1 mo, similar/same residential area or GP practice	ND	Lowest 5% for change of SD score; avg taken of SD scores for all wt bet 0-2 mo, expected wt from 3-18 mo calculated for “thrive index”	Ambidirectional longitudinal Five years from enrollment of age 1 y

Evidence Table 1. Studies associating anthropometrics to Failure to Thrive cases compared to healthy control group in developed countries
Part II

Author, Year	Correlates	Associations found	Potential biases	Comments
Mitchell, 1980 80166667	Weight - % of normal Height - % of normal HC - % of normal	Expect wt and HC of the FTT group was significantly lower than the controls ($p < .05$ each), wt remained ~15% below control group through age 5, ht ~5% below till age 4. Expected ht was not significant. FTT girls recovered more slowly.	Physical exams & growth status by PI not blinded	Government & privately funded
Haynes, 1984 84233543	Weight	All FTT had some wt gain during hospitalization, at reeval-some minor wt gain, 8 FTT gain > 20 percentile pts or within 5 percentile of birth wt percentile. There were no differences for both FTT groups compared to the controls after 6 mo for wt gain except in some minor cases.	"…because of scheduling, few admissions were not evaluated", 2 refused participation; 10 Gp1 & 3 Gp2 premature – overall similar from FTT vs. Ctrl; at 6 mo fwup: for FTT1 & FTT2 each-3 cases refused reevaluation & from1 dissolution of pair, 1Gp1 died SIDS, 1 Gp2 mother gave up child	Block assignment to Gp1 & Gp2 for hospital convenience & case load requirements; government funded
Kelleher, 1993 93234174	Anthropometric outcomes	FTT length, weight, & head circumference below 5th percentile at 12, 24, 36 mo, below Control averages, $p < 0.0001$.	Of 985 enrolled, 71 LTF	21% of sample developed FTT by 36 wks; ND on funding source
Reif, 1995 95362505	Final weight Final height Ideal weight Long-term weight of FTT Long-term height of FTT Mother's education Persons @ room	There were significant differences between FTT and Control groups for height ($p < .01$) and weight ($p < .001$), as well as compared to ideal ht/wt ($p < .001$). Mother's education was a significant covariate for FTT long-term wt ($p < .05$). Number of person's per room was a significant covariate for FTT long-term wt ($p < .05$) & long-term ht ($p < .0005$)	25 cases not re-evaluated because not located or refused participation; inpatient enrollment of FTT-48 & Ctrl-42; outpatient enrollment of FTT-13 & Ctrl-23(ER)	ND on funding source

Evidence Table 1. Studies associating anthropometrics to Failure to Thrive cases compared to healthy control group in developed countries
Part II

Author, Year	Correlates	Associations found	Potential biases	Comments
Corbett, 1996 97113595	Mean height SDS Mean weight SDS	Height and weight centiles were significantly lower ($p = .020$ & $p < .001$) in the FTT group at time of entering school	3 from each group refused consent at follow-up, LTF or moved - 2 cases, 3 controls, 1 case not originally studied participated for follow-up study, 4 of those cases were the slowest growing 5% - also removed from home, all controls stayed with parents. Edward's diagnostic criteria for growth measure considered limited.	ND on funding source.
Black, 1999 99162090	Height Weight Gender	Despite catch-up, wt & ht growth were significantly slower than controls for all fwup intervals; sex & education did not predict outcome; perception of poor child health correlates with poor growth; no gender differences for ht or wt, but girls grew faster than males.	---	Government funded
Drewett, 1999 99284054	Height Weight Head circumference	FTT children were smaller in ht ($t = 6.3$, $p < .01$), wt ($\chi^2 = 27.9$, $p < .001$), and head circumference ($t = 3.86$, $p < .01$), as well as have fathers who were also shorter than the controls.	Of 136 cases, 1 died, 9 LTF, 15 declined psychological testing, 4 moved; of 136 controls, 2 were preterm, 5 LTF, 12 declined psychological testing, 14 moved & were replaced. 2 FTT cases & 1 control with medical condition affecting growth, & 9 FTT cases & 2 controls with possible medical conditions	Testers blinded to child's status; privately funded

Evidence Table 2. Studies associating anthropometrics with malnourished patients compared to well-nourished control subjects in developing countries

Part I

Author, Year	Demographics	Maternal / household demographics	Inclusion criteria	Exclusion criteria	Definition of malnutrition	Study design
Branko, 1979 79228898	Country: Ethiopia Setting: Outpatient Gp1* Gp2† Ctrl Age(y) 5.5-14 5.5-12.8 5-14 Wt/age ND ND ND Ht/age ND ND ND Enrolled/eval 44 43 559 % Male 61 48 52 Race: 100% Black * Marasmus, † Kwashiorkor	Maternal educ: ND Income: ND Health insur: Free medical care	Formerly hospitalized & for successful treatment of marasmus or kwashiorkor	ND	Marasmus: nutritional etiology, wt < 60% of Boston 50th percentile for age/sex, absence of edema Kwashiorkor: nutritional edema, growth retardation, muscular atrophy, "psychomotor alterations", hair or pigment chg, or "moon face"	Ambidirectional Last assessment avg 7½ (2.5) y after D/C
Evans, 1980 81008912	Country: South Africa Setting: outpatient clinic Wt/age See Correlates column Ht/length See Correlates column Gp1 Ctrl1 Gp2 Ctrl2 Mean age(SD) 8.9 (0.5) 10.7 (1.0) 13 (1.9) 12 (2.1) Enrolled 14 14 14 14 Evaluated 14 13 14 13 % Male 64 54 100 77 Race: "Cape coloured"	ND	Gp1 – newborns of families with hx of undernutrition Ctrl1 – siblings with hx of undernourishment, record of `< 3rd percentile for ht & wt Gp2 – at least 1 hospitalization for kwashiorkor Ctrl2 – siblings closet in age Gp2 w/no hx of kwashiorkor but underweight	ND	ND	Prospective longitudinal Fwup 6 ½ y after intervention

Evidence Table 2. Studies associating anthropometrics with malnourished patients compared to well-nourished control subjects in developing countries

Part I

Author, Year	Demographics	Maternal / household demographics	Inclusion criteria	Exclusion criteria	Definition of malnutrition	Study design
Galler, 1985a 85241832	Country: Barbados Setting: Outpatient Age(y): 9-15 Gp / Ctrl Wt/age ND / ND Ht/length ND / ND Enrolled 141 / 129 Evaluated 108 / 107 % Male 57 / 60 Race: 100% Black	Maternal educ: ND, universal education, 95% population literate Income: lower for cases compared to control group Health insur: ND	Discharged 5 – 11 yr olds w/dx at age 1 yr with PEM Grade II-III, BW > 5 lbs Controls without PEM, matched for age, gender, handedness, & same school / neighborhood	Pre- or peri-natal complications, edema, seizures, head trauma, loss of consciousness, high fever 1985a/1985b: hx head seizures	Gomez Scale PEM: Grade II-61-75% or Grade III- ≤ 60% standard wt for age on Harvard Standard Scale	Ambidirectional longitudinal Fwup 6 – 12 y after D/C
Alvear, 1986 86185605	Country: Chile Setting: Outpatient Gp / Ctrl Age(mo) 16(8-20) / ND Wt/age* ND / ND Ht/length* ND / ND Enrolled/Eval 40 / 38 % Male 45 / 47 Race: ND* * See Inclusion criteria	ND	Hx of hospitalization for PEM at yrs 1-2, Chilean population & white Amerindian origin from Santiago Chile, SES grade 5 or 6 (modified Graffar scale) Controls matched for age/sex/SES, attend same nursery sch as cases, no hx of mal-nourishment, normal wt & ht (WHO)	Hormonal imbalance, debilitating disease not due to nutritional deficiency	PEM at yrs 1-2; < 60% wt for age, < 85% wt for length	Prospective longitudinal 4 y after D/C

Evidence Table 2. Studies associating anthropometrics with malnourished patients compared to well-nourished control subjects in developing countries

Part I

Author, Year	Demographics	Maternal / household demographics	Inclusion criteria	Exclusion criteria	Definition of malnutrition	Study design
Grantham-McGregor, 1987, 1982 82236679 87117313	Country: Jamaica Setting-Recruitment: hospital Follow-up: hospital & home Gp1* / Gp2† / Ctrl† Age: 12.8 (2.9) / 13.4 (4.5) / 12.2 (4.4) Ht/age‡: 89.0 (4.5) / 88.4 (4.4) / 101.3 (3.5) HC/age‡: 91.3 (3.7 / 91.2 (3.3) / 99.0 (3.8) Wt/ht‡: 74.9 (9.2) / 72.4 (10.2) / 89.0 (10.1) Enrolled: 21 / 18 / 21 Evaluated: 18 / 16 / 20 % Male: 67 / 38 / 60 Race: ND, assumed Black Mean (SD) for evaluated cases; * Intervention, † Standard care, ‡ % of expected value	Maternal educ: HS not completed Income: housing 'below certain defined standards' Health insur: ND Maternal PPVT Gp1 62.3(14.7) Gp2 59.7(15) Ctrll 67.4(9.3)	Gp, age 6 – 24 mo, attempt for SES of mothers who had not completed secondary education, substandard housing, residence in city of Kingston Control - included above criteria but adequately nourished, hospitalized with diseases other than malnutrition	Physical handicap, disease that might affect mental development (other than malnutrition)	Severe PEM based on Wellcome classification	Prospective longitudinal 6 fwups from 6 to 72 m after D/C l
Bénéfice, 1992 92296639	Country: Senegal Setting: Outpatient Age: ND Enrolled: 100 Evaluated: Gp 64, Ctrl 34 % Male: 46 Race: ND	ND	Age 9 – 14 y from 2 villages with per capita caloric intake of 2200 & 2400	Recent serious illness, clinical signs of malnutrition or anemia	Wt/age < -1 SD median WHO/NCHS	Prospective cross-sectional

Evidence Table 2. Studies associating anthropometrics with malnourished patients compared to well-nourished control subjects in developing countries

Part I

Author, Year	Demographics	Maternal / household demographics	Inclusion criteria	Exclusion criteria	Definition of malnutrition	Study design
Walker, 1996 97154651	Country: Jamaica Setting: Outpatient Mean age*: 18.7(4.1) mo Enrolled: Stunted 129 Nonstunted 32 Gp1† Gp2‡ Gp3§ Ctrl1|| Ctrl2¶ Eval 31 29 30 32 32 Wt(kg)** Ht(cm)** % Male†† Gp1 8.61(0.97) 73.3(3.5) 61 Gp2 8.43(0.90) 72.9(3.9) 55 Gp3 8.37(0.99) 72.9(3.6) 57 Ctrl1 8.65(1.03) 72.8(4.3) 59 Ctrl2 11.46(1.06) 82.3(4.6) 56 Race: ND Mean(SD), * N = 129, † Supplement, ‡ Psychosocial, § Both intervention, || No intervention, ¶ Nonstunted, ** Enrollment, †† Evaluation	ND	Stunted children 9 – 24 mo, weight for age < -2 SD, housing & maternal education below standard level, singleton, BW > 1,8 kg Nonstunted children matched for age, sex, & neighborhood	Physical or mental handicap	See Inclusion criteria	Prospective longitudinal Assessments @ 2 & 4 y after intervention

Evidence Table 2. Studies associating anthropometrics with malnourished patients compared to well-nourished control subjects in developing countries

Part II

Author, Year	Correlate & measures					Associations found	Potential biases	Comments
Branko, 1979 79228898		Gp1	Gp2	Ctrl*		Maramus gp was on avg 3 cm smaller than Ctrl ($p < .011$), weighed 2.1 kg less, ($p < .011$), and their HC was 0.85 cm less ($p < .007$); The Kwashiorkor gp was smaller than Ctrl on avg 0.84 cm ($p < .607$), weighed 0.6 kg less ($p < .082$), & their HC was 0.3 cm smaller ($p < .368$); Comparing Marasmus vs. Kwashiorkor gps, the Kwashiorkor gp was heavier ($p < .05$), taller ($p < .02$), & had larger HC ($p < .05$).	---	ND on funding source
	Ht (cm)	93-154	90.0-143	99.1(3.6)-144.7(3.3)				
	Wt (Kg)	11.4-35.0	11.0-29.5	14.6(1.2)-34.3(5.4)				
	HC (cm)	47.0-53.0	48.0-53	49.0(0.8)-53.4(1.1)				
	* mean range by sex & age ranges of 6 mo from age 5 to 14 y							
Evans, 1980 81008912		Gp1	Ctrl1	Gp2	Ctrl2	2 years after supplementation had ceased, height & weight were significantly higher for Gp1 ($p < 0.01$) vs. 3 other groups; by 6.5 + y post-intervention, there were no differences.	1 child died in each of the controls, sex unkn	Gp1 received supplements until mean 28 mo, examiner blinded to subject's group status, testing 6-7 y after cessation of supplements; US government & South African Medical Research Council
	~Wt1*	86	77	75	72			
	~Ht1y*	90	84	82.5	82			
	~Wt2†	79	78	77	76			
	~Ht2†	90	89.5	90	90			
	* 2 y after supplements, † 6.7 y after supplements							

Evidence Table 2. Studies associating anthropometrics with malnourished patients compared to well-nourished control subjects in developing countries

Part II

Author, Year	Correlate & measures					Associations found	Potential biases	Comments
Galler, 1985a 85241832		Gp?	Ctrl?	Gp?	Ctrl?	At ages 9-15, there was persistent poor height & weight gain for the index group with emphasis on the girls' weight ($F = 28.88$, $p < .001$). Early PEM was a predictor of sexual maturation for females ($F = 5.69$, $p < .001$).	1983-Withdraws/non-participation – 4 refused consent, 7 LTF, 1 cerebral palsy; Severe PEM	Relevant WISC subtests utilized & some items altered for cultural setting; findings of dominant hand performance of fine motor skill tasks deficient in formerly malnourished children correlates or co-varies with IQ & other soft neurologic signs; private & hospital funded
	Ht*	148.92 (12.5)	150.4 (12.18)	145.25 (11.4)	149.63 (11.02)			
	Wt†	37.02 (10.74)	39.37 (10.35)	35.42 (7.63)	41.9 (35.42)			
	*cm, † kg							
Alvear, 1986 86185605		Gp?	Gp?	Ctrl?	Ctrl?	At birth, the cases were smaller in wt (boys $p < 0.01$, girls $p < 0.001$) and length (boys $p < 0.01$, girls $p < 0.001$) compared to controls. At the end of follow-up, there was no difference in bone age between cases and control groups by group or by sex, but there was a significant difference for female cases who were smaller than male cases for bone age ($p < .01$). Arm fat areas were greater for controls vs. cases (girls $p < .001$, boys $p < .05$).	---	No data on whether children were failing to thrive at 4-6 years when anthropological data were collected; university funded
	Birth wt	3018.2 (490.3)	2654.6 (579.0)	3453.5 (522.3)	3328.4 (563.4)			
	Birth length	48.4 (2.2)	46.8 (2.6)	51.1 (2.3)	49.5 (2.2)			
	Bone age*	60.3 (8.6)	76.7 (14.2)	69.2 (9.7)	86.7 (27.2)			
	Arm fat area	73.5 (15.3)	64.5 (16.5)	91.0 (24.7)	95.7 (28.5)			
	* Gp n=25 (?=12, ?=13), Ctrl n=20 (?s=9, ?=11)							

Evidence Table 2. Studies associating anthropometrics with malnourished patients compared to well-nourished control subjects in developing countries

Part II

Author, Year	Correlate & measures						Associations found	Potential biases	Comments
Grantham-McGregor, 1987, 1982 82236679 87117313		Gp1	Gp2	Ctrl			Assessments 6, 12, 18, 24 months; weight for height measures were not statistically significant, but the two case groups were significantly shorter for all time points than the control group ($p < 0$). At 24, 36, 48, 60, & 72 month; height for age was significantly lower for the two groups vs. controls.	Controls had better housing than other 2 groups regardless of attempts to match; 2 died & 1 WD from intervention group, 1 from nonintervention moved & 1 was adopted by middle-class family, 1 from control WD; edema: Gp1 10 of 21, Gp2 4 of 18, Ctrl 0 of 21	Tester blinded to subjects' group, controls hospitalized mainly for gastroenteritis & respiratory infections; government & private funding
	Wt for ht *	91.7(7.5)	95.1(8.4)	92.5(6.8)					
	Ht for age*	94.9(2.5)	93.9(4.5)	100.6(3.8)					
	Assessment at 72 mo, * Mean percentages								
Bénéfice, 1992 92296639		Gp	Ctrl				Children with malnutrition had less body fat ($t = 3.5$, $p < .001$) & arm muscle ($t = 6.0$, $p < .001$) compared to nourished controls.	Child's age determined by recall, no records available; no explanation on missing case from each group not in analyses	ND on funding source
	% body fat	15.0(0.28)	16.9(0.39)						
	Arm muscle area	18.7(0.33)	21.8(0.47)						
	Adjusted mean (SD)								
Walker, 1996 97154651		Gp1	Gp2	Gp3	Ctrl1	Ctrl2	Signf for three measures of Ctrl2 vs. combined stunted groups, $p < .001$, covariates - sex & age (mean 7.7 @ gp) No difference between the different groups of stunted children in height, weight, and head circumference, but difference between the combined stunted groups with non-stunted children.	127 of 129 children completed studies; 4 yr after completion of intervention, of stunted gps - 3 relocated & 2 LTF	Observers blinded to child's group, evaluation 4 y after 2 y intervention; privately funded
	Ht(c)	119.8 (5.0)	119.5 (5.4)	118.8 (4.1)	118.9 (4.7)	130.9 (4.9)			
	Wt(k)	21.2 (3.5)	20.9 (3.1)	19.9 (1.9)	20.4 (2.2)	26.2 (2.3)			
	HC(c)	51.2 (1.3)	50.9 (1.4)	51.0 (1.3)	50.8 (1.5)	52.4 (1.4)			

Evidence Table 3. Studies associating immunologic response or infectious diseases with Failure to Thrive patients compared to healthy control subjects in developed countries

Part I

Author, Year, UI	Demographics	Maternal / household demographics	Inclusion criteria	Exclusion criteria	Definition of FTT	Study design
Carvalho, 1984 85145406	Country: Brazil Setting: Outpatient clinic Age: ND FTT Ctrl Enrolled/Eval 20 40 % Male: ND Race: ND	ND	Moderate & chronic primary PCM, > 6 mo < 5 y, body wt 25.1 & 40% of "standard values", subcutaneous tissue, absence of edema, arm circumference < 13.5 cm, ht "within normal limits", low SES Controls - same criteria but "normal" body weight, "good-economic level and enjoyed good nutritional intake"	Infection, transfusions, general anesthetics, corticosteroids or immunotherapy < 6 mo prior, drug tx	ND	Prospective cross-sectional
Sherrod, 1984 85026403	Country: US Setting-Recruitment: Prenatal clinic Follow-up: Pediatric clinic NOFTT Ctrl Birth wt(g) 3031 3054 Enrolled/ Eval* 31 24 Race-White 10 14 Black 21 10 % Male: ND * 4 arm study – Data for FTT & Ctrl only; abused or neglected cases excluded	NOFTT Ctrl Maternal educ 10.3 11.2 Income* 13 13 Health Insur† ND ND * # employed, † p < .05, ‡ p < .01	NOFTT, abused, or neglected Controls – no hx of abuse, FTT, or neglect	ND	Wt gain fallen below 2/3 of Harvard 50th percentile on growth curve	Retrospective longitudinal 3 annual assessments

Evidence Table 3. Studies associating immunologic response or infectious diseases with Failure to Thrive patients compared to healthy control subjects in developed countries

Part II

Author, Year, UI	Correlates		Measures				Method / Instruments utilized
Carvalho, 1984 85145406			FTT	Ctrl	% variation		Light microscope phagocytosis assay (% zymosan particles ingested)
	Phagocytosis						
	Eagle solution		18.7(7.3)	27.6(9.2)	-32.3	p < .01	
	Nl human serum		54.2(24.6)	78.5(7.8)	-30.9	p < .001	
	Patient serum		56.7(22.4)	75.9(10.9)	-25.3	p < .01	
	Chemotaxis						Boydan chamber (avg distance cells migrate)
	Eagle solution		25.4(10.0)	34.2(8.0)	-26.0	p < .01	
	LPS & nl human serum		42.6(17.7)	64.4(15.3)	-33.8	p < .001	
	LPS & patient serum		44.3(19.0)	68.5(18.4)	-35.3	p < .001	
	Total complement (u/ml)		235.2(55.1)	244.6(61.6)	-3.8	NS	Percent cell lysis
	C3 (mg/dl)		89.3(21.3)	80.5(19.3)	+10.9	NS	
	C4 (mg/dl)		38.5(11.2)	37.3(13.3)	+3.4	NS	
Sherrod, 1985 85026403	Infections		NOFTT	Ctrl			Chart review
		1y	1.13	.46			
		2y	.35	.29			
		3y	.03	.00			

Evidence Table 3. Studies associating immunologic response or infectious diseases with Failure to Thrive patients compared to healthy control subjects in developed countries

Part III

Author, Year	Associations found	Potential biases	Comments
Carvalho, 1984 85145406	The values for phagocytosis response and chemotactic function were significantly lower for the malnourished children in 3 tests: Zymosan incubated in Eagle, incubated with pooled normal human serum & incubated with serum from patient. The values were not significant for total complement, C3 and C4 components.	Cases and controls from different hospitals serving different SES groups; no data on age matching	Phagocytosis tests on 20 children, chemotaxis on other 20, total complement on 20 chosen at random; privately funded
Sherrod, 1985 85026403	NOFTT had more infections than controls during the 1st year (χ^2 = 5.38, $p < .025$) and across all 3 years (χ^2 = 5.79, $p < .025$). NOFTT illness were significantly increased during first 6 mo of life.	Attending physicians alerted to give special treatment to children suffering from maltreatment, analysis showed no increase in outcome variability; study design to identify relationship of illness to abuse, not FTT to illness	Data collectors blind to child group assignment; government & privately funded

Evidence Table 4. Studies associating immunologic response or infectious diseases with malnourished patients compared to well-nourished control subjects in developing countries

Part I

Author, Year, UI	Demographics	Maternal / household demographics	Inclusion criteria	Exclusion criteria	Definition of malnutrition	Study design
Ferguson, 1974 75022280	Country: Ghana Setting: Cases – inpatient Controls – ND Gp / Ctrl Mean age(mo): 28.9 (12-48) / 38.8 (24-55) Wt/age: ND / ND Ht/length: ND / ND Enrolled/Eval: 10 / 10 % Male: ND / ND Race: ND / ND	ND	Severe protein-calorie malnutrition Controls – "normal", matched for age	ND	Severe protein-calorie malnutrition	Prospective cross-sectional
Neumann, 1975 75106463	Country: Ghana Setting: hospital/in & outpatient clinic Age: 6 mo – 6 y Wt/age: ND Ht/length: ND Gpl* / Gp2† / Ctrl Enrolled/Eval: 34 / 42 / 41 % Male: 62 / 50 / 44 Race: Africans (assumed black) * Severely malnourished: kwashiorkor(23) & marasmus(11), † Moderately malnourished	ND	See Definition of FTT Controls matched for age, = 81% Harvard Std, nl serum albumin, no signs of malnutrition	ND	Gp1: 51-60% of 50th percentile Harvard Std for American children & albumin < 2.5 g/100ml, Gp2: 71-80% of Harvard Std & albumin > 2.5 g/100ml	Prospective cross-sectional

Evidence Table 4. Studies associating immunologic response or infectious diseases with malnourished patients compared to well-nourished control subjects in developing countries

Part I

Author, Year, UI	Demographics	Maternal / household demographics	Inclusion criteria	Exclusion criteria	Definition of malnutrition	Study design
Tuck, 1979 79254720	Country: Australia & Indonesia Setting: Hospital Age(mo): ND Wt/age: ND Ht/length: ND Enrolled/Eval: Gp1 marasmic 21 Gp2 underweight 23 Gp3 normal 25 % Male: ND Race: ND	ND	ND	Immunological deficiencies in normal children attending hospital in one site	NA (Patients classified according to Wellcome Working Party: underweight - 60-80% SWFA, marasmic - < 60% SWFA)	Prospective cross-sectional
Friedland, 1992 93159117	Country: South Africa Setting: Inpatient Gp / Ctrl Age(mo) 11 / 12 Enroled/Eval 1582 / 7282 % Male ND / ND Race: ND (assumed all black)	ND	Children w/kwashiorkor, marasmus, marasmic kwashiorkor admitted, ages 2 – 84 mo Controls - "well-nourished & children w/nutritional growth retardation admitted during same time period", same age range	ND	Wellcome criteria with growth charts from NCHS	Prospective cross-sectional

Evidence Table 4. Studies associating immunologic response or infectious diseases with malnourished patients compared to well-nourished control subjects in developing countries

Part I

Author, Year, UI	Demographics	Maternal / household demographics	Inclusion criteria	Exclusion criteria	Definition of malnutrition	Study design
Ballard, 1995 95239862	Country: Kenya Setting: Rural village/ community outreach Mean age*: 19.2 m (17.7-25.1) Wt/age: ND Ht/length: ND Enrolled: 114 Evaluated† Gp1 27 Gp2 51 Ctrl 31 49% Male (enrollment) Race: 100% Black Africans * At enrollment, † Gp1 Mod-severe malnutrition, Gp2 Mild malnutrition	Maternal reading level – average 3.5 yrs of schooling	14-25 mo, free from lower respiratory infections for = 4 wks Controls – "normal"	ND	Gp1 - ht/age < 90% of median Gp2 - ht/age 90% to <95% of median	Prospective longitudinal cohort Followed for max of 12 mos
Pandey, 1996 97246349	Country: India Setting: Outpatient Age(mo): Range 0-59, Mode 24-35 Enrolled: 200 households Evaluated: Gr1 37 GrII 56 GrIII 18 GrIV 4 Nl 85 % Male: ND Race: ND	ND	Random selection of < 5 y	ND	Graded nutritional status as GrI though GrIV clinically & by wt/age	Prospective longitudinal Assessments @ 2 wks for 1 y

Evidence Table 4. Studies associating immunologic response or infectious diseases with malnourished patients compared to well-nourished control subjects in developing countries

Part II

Author, Year	Correlates / Outcomes and measures	Associations found	Potential biases	Comments
Ferguson, 1974 75022280	Immunologic - Rosette forming cells	(percent of total lymphocytes) Gp - 16.6% (2.7 SE), Ctrl – 59.7% (1.4 SE) Marked decrease in rosette forming cells (measure of cellular immunity) in severe malnutrition; RFC re-measured in 5/10 cases 7-17 d after feeding high protein, high calorie diet – values returned to nl (%RFC = 63.2% ± 2.4). Other measures of impaired immune function – in vitro response of lymphocytes to PHA stimulation showed trend to be diminished in cases, but NS (no data)	7 diagnosed kwashiorkor & 3 with marasmus	US government funded

Evidence Table 4. Studies associating immunologic response or infectious diseases with malnourished patients compared to well-nourished control subjects in developing countries

Part II

Author, Year	Correlates / Outcomes and measures				Associations found	Potential biases	Comments
Neumann, 1975 75106463	Clinical infections / parasites Antibody responses				There was a marked increased in infections for severely malnourished group (Gp1), slight increase for the moderate malnourished group (Gp2) compared to Ctrl. The incidence of intestinal parasites were similar across the 3 gps, except for 10x increase in strongyloides stercoralis for Gp1, and 1 malarial case @ gp. Tonsil sz was decreased signf in Gp1 vs. Gp2 & Ctrl. Antibody responses were similar across all 3 gps. Lymphocyte response was signf lower in Gp1 vs. Gp2 or Ctrl. Cutaneous delayed hypersensitivity to PHA, monilia, SK-SD was signf lower in Gp1 & Gp2 vs. Ctrl. Response to KLH was slightly lower in the cases. Vitamin deficiencies in all groups, most prevalent in Gp1. Complement C3 decreased signf in Gp1 vs. Gp2 & Ctrl; NS results for C4. Other nutritional deficiencies included decreased iron & transferrin in Gp1.	Gp1 hospitalized cases, 16 of 34 had received nutritional tx before studies, Gp2 included 25 newly admitted & 17 living in orphanage or attendance at rehab clinic & were treated. Controls attended private nursery school or resided in orphanage & had some vitamin/mineral deficiencies	Government funded
		Gp1	Gp2	Ctrl			
	Tonsil size*	(%)	(%)	(%)			
	Score† 0	36	5	0			
	1+	52	50	34			
	2+	12	40	56			
	3+	0	5	10			
	Delayed hypersensitivity response						
	Lymphocyte response†	19	0	0			
	PHA‡	44	29	5			
	Monilia‡	59	38	20			
	SK-SD‡	76	57	23			
	KLH‡	5	0	0			
	Total serum proteins(SE)	5.1(.4)/ 6.3(.4)§	7.5(.1)	7.9(.1)			
	CBC & differential						
	Hemoglobin	60	17.5	12.5			
	Iron	44.8	29.7	20			
	%Transferrin saturation	41.3	55.3	50			
	Complement - C3	60.4(4.1)	86(3.9)	86.9(2.4)			
	* 0 = trace or absent, 1 = visible, 2 = enlarged beyond arch, 3 = extended past arch to uvula midline; † Percent reduced response; ‡ Percent nonresponders, § kwashiorkor/marasmus						

Evidence Table 4. Studies associating immunologic response or infectious diseases with malnourished patients compared to well-nourished control subjects in developing countries

Part II

Author, Year	Correlates / Outcomes and measures	Associations found	Potential biases	Comments
Tuck, 1979 79254720	Candida killing capacity Marasmic: 13.7% (3.4)* Underweight: 17.6% (4.4)* Normal: 44.5% (8.8)* * SEM	Candida-killing ability, as determined by Kolmogorov-Smirnov test, was reduced in each of two underweight populations compared with the well-nourished population ($p < .001$), NS between the underweight & marasmic gps	Normal adults included in the control group, number of adults not known, site(s) of adults unknown, one of the 3 sites had no malnourished children who may have also been outpatients	NS between the two malnourished groups on ability to resist candida; ND on funding source
Friedland, 1992 93159117	Bacteraemia: Gp (%) / Ctrl (%) Community acquired: 7.7 / 4.9 Nosocomial: 2.2 / 1.1 Overall: 9.9 / 6.0 Mortality Overall: 13.3 / 4.1 With bacteremia: 31 / 13	Index group are statistically significantly at higher risk than control group for community-acquired bacteremia ($p < 0.001$, RR for FTT 1.6, CI 1.3 – 1.9), nosocomial bacteremia ($p < 0.001$, RR for FTT 2.0, CI 1.4 – 3.0), and mortality, including mortality related to bacteremia ($p < 0.001$, RR for FTT 3.2, CI 2.7 – 3.8).	Index group considered severe malnutrition. Control group consisting of "nutritional growth retardation" which most likely represents what is recognized as FTT. Both factors invalidates the "controls'	Risk of death of malnourished children 2.5 more likely to die than bacteremic non-malnourished; ND on funding source; Government, private, & hospital funded
Ballard, 1995 95239862	Acute lower respiratory infection	Children classified as having moderate to severe stunting/malnutrition were at higher risk for ALRI (RR = 4.5, ht/age < 90% median) compared to non-stunted/malnourished children (ht/age = 95% of median) (classification by NCHS criteria)	8 LTF within 1 month of enrollment or had ALRI 4-8 wk period prior to observation; inconsistent data for # pts at evaluation; potential recall bias	US government & privately funded

Evidence Table 4. Studies associating immunologic response or infectious diseases with malnourished patients compared to well-nourished control subjects in developing countries

Part II

Author, Year	Correlates / Outcomes and measures	Associations found	Potential biases	Comments
Pandey, 1996 97246349	No. of children / # ARI episodes per child / yr Vit A deficient: 28 / 7.4 Not deficient: 172 / 5.6 Age(mo): 0-11 / 12-23 / 24-35 / 36-47 / 48-59 # ARI: 6.2 / 5.8 / 5.7 / 5.9 / 5.8 Sample n: 27 / 31 / 62 / 34 / 46 ARIs / year GrI: 5.6 GrII: 6.9 GrIII: 7.4 GrIV: 7.7 NI: 4.8	The 28 children with evidence of vitamin A deficiency had significantly higher # ARI than children without vit A deficiency ($\chi^2 = 8.64$, $p < .01$). There was association of increased malnutrition with more frequent # ARIs ($\chi^2 = 36.17$, $p < .05$). There was no age or sex difference.	Vit A deficiency diagnosed by "ocular signs using a brightly illuminated torch"	Follow-up intervals @ 2 wk for 1 yr; ND on funding source

Evidence Table 5. Studies associating behavioral problems with Failure to Thrive patients compared to healthy control subjects in developed countries

Part I

Author, Year, UI	Demographics	Maternal / household demographics	Inclusion criteria	Exclusion criteria	Definition of FTT	Study design
Pollitt, 1976 76109110	Country: US Setting: Outpatient FTT Ctrl Mean age*: Male 33(14) 34(13) Female 39(14) 39(15) Mean ht†: Male 93(2) 101(1) Female 90(2) 102(3) Enrolled/Eval 19 19 % Male 47 47 Race: ND * Months, † centimeters	FTT Ctrl Maternal educ 11 (2) 12 (1) Income - Gross annual 6943 (3444) 9541 (4768) Per capita 1557 (725) 2648 (1517) Health insur ND ND	Outpatient clinic, 12-60 mo, ht & wt < 3%, bw = 2500 gm, GA = 36 wks, nl birth, nonorganic, singleton, maternal ht = 154.5 cm & English-speaking ability Controls matched for age (± 3 mo), sex, race, ht & wt = 25%	Birth complications, physical disability, genetic or organic retardation, brain damage, organic growth retardation	Boston Growth Standards – ht & wt = 3rd percentile	Prospective cross-sectional Weekly interviews for 7-11 sessions
Mitchell, 1980 80166667	Country: US Setting: Outpatient clinic FTT Ctrl Age(y) 2-5 2-5 Wt/age ND ND Ht/length ND ND Enrolled : cohort of 312(323)* Evaluated 30 282 % Male 36.7 51.8 % Black 70 70 * See Potential biases column	Maternal education: ND Income: ND Health insur: FTT-53% Medicaid Ctrl-49% Medicaid	See definition of FTT Controls: wt = 80% of nl, matched for age, sex, mother's age/ marital status & family problems	Organic cause of FTT, single anomalous low wt recorded, clinic registration by age 6 mo, < 3 visits	Wt for age < 80% of nl up to age 24 mo	Ambidirectional longitudinal 1 fwup at age 3 – 6 y

Evidence Table 5. Studies associating behavioral problems with Failure to Thrive patients compared to healthy control subjects in developed countries

Part I

Author, Year, UI	Demographics	Maternal / household demographics	Inclusion criteria	Exclusion criteria	Definition of FTT	Study design
Polan, 1991 92098539	Country: US Setting: Outpatient clinic FTT / Ctrl Mean age*: 16.7(6.9) / 18.9(7.3) Wt/age: ND / ND Ht/age: ND / ND Enrolled/Eval: 28 / 14 % Male: 50 / 43 Race: ND / ND * Months	Maternal education: ND Income($1,000): FTT / Ctrl Mean: 39.4 (51.4) / 40.1 (49.6) Median: 27.5 / 28.5 Health insur: ND / ND	FTT, age 6 – 36 mo Controls from same site, wt & ht = 10th percentile on NCHS growth charts	Life threatening or terminal illnesses	= 35 wks gestation & normal birth wt, wt fell < 5th percentile, or decrease in wt gain in 6 mo = 2 major percentiles based on NCHS	Prospective cross-sectional
Drotar, 1992 92372721	Country: US Setting: Outpatient fwup FTT / Ctrl Mean age*: 4.92(2.81) / 5.05(2.85) Wt/age: ND / ND Ht/length: ND / ND Enrolled: 68 / 68 Evaluated: 48 / 47 % Male: 71 / 57 Race: Black: 29(60%) / 35(74%) White: 29(40%) / 12(26%) *At intake	FTT / Ctrl Maternal educ: 10.94 (1.74) / 11.51 (1.57) Income: 5446 (5561) / 7792 (10309) Health insur: ND / ND Mean (SD)	Hospitalized for NOFT with nutritional intervention, age 1 – 9 months Controls matched for age at intake, sex, race, birth order, gestational age, maternal educ & age, family income & size	Physical abuse, residence > 1 hr from hospital, bw < 1500 gm	Wt < 5th percentile based on NCHS, absence of disease, wt gain in hospital, poor wt velocity	Prospective longitudinal 1 fwup at age 42-48 months

Evidence Table 5. Studies associating behavioral problems with Failure to Thrive patients compared to healthy control subjects in developed countries

Part I

Author, Year, UI	Demographics	Maternal / household demographics	Inclusion criteria	Exclusion criteria	Definition of FTT	Study design
Hutcheson, 1993 94015754	Country: US Setting: Primary care clinic FTT / Ctrl Mean age*: 15.1(5.2) / 14.9(5.1) Wt/age: 2.83 / 63.17 Ht/age: 23 / 63 Enrolled/Eval: 34 / 34 % Male: 62 / 62 Race: Black: 32 / 32 * Months	FTT / Ctrl Maternal educ*: 38 / 70 Income†: 64 / 70 Health insur: ND / ND * % HS graduate † % receiving AFDC	NOFTT, age 8 – 24 mo Controls matched for age, sex, race	Congenital disorder, chronic disease, < 37 wk gestation, SGA	Wt for age ≤ 5th percentile, or wt for ht ≤ 10th percentile, based on NCHS	Prospective cross-sectional
Kelleher, 1993 93234174	Country: US Setting: Primary care clinic FTT / Ctrl GA(wk)*: 33.0 / 33.1 Wt(g)*: 1679 / 1845 Enrolled: 842* Evaluated: 180 / 591 % Male: 52.2 / 47.9 Race: % Black: 50 / 53.8 * At birth	FTT / Ctrl Maternal educ* <HS: 40.6 / 38.1 HS: 30.0 / 29.3 Some col: 14.4 / 20.8 ≥col grad: 15.0 / 11.8 Income - <10K: 38.6 / 34.5 10-20K: 19.9 / 23.9 >20K: 38.1 / 37.4 Health insur: ND / ND * % HS graduate	Gestation age ≤ 37 wks, birth wt ≤ 2500 g, FTT Controls matched for – birth wt +/- 250 g, maternal education, maternal race, & infant sex	Live outside catchment area, D/C outside recruitment period, D/C or died within 48 hr, hospitalized > 60 d, oxygen support > 90 d, twin, triplet or quadruplet of ineligible child, maternal drug/alcohol abuse, insufficient English skills, psychiatric hosp	< 5th percentile for gestation corrected age based on NCHS, growth status on "wt curve below that recorded at last regular assessment visit."	Prospective longitudinal Fwup at ages 12, 24, 36 mo

Evidence Table 5. Studies associating behavioral problems with Failure to Thrive patients compared to healthy control subjects in developed countries

Part I

Author, Year, UI	Demographics	Maternal / household demographics	Inclusion criteria	Exclusion criteria	Definition of FTT	Study design
Skuse, 1994 94253258	Country: UK Setting: Outpatient FTT / Ctrl Age(mo)* 14.6(1.4) / 14.2(1.4) Wt/age† -2.07(.44) / .10(.96) Ht/length† -1.27(.94) / .18(.73) Enrolled 49 / 50 Evaluated 47 / 47 % Male 49 / 49 % Non-white 43 / 34 * Mean (SD), † z score, p < .001	Maternal educ: ND Income: income/welfare support FTT-16, Control-11 Health insur: National healthcare	District-centered until 12 mo of age, singleton deliveries of 38-41 wks gestation Controls matched for sex, age, ethnic origin, bw within 300 g, ordinal position, SES	≤ 3rd centile, no wt data	Wt for age ≥ -1.88 by 12 mo of age & sustained 3 mo (based on NCHS)	Prospective longitudinal Assessments at age 15 mo & 4y
Puckering, 1995 95378341	Country: UK Setting: Outpatient FTT / Ctrl Age(mo) 48.9(1.8) / 48.2(0.8) Wt/age(SDS)* -2.01(0.6) / -0.32(1.1) Ht/length(SDS)* -2.24(0.5) / -0.6(0.9) Enrolled/Eval 23 / 23 % Male 48 / 48 Race: 100% White * based on NCHS, p < .001	FTT / Ctrl Maternal educ* 15.6 (1.4) / 15.6 (1.4) Income† 11 / 7 48% / 30% Health insur: Socialized medicine * Age leaving full-time education † Income support/welfare	From inner city population sample - Caucasian born in 1980 with longitudinal growth data from birth to 4 years Controls matched for sex, gestational age ≥ 38 wks, & ethnic origin	Prematurity, congenital defects/ diseases affecting growth, no perinatal insults	Ht & wt < 10% based on standard British growth charts (Tanner & Whitehouse)	Ambidirectional cross-sectional

Evidence Table 5. Studies associating behavioral problems with Failure to Thrive patients compared to healthy control subjects in developed countries

Part I

Author, Year, UI	Demographics	Maternal / household demographics	Inclusion criteria	Exclusion criteria	Definition of FTT	Study design
Corbett, 1996 97113595	Country: UK Setting: Clinic Age at follow-up: 6-7 yr FTT / Ctrl Wt/age ND / ND Ht/length ND / ND Enrolled 52 / 52 Evaluated 48 / 46 % Male: ND Race: 100% White	Maternal educ: ND Income: "…most economically deprived wards in Newcastle" Health insur: National healthcare	Full term singleton with records of 6 or more weights over first 18 months age Consecutive controls matched for age & sex	Non-Caucasian, "poor growth resulting from major organic disease"	Weight deviated downward from maximal centile achieved at 4-8 wks, across ≥ 2 centile lines, & remained at level ≥ 2 measurements ≥ 1 mo – chart based on Tanner & Whitehouse	Ambidirectional longitudinal 5 year follow-up of cases
Wilensky, 1996 97022837	Country: Israel Setting: Community pediatric clinic FTT / Ctrl Mean age(mo)* 15/20 / 15/20 Wt/age ND / ND Ht/length ND / ND Enrolled† 55 / 1352 Evaluated 50 / 50 % Male ND / ND Race: ND; Maternal country of birth – 68% Israel, 25% Europe/America, 5% N Africa, 2% Asia * At entry / assessment	FTT / Ctrl Maternal educ* 13.8 (1.62) / 13.4 (1.44) Income: AFDC 76% Health insur: ND * Mean (SD), based on record review of potential subjects	FTT infants by review of records who have reached 15 months born in 1991 Controls from same maternal & child health clinic matched for birth month, maternal educ, maternal age, parity, and infants' birth wt	Birth wt < 2500 gm, < 37 weeks, wt/ht ratio > 10 %, organic cause of FTT	Wt < 3% by NCHS for = 3 months prior to age 15 months	Ambidirectional cross-sectional

Evidence Table 5. Studies associating behavioral problems with Failure to Thrive patients compared to healthy control subjects in developed countries

Part I

Author, Year, UI	Demographics	Maternal / household demographics	Inclusion criteria	Exclusion criteria	Definition of FTT	Study design
Chatoor, 1998 99026462	Country: US Setting: Outpatient Gp1* / Gp2† / Ctrl Age(mo): 21.4 / 23.7 / 22.5 range: (12-37) / (13-37) / (13-36) Wt/age: ND / ND / ND Ht/length: ND / ND / ND Enrolled: 34 / 34 / 34 Evaluated: 33 / 34 / 34 % Male: 39 / 58 / 44 Race White: 58 / 58 / 59 Af-Am: 27 / 27 / 29 Latino: 3 / 6 / 6 Asian: 15 / 12 / 6 * Infantile anorexia, † Picky eaters	Maternal educ: ND Income: Gp1 / Gp2 / Ctrl SES* II / II / II † I: 41 / 35 / 32 II: 29 / 32 / 44 III: 9 / 26 / 9 IV: 9 / 3 / 12 V: 12 / 3 / 3 Health insur: ND * Mean Hollingshead Four Factor Index rating of SES † % toddlers in each Hollingshead category	Infantile anorexia, toddlers who are picky eaters Controls & picky eaters matched for age, sex, SES ethnicity	Organic cause for feeding problems, food refusal after traumatic event/post-traumatic feeding disorder, gestational age < 36 wks, psychiatric illness, mother with medical or mental illness that compromised ability to care for child or was nonEnglish speaking	Infantile anorexia: onset 6-36 mo, food refusal ≥ 1mo, acute and/or chronic malnutrition, parental concern & anxiety, conflictual feeding interactions Picky eating: food selectivity ≥ 1mo, no malnutrition, variable parental concern	Prospective cross-sectional
Wright, 2000 20161504	Country: UK Setting: Outpatient FTT / Ctrl Age(mo): 15.1* (7-28) / ND (16-18) Wt/age: -2.00(.93) / ND Ht/length: -1.06(.96) / ND Enrolled: 120 / 40 Evaluated: 97 / 28 % Male: 54 / 61 % Nonwhite: 9 / 0 * Median	Maternal educ: ND Income: ND FTT* / Ctrl I* Unemployed parent: 39 / 13 Nonhome-owner: 54.7 / 53.6 No car: 48.3 / 50 Health insur: National healthcare * Percent	Baseline wt at 6-8 wk & 2nd wt at 9-18 mo Controls from 3 "generally representative" of Newcastle	2nd twin sibling	Weight decline of 1.26 SD from age 6-8 wks to 2nd weighing at 9-18 months	Prospective cross-sectional

Evidence Table 5. Studies associating behavioral problems with Failure to Thrive patients compared to healthy control subjects in developed countries

Part I

Author, Year, UI	Demographics	Maternal / household demographics	Inclusion criteria	Exclusion criteria	Definition of FTT	Study design
Kerr, 2000 20277217	Country: US Setting: Inner-city hospital clinic Age (mo) / Mean wt/age / Ht/ length Gp1* 73.3±1.9 ND ND Gp2† 74.2±3.2 ND ND Ctrl1‡ 73.0±1.2 ND ND Ctrl2§ 73.5±1.9 ND ND Evaluated / % Male / % Race‖ Gp1 64 56 88 Gp2 28 48 87 Ctrl1 21 53 94 Ctrl2 80 51 97 Mean, * FTT, † FTT & maltreatment, ‡ Maltreatment, § Neither, ‖ % African Am	Maternal educ / Income* Gp1 11.2(1.9) 56 Gp2 10.4(1.7) 81 Ctrl1 11.2(1.4) 65 Ctrl2 11.4(1.9) 62 Health insur: ND Mean, * percent AFDC	FTT, < 24 mo, wt/age < 5th %, gestational age = 37 wks & appropriate birth wt Ctrl from same site, bet ages 3 – 30 mo, wt/age > 10th %, gestational age = 37 wks & appropriate birth wt Subgroups Gp2 & Ctrl1: including hx of maltreatment defined as at least one report with Child Protective Services (CPS) by age 6, including neglect, physical abuse, & sexual abuse	History of perinatal complications, congenital disorders, chronic illness	Wt/age < 5th % by NCHS growth charts	Ambidirectional longitudinal Assessment at age 6 y
Steward, 2001 21291243	Country: US Setting: Outpatient primary care clinic FTT / Ctrl Age (mo) 9.2 8.6 Wt/age(kg)* 7.14 8.54 Ht/length ND ND Enrolled 17 16 Evaluated 14 14 % Male 36 36 Race: white 9 9 black 5 5 Mean * p < 0.05	FTT / Ctrl Maternal educ* 12.2 12.5 Income: ND Health insur: ND * NS for educ & age	Diagnosed FTT, 2-12 months, birthweight ≥ 2500g Controls matched for age, sex, & race – “growing appropriately”	Absence of disease process, pre- or post-natal complications	Weight for age fallen below 5 percentiles or fallen across 2 major percentiles	Prospective cross-sectional

Evidence Table 5. Studies associating behavioral problems with Failure to Thrive patients compared to healthy control subjects in developed countries

Part II

Author, Year	Correlates & correlate measures			Method / Instrument	Associations found
Pollitt, 1976 76109110		FTT	Ctrl	Reported or observed feeding, history of other behaviors, direct measures	FTT were reported to have significantly more feeding behavior problems than controls in difficulty in feeding (χ^2 = 5.97, p < .02); eating patterns (χ^2 = 8.74, p < .03); supported by caloric intake measures (t = 2.06, p = .03). FTT had a trend for exhibiting autoerotic & self-harm behavior problems; analyzed for sum any of these atypical behaviors, the FTT exhibited significant higher incidence (χ^2 = 8.19, p < .01)
	Feeding difficulty	10	2		
	Meal pattern-often skipped/skimpy	16	6		
	Caloric intake	1400(300)	1700(500)		
	Response to food - correlation to wt %	ND	ND		
	Eating disorder – FTT 4 exhibiting eating & drinking nonfood items, polydipsia, gorging, & hiding food Ctrl none reported				
	Autoerotic	2	0		
	Self harm	2	0		
	Sum children with abnormal behavior	10	1		
Mitchell, 1980 80166667	Behavior problems	FTT 3.3%	Ctrl 2.8%	Behavior problems questionnaire	NS but FTT group had higher incidence of behavioral problems.
Polan, 1991 92098539	FTT status on positive & negative affect in feeding in 4 channels of emotion – facial display pattern, vocalization, gesture, body posture & movement			Kiddie Affect Inventory and Assessment of 11 affects scored independently	FTT had significantly decreased positive affect during feeding & nonfeeding (t=-2.92, p=.04; t=-3.151, p = .003, respectively) Also FTT had significantly increased negative affect during feeding (t=2.567, p=.01).
Drotar, 1992 92372721		FTT	Ctrl	California Child Q-set Lock box – Rectangular container w/10 locked compartments Child Behavior Checklist	FTT children have poor problem-solving, behavior problems, & "deficiencies in personality development" versus controls. The ego development score was lower, ego resiliency score was significantly lower (p<.05). FTT behavior organization & problem scores were significant lower (p<.001, p<.05, respectively)
	Personality development				
	• ego control	376.67(32.28)	413.42(30.73)		
	• ego resiliency	376.06(41.21)	397.37(41.45)		
	Behavioral organization	.95(1.92)	8.45(12.08)		
	Behavioral problems	58.5(10.7)	53.2(12.7)		

Evidence Table 5. Studies associating behavioral problems with Failure to Thrive patients compared to healthy control subjects in developed countries

Part II

Author, Year	Correlates & correlate measures					Method / Instrument	Associations found
Hutcheson, 1993 94015754	Child temperament	FTT1*	FTT2†	Ctrl1*	Ctrl 2†	Infant Characteristics Questionnaire	The FTT cases rated as more difficult with significant finding on effect of infant age on maternal report of infant level of difficulty (F=4.21, p = 0.04). Though no age or group differences found on perceived life stresses, parenting stresses, informal support, and negative affectivity, the FTT infants had fewer life events than FTT toddlers, whereas the reverse was true for the comparison group. The maternal effect was less positive toward FTT toddlers than FTT infants. Controlling for maternal education, wt for age, & ht for age - significant group by age interaction for maternal factors (F=4.98, p = 0.02) due to maternal affective tone (F=9.33, p = 0.005)
		0.48	0.49	0.06	-0.19		
	* Infants: 8 – 13.4 mo † Toddlers: 13.5 – 24 mo						
Kelleher, 1993 93234174	Behavioral disorder	FTT	Ctrl				Sample of LBW or premature infants followed had lower HOME scores at 12 months, NS. There was a trend towards more behavioral problems for the FTT as reported by parents.
	Age(m) 12	73.0	73.6			Bates Temperament scale	
	24	9.4	8.9			CBCL	
Skuse, 1994 94253258	Behavior Assessment at 15 mo					TRIB	No difference between groups for expression of positive affect in relation to task directed behavior or task persistence
Puckering, 1995 95378341	Behavior score	FTT	Ctrl			Behavior Screening Questionnaire (BSQ)	There was no difference in BSQ scores for the two groups (p=.2). MANOVA performed on calculated mean GCI & BSQ scores vs. unconditional & conditional interactions grouped by high or low (above & below overall mean value for interaction) – results indicate that parenting style does not account for GCI or BSQ differences between FTT & Ctrl.
		8.7(4.4)	6.9(3.5)				
Corbett, 1996 97113595	Behavioral disorder	FTT	Ctrl			CBCL	There was a trend towards more behavioral problems for the FTT as reported by teachers (NS, p = .296)
	Parental reporting	33	34				
	Teacher reporting	23	14				
	Median						

Evidence Table 5. Studies associating behavioral problems with Failure to Thrive patients compared to healthy control subjects in developed countries

Part II

Author, Year	Correlates & correlate measures					Method / Instrument	Associations found
Wilensky, 1996 97022837	Feeding problems		FTT	Ctrl		Maternal questionnaire	FTT children had significantly more feeding problems than the controls ($p < .05$)
	• showing hunger		53.4%	46.2%			
	• turns head from food		59.7%	20.7%			
	• shows pleasure at meals		76.7%	94.3%			
	• nervous at meals		23.2%	5.6%			
	• eats variety		48.8%	69.8%			
	• spits out food		65.1%	33.9%			
Chatoor, 1998 99026462		Gp1	Gp2	Ctrl		Ainsworth & Cassidy & Marvin attachment classification Strange Situation Security Scale / 9 point Likert	There was significant relationship between diagnostic group and frequency of insecure attachments ($\chi^2 = 8.0$, $p < .05$). Infant anorexia group exhibited more frequent insecure relationships compared to picky eater or healthy eater groups ($\chi^2 = 6.7$, $p < .01$; $\chi^2 = 3.9$, $p < .05$). There was main effect for group for Attachment security scale ($F = 5.8$, $p < .01$) with the infantile anorexia group as least secure. The closer to ideal weight was correlated to increased security ($r = 0.31$, $p < .01$).
	Attachment classification						
	Secure	20	30	28			
	Avoidant	4	3	3			
	Resistant	7	1	3			
	Disorganized	2	0	0			
	Attachment security scale rating	4.9(2.1)	6.1(1.3)	6.0(1.5)			
	Percent ideal weight						
Wright, 2000 20161504	Behavior & temperament		FTT	Ctrl		Parental reporting / Likert scale	FTT had higher maternal reporting of infants as undemanding & shy in temperament ($p = .005$ & $p = .002$, respectively). Higher maternal reporting of infancy feeding problems, variable eating pattern.
		Sociable	47	26			
		Average	17	2			
		Shy	12	0			
		Demanding	18	13			
		Average	48	15			
		Undemanding	11	0			
Kerr, 2000 20277217		Gp1	Gp2	Ctrl1	Ctrl2		There is main effect from risk status (FTT, FTT & maltreatment, maltreatment alone) as being associated with worse scores in cognitive & adaptive performance ($F = 3.527$, $p < .01$), school & home behavior ($F = 2.986$, $p < .01$; $F = 2.453$, $p < .05$, respectively). There was a trend for worse scores in all areas for FTT vs. no risks factors or maltreatment alone.
	Adaptive functioning at school	15.85 (7.2)	13.88 (6.9)	16.92 (6.9)	17.85 (9.7)	Teacher Report Form (↑ numbers = better score)	
	School behavior	31.45 (27.1)	53.53 (35.7)	29.18 (25.0)	28.87 (29.1)	Teacher Report Form (↓ numbers = better score)	

Evidence Table 5. Studies associating behavioral problems with Failure to Thrive patients compared to healthy control subjects in developed countries

Part II

Author, Year	Correlates & correlate measures					Method / Instrument	Associations found
	Home behavior	28.11 (22.8)	34.85 (21.2)	29.00 (20.5)	26.67 (18.4)	Child Behavior Checklist (↓ numbers = better score)	
Steward, 2001 21291243		FTT	Ctrl			PCERA subscale	FTT group scored significantly lower on the communication subscale ($p < 0.02$); during interactions with the mother had less visual contact, more gaze aversion & vocalized less than controls, had difficult to read cues. They also scored lower than controls on the mood scale, were more irritable & apathetic ($p < 0.05$).
	Communication	3.19	4.07				
	Mood effect	3.65	4.26				

Evidence Table 5. Studies associating behavioral problems with Failure to Thrive patients compared to healthy control subjects in developed countries

Part III

Author, Year	Potential biases	Comments
Pollitt, 1976 76109110	4 cases with FTT hx within ht 3rd & 10th percentiles included in study	Government & privately funded
Mitchell, 1980 80166667	Physical exams & growth status by PI not blinded	Government & privately funded
Polan, 1991 92098539	37% of mothers of normal growth children refused study or failed to appear for 1st appointment, no FTT mothers refused study; randomly selected subset of 107 who completed video lab observation session; acute and chronic conditions in sample, 6 organic FTT based on Woolston score	FTT subgroup analyses no difference in sex, mother's marital status, family income, but organic FTT significantly younger at 10.8 mo vs. 18.3 for NOFTT, p = 0.016. NS for degree of acute or chronic malnutrition and positive or negative affect in feeding & nonfeeding activities; government & privately funded
Drotar, 1992 92372721	---	No difference for attrition group vs group evaluated, index gp hospitalized avg 14 d for dx & nutritional intervention; government funded
Hutcheson, 1993 94015754	76% of index group met both criteria for NOFTT (wt for age, & ht for age), 24% met one criterion; unknown n for age by group comparisons	Government & privately funded
Kelleher, 1993 93234174	Of 985 enrolled, 71 LTF, 12%(20) OFTT, 16%(28) were both OFTT & NOFTT	21% of babies develop FTT by 36 wks; ND on funding source
Skuse, 1994 94253258	2 cases & 3 controls didn't complete assessments & were excluded from analyses, 1 case had microcephaly, hypotonia, & an action tremor or ataxia of unknown origin	Researchers blinded to patient's status in measures except anthropometry; privately funded

Evidence Table 5. Studies associating behavioral problems with Failure to Thrive patients compared to healthy control subjects in developed countries

Part III

Author, Year	Potential biases	Comments
Puckering, 1995 95378341	---	Other than clinic anthropometric measures, home visits by assessors blinded to child's group status; The FTT children were significantly smaller than the controls; government funded
Corbett, 1996 97113595	3 from each group refused consent at follow-up, LTF or moved - 2 cases, 3 controls, 1 case not originally studied participated for follow-up study, 4 of those cases were the slowest growing 5% - also removed from home, all controls stayed with parents. Edward's diagnostic criteria for growth measure considered limited.	Additional aubgroup analyses for FTT cases showed significant association between full-scale IQ and cases with lowest Thrive Index values, p = 0.03; ND on funding source
Wilensky, 1996 97022837	Feeding behaviors and HOME environment are causal factors given time dissociation as FTT was established at 15 months, where as, maternal interview/home assessment at 25 months	2/5th of infants diagnosed as FTT no longer fit the criteria at 20-month follow-up, yet had positive association on Bayley MDI. Reported associations for FTT without specific data: paternal age (p<.01), maternal education, & behavioral observations of lower sociability (p<.05) & fear of examiner (p<.05); ND on funding source
Chatoor, 1998 99026462	1 infant anorexia withdrew because mother became ill	Testers blinded to child's status; poor discussion of SES markers, no quantification of malnutrition, no demonstration of equivalency of control groups; government funded
Wright, 2000 20161504	Of 120 cases, 23 recovered above screening threshold & had no subsequent data, 21 families received social work input of which, 4 cases registered at risk of abuse or neglect, 17 cases had "relevant organic conditions"…but only 4 said to be main explanation for their FTT", age difference between groups	Government & privately funded
Kerr, 2000 20277217	Hx of maltreatment not part of original recruitment criteria; unknown number of original sample, also in Mackner 1997 sample (n=177) is reported to be a subsample; maltreatment group may not include all because of definition of a CPS report filed	At 6 year, most FTT children had recovered & 3% had weight for height < 5th percentile; government funded
Steward, 2001 21291243	Withdraws include: mother changed mind, not available for home visit, opposition of mother's significant other (numbers of each not given)	Majority of single mothers, difference in birthwt – FTT, 2822 g vs. controls, 3344 g (p < 0.013); government & privately funded

Evidence Table 5. Studies associating behavioral problems with Failure to Thrive patients compared to healthy control subjects in developed countries

Part III

Author, Year, UI	Demographics	Maternal / household demographics	Inclusion criteria	Exclusion criteria	Definition of FTT	Study design
Galler, 1983b 83136863	Country: Barbados Setting-Outpatient Age(y): 5-11 Gp / Ctrl Wt/age ND / ND Ht/length ND / ND Enrolled 141 / 129 Evaluated 129 / 129 % Male 60 / ND Race: 100% Black	Maternal educ: ND, universal education, 95% population literate Income: lower for cases compared to controls Health insur: ND	Discharged 5 – 11 y olds w/dx at age 1 y with PEM Grade II-III, BW > 5 lbs Controls without PEM, matched for age, gender, handedness, & same school / neighborhood	Pre- or peri-natal complications, edema, seizures, head trauma, loss of consciousness, high fever	Gomez Scale PEM: Grade II- 61-75% or Grade III- ≤ 60% standard wt for age on Harvard Standard Scale	Ambidirectional longitudinal Fwup 4 – 10 y after D/C

Evidence Table 6. Studies associating behavioral problems with malnourished patients compared to healthy control subjects in developing country
Part II

Author, Year	Correlates & correlate measures	Method / Instrument	Associations found	Potential biases	Comments
Galler, 1983b 83136863	Classroom behavior – Gp status by Factor 1-attention deficit Factor 2-social interaction Factor 3-physical appearance	Study specific teacher questionnaire	From ages 5-11, The index group's behavioral development was lower than the comparison group. Early PEM is associated with increased problems in attention, deficit, social interaction, & physical appearance. Signf for – Factor 1 / Factor 2 / Factor 3 Gp status: F = 37.2, p ≤ .001 / F = 8.3, p ≤ .05 / F = 14.3, p ≤ .001 Gp vs. Ctrl: t = 5.5, p ≤ .01 / t =4.1, p ≤ .01 / t = 3.1, p ≤ .01	Withdraws/non-participation – 4 refused consent, 7 LTF, 1 cerebral palsy; severe PEM	Private & hospital funded

Evidence Table 7. Studies associating cognitive & neurological development with Failure to Thrive patients compared to healthy control subjects in developed countries

Part I

Author, Year, UI	Demographics	Maternal / household demographics	Inclusion criteria	Exclusion criteria	Definition of FTT	Study design
Mitchell, 1980 80166667	Country: US Setting: Outpatient clinic FTT / Ctrl Age(y) 2-5 / 2-5 Wt/age ND / ND Ht/length ND / ND Enrolled : cohort of 312(323)* Evaluated 30 / 282 % Male 36.7 / 51.8 % Black 70 / 70 * See Potential biases column	Maternal educ: ND Income: ND Health insur: FTT-53% Medicaid Ctrl-49% Medicaid	See Definition of FTT Controls: wt = 80% of nl, matched for age, sex, mother's age/ marital status & family problems	Organic cause of FTT, single anomalous low wt recorded, clinic registration by age 6 mo, < 3 visits	Wt for age < 80% of nl up to age 24 mo	Ambidirectional longitudinal 1 fwup at age 3 – 6 y
Hack, 1982 82227864	Country: US Setting-Recruitment: Hospital Follow-up: hospital/clinic Gp1* / Gp2† Mean age‡ 32(2.8) / 29(1.9) Wt/age(g) 1141(285) / 1197(206) Length(cm) 37.9(3.8) / 38(2.7) Enrolled|| ND / ND Evaluated 38 / 154 % Male 47 / 47 % Black 52 / 63 * SGA, † AGA, ‡ wks gestation, || n = 204	Gp1 / Gp2 Maternal educ <HS 12 / 32 Income* 28 / 99 Health insur ND / ND * Hollingshead Social Class 4 & 5	VLBW, < 1500g, divided into two groups: SGA < 2 SD or AGA	ND	Wt < 2 SD below mean for age @ term and/or @ 8 mo of age	Prospective longitudinal Assessments at age 40 wk & 8 m

Evidence Table 7. Studies associating cognitive & neurological development with Failure to Thrive patients compared to healthy control subjects in developed countries

Part I

Author, Year, UI	Demographics	Maternal / household demographics	Inclusion criteria	Exclusion criteria	Definition of FTT	Study design
Singer, 1984 85057547	Country: US Setting-Recruitment: hospital Follow-up: ND NOFTT / OFTT / Ctrl GA(wk)* 39(1.8) / 37(3.5) / 38(1.8) range 36-40 / 28-40 / 36-40 PA(wk)† 30(7.0) / 30(7.5) / 30(10.1) range 20-44 / 21-44 / 20-44 Birth wt 2847 / 2378 / 3027 Enrolled 13 / 13 / 13 Eval‡ 11 / 11 / 11 Age: 20.6 mo % Male: ND Race: ND Mean (SD), * gestational age, † postnatal age, ‡ 20 mo follow-up	NOFTT / OFTT / Ctrl Maternal educ* 12.5 (1.4) / 11.4 (1.4) / 12.5 (12.5) Income: ND Health insur: ND * At evaluation	NOFTT-unknown organic cause of condition, absence of wt gain during or shortly after hospitalization NFTT-documented organic cause of condition Controls -"not FTT"	ND	ND	Prospective longitudinal Assessments at age 8 mo, 20 mo, 3 y
Haynes, 1984 84233543	Country: US Setting: In & Out-patient Age: ND Wt/age: ND Ht/length: ND FTT1* / FTT2† / Ctrl Enrolled/Eval 25 / 25 / 25 % Sp-Am? 44 / 44 / 44 Sp-Am? 40 / 52 / 52 White? 36 / 44 / 36 White? 36 / 24 / 28 Black? 20 / 12 / 20 Black? 24 / 24 / 20 % Male: ND * std care & lay health visitor intervention, † std care only	FTT1 / FTT2 / Ctrl Maternal educ 10 / 11 / 10 Income* 379 (0-750) / 372 (0-950) / 362 (0-1100) Health insur: ND * @ mo	Consecutive admissions for NOFTT Controls - thriving non-hospitalized patients matched for age, sex, birth wt, & mother's age, ethnicity, number of living children	ND	< 5 percentile or significant decline from birth wt percentiles	Prospective longitudinal 1 assessment 6 mo after intake

Evidence Table 7. Studies associating cognitive & neurological development with Failure to Thrive patients compared to healthy control subjects in developed countries

Part I

Author, Year, UI	Demographics	Maternal / household demographics	Inclusion criteria	Exclusion criteria	Definition of FTT	Study design
Drotar, 1992 92372721	Country: US Setting: Inpatient with outpatient follow-up FTT / Ctrl Mean age* 4.92(2.81) / 5.05(2.85) Wt/age ND / ND Ht/length ND / ND Enrolled 68 / 68 Evaluated 48 / 47 % Male 71 / 57 Race: Black 29(60%) / 35(74%) White 29(40%) / 12(26%) * Age in months, at intake	FTT / Ctrl Maternal educ 10.94 (1.74) / 11.51 (1.57) Income 5446 (5561) / 7792 (10309) Health insur ND / ND Mean (SD)	Hospitalized for NOFT with nutritional intervention, age 1 – 9 months Controls matched for age at intake, sex, race, birth order, gestational age, maternal educ & age, family income & size	Physical abuse, residence > 1 hr from hospital, bw < 1500 gm	Wt < 5th percentile based on NCHS, absence of disease, wt gain in hospital, poor wt velocity	Prospective longitudinal 1 fwup at age 42-48 mo
Kelleher, 1993 93234174	Country: US Setting: Primary care clinic FTT / Ctrl GA(wk)* 33.0 / 33.1 Wt(g)* 1679 / 1845 Enrolled: 842* Evaluated 180 / 591 % Male 52.2 / 47.9 Race: % Black 50 / 53.8 * At birth	FTT / Ctrl Maternal educ* - <HS 40.6 / 38.1 HS 30.0 / 29.3 Some col 14.4 / 20.8 ≥col grad 15.0 / 11.8 Income – <10K 38.6 / 34.5 10-20K 19.9 / 23.9 >20K 38.1 / 37.4 Health insur ND / ND * % HS graduate	Gestation age ≤ 37 wks, birth wt ≤ 2500 g, FTT Controls matched for – birth wt +/- 250 g, maternal education, maternal race, & infant sex	Live outside catchment area, D/C outside recruitment period, D/C or died within 48 hr, hospitalized > 60 d, oxygen support > 90 d, twin, triplet or quadruplet of ineligible child, maternal drug/ alcohol abuse, insufficient Eng skills, psychiatric hospitalization	< 5th percentile for gestation corrected age based on NCHS, growth status on "wt curve below that recorded at last regular assessment visit."	Prospective longitudinal Fwup at ages 12, 24, 36 mo

Evidence Table 7. Studies associating cognitive & neurological development with Failure to Thrive patients compared to healthy control subjects in developed countries

Part I

Author, Year, UI	Demographics	Maternal / household demographics	Inclusion criteria	Exclusion criteria	Definition of FTT	Study design
Skuse, 1994 94253258	Country: UK Setting: Outpatient FTT / Ctrl Age(mo)* 14.6(1.4) / 14.2(1.4) Wt/age† -2.07(.44) / .10(.96) Ht/length† -1.27(.94) / .18(.73) Enrolled 49 / 50 Evaluated 47 / 47 % Male 49 / 49 % Non-white 43 / 34 * Mean (SD), † z score, p < .001	Maternal educ: ND Income: Income/welfare support- FTT 16, Ctrl 11 Health insur: National healthcare	District-centered until 12 mo of age, singleton deliveries of 38-41 wks gestation Controls matched for sex, age, ethnic origin, bw within 300 g, ordinal position, SES	≤ 3rd centile, no wt data	Wt for age ≥ -1.88 by 12 mo of age & sustained 3 mo (based on NCHS)	Prospective longitudinal Assessments at age 15 mo & 4 y
Reif, 1995 95362505	Country: Israel Setting: Outpatient fwup FTT / Ctrl Mean age(y)* 6.2 / 6.8 Wt/age* 18.05 / 36.15 Ht/length* 21 / 33.55 Enrolled 86 / 65 Evaluated 61 / 65 % Male 52.5 / 54 Race: Sephardic 38 / 36 Ashkenazi 23 / 29 * At re-evaluation	FTT / Ctrl Maternal educ* 12.27 (0.29) / 12.14 (0.24) Income ND / ND Health insur: Socialized medicine * Mean (SD)	FTT, < 2 yrs, term infants > 2500g birth wt Controls matched for age, sex, social class, & ethnic affiliation; admitted or evaluated in ER for intercurrent & nonsign disease	Organic cause of FTT, malnutrition, serious perinatal morbidity	Ht & wt < 5% in ≥ 2 measurements within 6 mo on Hamill PVV, Drizd TA growth chart,	Ambidirectional longitudinal Re-evaluation at mean 5.12 y

Evidence Table 7. Studies associating cognitive & neurological development with Failure to Thrive patients compared to healthy control subjects in developed countries

Part I

Author, Year, UI	Demographics	Maternal / household demographics	Inclusion criteria	Exclusion criteria	Definition of FTT	Study design
Puckering, 1995 95378341	Country: UK Setting: Outpatient FTT / Ctrl Age(mo) 48.9(1.8) / 48.2(0.8) Wt/age(SDS)* -2.01(0.6) / -0.32(1.1) Ht/length(SDS)* -2.24(0.5) / -0.6(0.9) Enrolled/Eval 23 / 23 % Male 48 / 48 Race: 100% White * based on NCHS, p < .001	FTT / Ctrl Maternal educ* 15.6 (1.4) / 15.6 (1.4) Income† 11 / 7 48% / 30% Health insur: Socialized medicine * Age leaving full-time education † Income support/welfare	From inner city population sample - Caucasian born in 1980 with growth data from birth to 4 years Controls matched for sex, gestational age ≥ 38 wks, ethnic origin	Prematurity, congenital defects/ diseases affecting growth, no perinatal insults	Ht & wt < 10% based on standard British growth charts (Tanner & Whitehouse)	Ambidirectional cross-sectional
Corbett, 1996 97113595	Country: UK Setting: Clinic Age at follow-up: 6-7 y FTT / Ctrl Wt/age ND / ND Ht/length ND / ND Enrolled 52 / 52 Evaluated 48 / 46 % Male: ND Race: 100% White	Maternal educ: ND Income: "…most economically deprived wards in Newcastle" Health insur: National healthcare	Full term singleton with records of 6 or more weights over first 18 months age Consecutive controls matched for age & sex	Non-Caucasian, "poor growth resulting from major organic disease"	Weight deviated downward from maximal centile achieved at 4-8 wks, across ≥ 2 centile lines, & remained at level ≥ 2 measurements ≥ 1 mo – chart based on Tanner & Whitehouse	Ambidirectional longitudinal 5 year follow-up of cases

Evidence Table 7. Studies associating cognitive & neurological development with Failure to Thrive patients compared to healthy control subjects in developed countries

Part I

Author, Year, UI	Demographics	Maternal / household demographics	Inclusion criteria	Exclusion criteria	Definition of FTT	Study design
Wilensky, 1996 97022837	Country: Israel Setting: Community pediatric clinic FTT Ctrl Mean age(m)* 20 20 Wt/age ND ND Ht/length ND ND Enrolled† 55 1352 Evaluated 50 50 % Male ND ND Race: ND; Maternal country of birth: 68% Israel, 25% Europe/America, 5% N Africa, 2% Asia * At assessment	FTT Ctrl Maternal educ* 13.8 (1.62) 13.4 (1.44) Income: AFDC 76% Health insur: ND * Mean (SD), based on record review of potential subjects	FTT infants by review of records who have reached 15 months born in 1991 Controls from same health clinic matched for birth month, maternal educ, maternal age, parity, and infants' birth wt	Birth wt < 2500 gm, < 37 weeks, wt/ht ratio > 10 %, organic cause of FTT	Wt < 3% by NCHS for = 3 months prior to age 15 months	Ambidirectional cross-sectional
Mackner,[a] 1997 97381196	Country: US Setting: Inner-city hospital prenatal clinic Age* (mo) Mean wt/age Ht/ lngth Enrolled /Eval Gp1† 14±5.3 <5% ND 27 Gp2‡ 14±5.6 <5% ND 70 Ctrl1§ 16±5.9 >10% ND 23 Ctrl2|| 18±6.9 >10% ND 57 % Male: 58 Race: 94.4 % African American 5.6 % White * p < 0.001, † FTT & neglect, ‡ FTT only, § Neglect only, || Neither	Maternal* educ Income† Health insur‡ Gp1 10.58 70 89 Gp2 11.09 68 78 Ctrl1 11.04 74 82 Ctrl2 11.72 81 89 * p < 0.05, † percent AFDC, ‡ percent Medicaid	Original criteria: FTT, , 24 mo, wt/age < 5th %, gestational age = 37 wks & appropriate birth wt Controls from same site, bet ages 3 – 30 mo, wt/age > 10th %, gestational age = 37 wks & appropriate birth wt Neglect defined = 33rd % & normal > 50th % by HOME scale	History of perinatal complications, congenital disorders, chronic illness	Wt/age < 5th % by NCHS growth charts	Ambidirectional cross-sectional

Evidence Table 7. Studies associating cognitive & neurological development with Failure to Thrive patients compared to healthy control subjects in developed countries

Part I

Author, Year, UI	Demographics	Maternal / household demographics	Inclusion criteria	Exclusion criteria	Definition of FTT	Study design
Drewett, 1999 99284054	Country: UK Setting: Clinic / home visits FTT / Ctrl Age(y) 8.12(0.62) / 8.10(0.57) Wt(kg)* 23.8 / 27.9 BMI* 14.9 / 16.3 Enrolled 136 / 136 Evaluated† 107/111 / 117/122 % Male‡ 40 / 38 %White‡ 91 / 91 * Median, † Psychological / anthropometric evaluation, ‡ FTT = 107, Ctrl = 117	FTT / Ctrl Maternal educ* 72 / 66 Income: NA Health insur: National healthcare * % left school at 16 y	At least 1 wt at age 0-2 mo & 2 subsequent wts, thrive index < 5th centile = 2 occasions between 3 & 18 mo Controls with at least 1 wt at age 0–2 mo & 2 subsequent wts, no thrive index < 10th centile, age ± 1 mo, similar/same residential area or GP practice	ND	Lowest 5% for change of SD score; avg taken of SD scores for all wt bet 0-2 mo, expected wt from 3-18 mo calculated for "thrive index"	Ambidirectional longitudinal Five years from enrollment of 1 y old cases
Kerr,[a] 2000 20277217	Country: US Setting: Inner-city hospital clinic Age (mo) / Mean wt/age / Ht/ lngth Gp1* 73.3±1.9 / ND / ND Gp2† 74.2±3.2 / ND / ND Ctrl1‡ 73.0±1.2 / ND / ND Ctrl2§ 73.5±1.9 / ND / ND Evaluated / % Male / % Race‖ Gp1 64 / 56 / 88 Gp2 28 / 48 / 87 Ctrl1 21 / 53 / 94 Ctrl2 80 / 51 / 97 Mean, * FTT, † FTT & maltreatment, ‡ Maltreatment, § Neither, ‖ % African Am	Maternal educ / Income* Gp1 11.2(1.9) / 56 Gp2 10.4(1.7) / 81 Ctrl1 11.2(1.4) / 65 Ctrl2 11.4(1.9) / 62 Health insur: ND Mean, * percent AFDC	History of FTT & Controls see Mackner 1997 Subgroups - Gp2 & Ctrl1: hx of maltreatment defined as at least one report with Child Protective Services (CPS) by age 6, including neglect, physical abuse, & sexual abuse	History of perinatal complications, congenital disorders, chronic illness	Wt/age < 5th % by NCHS growth charts	Ambidirectional longitudinal Assessment at age 6 y

Evidence Table 7. Studies associating cognitive & neurological development with Failure to Thrive patients compared to healthy control subjects in developed countries

Part II

Author, Year	Development measures	Instruments utilized & criteria	Associations found
Mitchell, 1980 80166667	General cognitive index FTT: 87.5 Ctrl: 92.5	McCarthy scale	Though there was a trend for lower GCI scores for FTT group, there was no statistical difference between the two groups.
Hack, 1982 82227864	Gp1Sub*: 99(18); Gp2Sub1†: 89(22); Gp2Sub2‡: 93(17); Ctrl§: 108 Neurosensory impairment: 6(32%); 6(46%); 8(27%); 13(10%) * SGA-subnormal wt at 40 wk & 8 m (n=19), † AGA-subnormal wt at 8 m (n=13), ‡ AGA-subnormal wt at 40 wk & 8 m (n=30), § 4 subgroups - appropriate for age (n=130)	Bayley Neurological examine	At 8 months, infants from both groups had similar developmental quotients if catch-up growth is achieved. Subnormal wts at 8 months experienced by subset of both groups is associated with lower DQ scores ($p < .005$) and higher rate of neurological impairment.
Singer, 1984 85057547	Cognitive & sensorimotor development 8 m assessment / 20 m assessment / Placed outside home* / Home placement* NOFTT: 77.6(20.5) / 80.5 / 70.2 / 67.4 OFTT: 67.7(13.8) / 75.4 / 90 / 83.3 Ctrl: 120.2(10.7) / ND / ND / ND * 20 mo assessment, sample size unknown	Bayley MDI/Kent Scoring Adaptation	At initial 8 month assessment, there was main effect of group ($F = 23.98$, $p < .001$). Both FTT groups showed a significant delay in sensorimotor skills compared to control group ($F=46.45$, $p < .001$). At 20 months, it was also reported that there was a main effect of group ($F = 21.3$, $p < .001$). Home placement or placement outside the home affected the MDI scores with mean MDI home scores higher regardless of group status (87.5 vs. 68.8).
	Visual recognition memory (8 m assessment) NOFTT: 68%(9.1); OFTT: 52.6(8.5); Ctrl: 62.5(9.2)	Recognition memory tasks - fixation of familiar vs. novel	At 8 month assessment, the OFTT showed a significant delay in visual perceptual-cognitive abilities compared to NOFTT vs. controls where there were no significant differences ($F = 19.88$, $p < .001$).
Haynes, 1984 84233543	Cognitive & motor development FTT*(%) / Ctrl(%) Intake† ≥ 90: 19(38) / 21(81) < 70-89: 31(62) / 5(19) Fwup‡ ≥ 90: 15(40.5) / 17(81) < 70-89: 22(59.5) / 4(19) * intervention & non-intervention combined, † FTT=50 Ctrl=25, ‡ FTT=37 Ctrl=21	Bayley Scale of Infant Development	There were no differences for the FTT groups after 6 mo for development except for a few cases. Approximately 60% FT were developmentally delayed or retarded vs. 5 Ctrls as delayed. Intervention, or home vs. foster care had no effect.

Evidence Table 7. Studies associating cognitive & neurological development with Failure to Thrive patients compared to healthy control subjects in developed countries

Part II

Author, Year	Development measures	Instruments utilized & criteria	Associations found
Drotar, 1992 92372721	Intelligence quotient FTT: 86.3(15.34) Ctrl: 88.74(14.32)	Stanford Binet Intelligence Scale	---
Kelleher, 1993 93234174	FTT / Ctrl Mental: 103.7 / 92.6 / 109.5 / 98.1 Psychomotor: 90.9 / 90.1 / 98.2 / 95.8 age 12 m / age 24 m	Bayley MDI & PDI	LBW & premature infants were followed & subjects who developed FTT scored significantly lower in cognitive & motor development at 12 and 24 months ($p < 0.005$).
Skuse, 1994 94253258	FTT / Ctrl Mental: 98.2(19.0) / 108.5(14.4) Psychomotor: 96.7(17.3) / 103.6(14.4)	Bayley MDI & PDI	At 15 months of age, FTT had lower cognitive & motor development scores than controls ($F = 8.07$, $p = .007$). Model predicted lowering wt up to 6 months of age to lower MDI & PDI scores at 15 months. Increased oral motor score was negative correlated with FTT MDI score ($r = -.38$, $p = .008$).
Reif, 1995 95362505	FTT / Ctrl Developmental delay: 7(11.5%) / 0 Learning difficulties: 11(18%) / 2(3.1%)	Reporting/survey	FTT had reported developmental delays and none were for Controls ($p < .005$). Academic performance was lower for the FTT compared to Controls ($p < .01$).
Puckering, 1995 95378341	General cognitive index FTT: 77.1(17.6) Ctrl: 97.7(15.2)	McCarthy scale	The FTT children had significantly lower DQ scores ($t = -3.93$, $p = .001$) & had few positive & more negative mother – child interactions than the controls. MANOVA performed on calculated mean GCI & BSQ scores vs. unconditional & conditional interactions grouped by high or low (above & below overall mean value for interaction) – results indicate that parenting style does not account for GCI or BSQ differences between FTT & Ctrl.
Corbett, 1996 97113595	Intelligence quotient FTT: 83.6(11.5) Ctrl: 87.0(11.9)	WPPSI-R omitting optional animal pegs & sentences subtests	Though not statistically significant, there was a trend for lower IQ score for FTT group with correlation to the severity of FTT ($p = .160$).

Evidence Table 7. Studies associating cognitive & neurological development with Failure to Thrive patients compared to healthy control subjects in developed countries

Part II

Author, Year	Development measures					Instruments utilized & criteria	Associations found
Wilensky, 1996 97022837		FTT	Ctrl			Bayley MDI	At 20 months, the FTT group mental development lagged behind the control group ($p < .05$). In addition, an assessment showed the home environment to be less stimulating. 2/5th of infants diagnosed as FTT no longer fit the criteria at 20 mo fwup, yet had positive association on Bayley MDI.
	Mental	99.7	107.2				
Mackner,[a] 1997 97381196		Gp1	Gp2	Ctrl1	Ctrl2	Bayley MDI	Main effect for grouping ($F = 4.899$, $p < .01$). The Neglect & FTT group scored significantly lower than FTT only or Neglect only group, both of which scored lower than the group with neither risk factors in cognitive development, ($p < .01$). Maternal IQ & child age as covariates –significant relationship with Bayley MDI, $F = 4.90$, $p < .01$
	Mental*	85.45 (13.62)	97.38 (13.79)	97.72 (12.25)	100.81 (16.4)		
	* Adjusted score						
Drewett, 1999 99284054		FTT	Ctrl				The IQs & reading scores from the FTT to the controls were not significantly different, but there was a significant relationship between the child's IQ & their mother's IQ ($\beta = 0.76 \pm 0.06$, $t = 12.09$, $p < .0001$). Also a significant relationship between the child's reading score & their mother's IQ ($\beta = 0.56 \pm 0.07$, $t = 8.21$ $p < .0001$). There was a relationship between reading scores & FTT cases (n=9) with possible organic causes ($\beta = -11.91 \pm 4.49$, $t = 2.65$, $p < .01$).
	Mean IQ*	87.6(17.4)	90.6(17.1)			WISC-III	
	Mean Reading†	93.5(162)	94.5(15.6)			WORD test	
	* FTT n = 105, Ctrl n = 117						
	† FTT n = 105, Ctrl n = 116						
Kerr,[a] 2000 20277217	Gp1	Gp2	Ctrl1	Ctrl2		WPPSI-R: scores standardized score with mean of 100 ± 15	In all four outcome measures were consistent for main effect from risk status (FTT, FTT & maltreatment, maltreatment alone) as being associated with worse scores in cognitive & adaptive performance, school & home behavior ($F = 2.930$, $p < .01$). In addition, there was a significant difference between the FTT & maltreatment group vs. the group with no risk factors for cognitive & adaptive development, and school performance ($p < .05$).
	81.98 (12.8)	77.98 (13.8)	83.58 (12.4)	83.95 (12.5)			

Evidence Table 7. Studies associating cognitive & neurological development with Failure to Thrive patients compared to healthy control subjects in developed countries

Part III

Author, Year	Potential biases	Comments
Mitchell, 1980 80166667	Physical exams & growth status by PI not blinded	Government & privately funded
Hack, 1982 82227864	8 LTF, 4 incomplete data	SGA mothers incr % pregnancy HTN ($p < .05$) & multiple births ($p < .05$) than AGA, also incr antepartum risk score ($p < .005$) & greater gestational age ($p < .005$); privately funded
Singer, 1984 85057547	Recognition memory tasks differed based on age; etiology for OFTT includes primary neurological disease, methadone addiction, cerebral palsy, congenital heart disease, pulmonary stenosis, cyanotic heart disease, polycystic renal disease, necrotizing enterocolitis, & Aarskoog syndrome	Government funded
Haynes, 1984 84233543	"…because of scheduling, few admissions were not evaluated", 2 refused participation; 10 Gp1 & 3 Gp2 premature – overall similar from FTT vs. Ctrl; at 6 mo fwup: for FTT1 & FTT2 each-3 cases refused reevaluation & from1 dissolution of pair, 1Gp1 died SIDS, 1 Gp2 mother gave up child	Block assignment to Gp1 & Gp2 for hospital convenience & case load requirements; government funded
Drotar, 1992 92372721	---	No difference for attrition group vs. group evaluated, index gp hospitalized avg 14 d for dx & nutritional intervention; government funded
Kelleher, 1993 93234174	Of 985 enrolled, 71 LTF, 12%(20) OFTT, 16%(28) were both OFTT & NOFTT	21% of babies develop FTT by 36 wks; ND on funding source
Skuse, 1994 94253258	2 cases & 3 controls didn't complete assessments & were excluded from analyses, 1 case had microcephaly, hypotonia, & an action tremor or ataxia of unknown origin	Researchers blinded to patient's status in measures except anthropometry; government & privately funded
Reif, 1995 95362505	25 cases not re-evaluated because not located or refused participation; inpatient enrollment of FTT-48 & Ctrl-42; outpatient enrollment of FTT-13 & Ctrl-23(ER)	ND on funding source

Evidence Table 7. Studies associating cognitive & neurological development with Failure to Thrive patients compared to healthy control subjects in developed countries

Part III

Author, Year	Potential biases	Comments
Puckering, 1995 95378341	---	Other than clinic anthropometric measures, home visits by assessors blinded to child's group status; The FTT children were significantly smaller than the controls; government funded
Corbett, 1996 97113595	3 from each group refused consent at follow-up, LTF or moved - 2 cases, 3 controls, 1 case not originally studied participated for follow-up study, 4 of those cases were the slowest growing 5% - also removed from home, all controls stayed with parents. Edward's diagnostic criteria for growth measure considered limited.	Additional aubgroup analyses for FTT cases showed significant association between full-scale IQ and cases with lowest Thrive Index values, p = 0.03; ND on funding source.
Wilensky, 1996 97022837	Feeding behaviors and HOME environment are causal factors given time dissociation as FTT was established at 15 months, where as, maternal interview/home assessment at 25 months.	Reported associations for FTT without specific data: paternal age (p<.01), maternal education, & behavioral observations of lower sociability (p<.05) & fear of examiner (p<.05); ND on funding source
Mackner,[a] 1997 97381196	By group sex data not given, unknown whether Bayley tester was blinded to subject's group assignment	Government funded
Drewett, 1999 99284054	Of 136 cases, 1 died, 9 LTF, 15 declined psychological testing, 4 moved; of 136 controls, 2 were preterm, 5 LTF, 12 declined psychological testing, 14 moved & were replaced. 2 FTT cases & 1 control with medical condition affecting growth, & 9 FTT cases & 2 controls with possible medical conditions	Testers blinded to child's status; privately funded
Kerr,[a] 2000 20277217	Hx of maltreatment not part of original recruitment criteria; unknown number of original sample, also in Mackner 1997 sample (n=177) is reported to be a subsample; maltreatment group may not include all because of definition of a CPS report filed	At 6 year, most FTT children had recovered & 3% had weight for height < 5th percentile; government funded

[a] Overlapping sample for Mackner 1997 & Kerr 2000.

Evidence Table 8. Studies associating cognitive & neurological development with malnourished patients compared to well-nourished control subjects in developing countries

Part I

Author, Year	Demographics	Maternal / household demographics	Inclusion criteria	Exclusion criteria	Definition of malnutrition	Study design
Bartel, 1978, 1979 78180773 79162492	Country: South Africa Setting: Outpatient Age: ND Wt/age: ND Ht/length: ND Gp: Enrolled* 31/30, Eval* 31/30, Race Black Ctrll1: Enrolled 31/30, Eval 31/30, Race Black Ctrll2: Enrolled 31/30, Eval 31/30, Race Black Ctrll3†: Enrolled NA/90, Eval NA/90, Race White % Male: ND * Bartel 1978 / Bartel 1979 † reported in Bartel 1979	ND	Bk 6 – 12 yr olds hospitalized during first 27 months of life for kwashiorkor, 5 – 10 yrs prior to commencement of study Controls close in age, no hx of PCM: Ctrl1-Siblings close in age Ctrl2-Yardmates of cases Ctrl3-High SES Whites	Neurological involvement, brain damage, fits, birth trauma, hospital coma, hypoglycemia	Wellcome criteria for kwashiorkor: <3rd percentile, edematous, and dermatitis and/or nutritional hair changes	Ambidirectional longitudinal Assessment at 4 – 12 y after hospitalization
Evans, 1980 81008912	Country: South Africa Setting: Outpatient clinic Wt/age: See Cognitive development measures column Ht/length: See Cognitive development measures column Mean age(SD): Gp1 8.9 (0.5), Ctrl1 10.7 (1.0), Gp2 13 (1.9), Ctrl2 12 (2.1) Enrolled: 14, 14, 14, 14 Evaluated: 14, 13, 14, 13 % Male: 64, 54, 100, 77 Race: "Cape coloured"	ND	Gp1 – newborns of families with hx of undernutrition Ctrl1 – siblings with hx of undernourishment, record of `< 3rd percentile for ht & wt Gp2 – at least 1 hospitalization for kwashiorkor Ctrl2 – siblings closet in age Gp2 w/no hx of kwashiorkor but underweight	ND	ND	Prospective longitudinal Fwup 6 ½ y after intervention

Evidence Table 8. Studies associating cognitive & neurological development with malnourished patients compared to well-nourished control subjects in developing countries

Part I

Author, Year	Demographics	Maternal / household demographics	Inclusion criteria	Exclusion criteria	Definition of malnutrition	Study design
Galler, 1983a, 1985b 83136873 85241833	Country: Barbados Setting: Outpatient Age(y): 5-11 (1983) 9-15 (1985) Gp / Ctrl Wt/age: ND / ND Ht/length: ND / ND Enrolled: 141 / 129 Eval 1983a: 129 / 129 1985b: 109 / 107 % Male 1983a: 60 / ND 1985b: 58 / 60 Race: 100% Black	Maternal educ: Universal education, 95% population literate Income: lower for cases compared to Ctrl Health insur: ND	5 – 11 yr olds with hx at age 1 yr of hospitalization for PEM Grade II-III, BW > 5 lbs Controls without PEM, matched for age, gender, handedness, & same school / neighborhood	Pre- or peri-natal complications, edema, seizures, head trauma, loss of consciousness, high fever	Gomez Scale PEM: Grade II- 61-75% or Grade III- ≤ 60% standard wt for age on Harvard Standard Scale	Ambidirectional longitudinal Fwup 4 – 10 y after D/C
Grantham-McGregor, 1987, 1978, 1980, 1982, 1983 87117313 79086701 81051042 82236679 83246270	Country: Jamaica Setting-Recruitment: hospital Follow-up: hospital & home Gp1* / Gp2† / Ctrl† Age(m): 12.8 (2.9) / 13.4 (4.5) / 12.2 (4.4) Ht/age‡: 89.0 (4.5) / 88.4 (4.4) / 101.3 (3.5) HC/age‡: 91.3 (3.7 / 91.2 (3.3) / 99.0 (3.8) Wt/ht‡: 74.9 (9.2) / 72.4 (10.2) / 89.0 (10.1) Enrolled: 21 / 18 / 21 Evaluated: 18 / 16 / 20 % Male: 67 / 38 / 60 Race: ND, assumed Black Mean (SD) for evaluated cases; * Intervention, † Standard care, ‡ % of expected value	Maternal educ: HS not completed Income: housing 'below certain defined standards' Health insur: ND Maternal PPVT Gp1 62.3(14.7) Gp2 59.7(15) Ctrl 67.4(9.3)	PEM, age 6 – 24 mo, attempt for SES of mothers who had not completed secondary education, substandard housing, residence in city of Kingston Controls, included above criteria but adequately nourished, hospitalized with diseases other than malnutrition	Physical handicap, disease that might affect mental development (other than malnutrition)	Severe PEM based on Wellcome classification	Prospective longitudinal 6 fwups from 6 to 72 m after D/C

Evidence Table 8. Studies associating cognitive & neurological development with malnourished patients compared to well-nourished control subjects in developing countries

Part I

Author, Year	Demographics	Maternal / household demographics	Inclusion criteria	Exclusion criteria	Definition of malnutrition	Study design
Agarwal, 1992 92372206	Country: India Setting: Outpatient Age: NA Wt/age: ND Ht/age: ND Enrolled: 650 Gpl* Gp2† Ctrl Evaluated: 245 324 64 % Male: ND Race: ND (assumed Indians) * Grade I, † Grade II/III	Maternal educ: < 4% > grade school, 31.9% overall women's literacy Income: 40% household per capita < Rs.60 p.m. Health insur: ND	Newborns between 11/1981 – 31983; see Definition of malnutrition Controls > 80% of 50th % wt for age,	ND	Malnutrition based on NCHS 50th centile wt for age as reference pt: wt ≥ 80% of 50th% = normal, Grade I < 80-70%, Grade II < 70-60%, Grade III < 60%	Prospective longitudinal Assessments at age 18, 24, 30, 36 m
Drewett, 2001 21174599	Country: Ethiopia Setting: Outpatient Gp1* Gp2† Ctrl Age‡ ND ND ND Wt§ ? 8.3(1.6) 8.9(1.0) 10.4(1.0) ? 8.5(1.1) 9.4(1.0) 10.6(1.1) Lngth§? 72.6 (5.0) 75.2 (4.4) 79.6 (3.2) ? 74.9 (2.5) 76.2 (3.6) 80.4 (3.9) Enrolled 27 70 100 Evaluated 27 70 100 % Male 33 70 55 Race: ND * Early growth faltering, † Late growth faltering, ‡ criteria < 16 d, § age 2 y, (SD), wt in kg, length in cm	Maternal educ* Income† Health insur Gp1 37 37 ND Gp2 51 41 ND Ctrl 41 35 ND * % > 3 y, † % > 2 key possessions	All subjects: < 2 y on Nov 1, 1994, recorded initial (< 16 d) wt ≥ 2500 g, recorded 7th visit (alive at 1 yr) Gp1: wt < 3rd centile at visits 2 or 3(2 & 4 mo) Gp2: wt < 3rd centile at visits 6 or 7(10 & 12 mo), & not visits 2 or 3 Control: wt ≥ 3rd centile at visit 2, 3, 6, & 7	ND	Centiles based on NCHS	Ambidirectional longitudinal Assessment at age 2 y (22-24 m) See Comments section

Evidence table 8. Studies associating cognitive & neurological development with malnourished patients compared to well-nourished control subjects in developing countries

Part II

Author, Year	Development measures				Instrument	Associations found
Bartel, 1978, 1979 78180773 79162492	Psychomotor development	Gp	Ctrl1	Ctrl2	LOMDS	There were no significant difference (F=1.50) between the children with history of kwashiorkor, siblings, & yardmates on motor skills except for intergroup comparisons for 2 of 93 items tested of LOMDS. The groups did not differ significantly on grip strength (F=1.45) or finger tapping tests (F=1.43).
	Motor development	80.73	91.16	82.55		
	Grip strength*	14.80 (5.24)	16.59 (6.22)	15.15 (5.41)	Smedley hand dynamometer	
	Finger-tapping / fine motor speed*	34.47 (6.35)	37.25 (8.22)	35.21 (5.17)	Reitan Indiana & Halstead neuropsychological test batteries	
	Mean(SD), * Dominant hand scores					
Evans, 1980 81008912		Gp1	Ctrl1	Gp2	Ctrl2	New S. African Individual Intelligence scale Bender-Gestalt test/Koppitz scoring	6-7 years after early infant supplements, the Gp1 full scale intelligence score was significantly higher than Ctrl1 (older siblings), $p < .05$; or Gp2 (kwashiorkor), $p < .01$; or Ctrl2 (siblings of kwashiorkor), $p < .05$. There were higher trends for verbal & performance scores with Gp1 verbal score higher than Ctrl1, $p < 05$; and Gp 1 higher than Gp2, $p < .05$; or Ctrl2, $p < .01$. Bender-Gestalt test reported NS findings.
	Full scale	82.0 (13.0)	71.9 (12.5)	70.0 (13.5)	72.0 (14.6)		
	Verbal	81.3 (13.0)	70.6 (13.3)	74.3 (16.1)	75.0 (17.3)		
	Performance	86.3 (10.4)	80.5 (11.2)	71.3 (8.8)	74.4 (9.2)		
	mean(SD)						
Galler, 1983a, 1985b 83136873 85241833		Gp?	Ctrl?	Gp ?	Ctrl?	WISC	**1983 -** From ages 5-11, the index group scored significantly lower than the controls by sex, $p < .05$; the mean score for the index group was 12 points lower than the controls. There was no effect on Full IQ by sex, age, or SES. **1985 -** At ages 9-14The index group had statistically significant deficits in fine motor coordination of the dominant hand compared to controls ($F = 2.85$, $p < .05$) with significant effect by age ($F = 6.3$, $p < .001$).
	Full scale IQ	91.3 (14.3)	100.1 (13.0)	90.5 (16.7)	107.7 (12.1)		
	Motor coordination deficiency –	8-10 yr	11-13 yr	14-15 yr	Purdue pegboard tasks, Neuman-Keuls	
	Dominant hand performance					
	Gp	11.24(2.22)	13.1(2.38)	12.81(2.07)		
	Ctrl	12.41(0.94)	13.53(1.72)	12.73(2.02)		
	Assembly tests					
	Gp	23.94(4.08)	29.40(4.51)	30.27(5.66)		
	Ctrl	23.00(4.21)	26.77(6.00)	29.81(7.21)		

Evidence table 8. Studies associating cognitive & neurological development with malnourished patients compared to well-nourished control subjects in developing countries

Part II

Author, Year	Development measures				Instrument	Associations found
Grantham-McGregor, 1987, 1978, 1980, 1982, 1983 87117313 79086701 81051042 82236679 83246270		Gp1	Gp2	Ctrl	Griffith's Mental Development Scales for Babies and Young Children including subscales – hand & eye coord, hearing & speech, performance, practical reasoning, & locomotor	Development assessment taken at D/C, 6, 12, 18, 24 months, and annual thereafter showed consistently the nonintervention group (Gp2) was significantly behind the control group with intervention group (Gp1) scoring higher than the nonintervention group, but still behind the control group. At 6 months, the Gp1 was significantly behind the Gp2, ($F = 4.43$, $p < 0001$), but NS vs. Ctrl ($F = 1.85$). Gp2 was significantly behind the Ctrl ($F = 5.83$, $p < .0001$). PPVT at 36 months, showed effect by group, $p < .005$. At 60 months after D/C, (2 yr post intervention) both Gp1 & Gp2 were statistically behind the control group, $p < 0.01$. At 60 months, the results of Stanford-Binet Test showed that the "relative positions of groups maintained".
	DQ at D/C	86(12.7)	77(12.0)	98(14.8)		
	DQ at 6 m	96(11.3)	82(12.1)	105(11.2)		
	DQ at 60 m	86.1(8.2)	78.1(9.7)	93.2(11.2)		
	PPVT at 36 m	26.9(10.6)	18.3(7.5)	26.2(12.2)	Peabody Picture Vocabulary Test	
	IQ at 60 m	71.5(8.7)	63.3(7.8)	75.2(10.5)	Stanford-Binet Test	
Agarwal, 1992 92372206		Gp1	Gp2	Ctrl	Binet Kulshrestha Intelligence Scale	At 36 month assessment, there were differences in scores between the normal, Grade I, and Grade II/III for cognitive ($F = 13.27$, $p < .001$) & language ($F = 9.308$, $p < .001$) development, motor coordination ($F = 10.52$, $p < .001$), concept formation ($F = 6.235$, $p < .01$), and reasoning ($F = 7.774$, $p < .001$). The mean scores decreased with increasing degrees of malnutrition. Home environment was most important variable in predicting IQ, accounting for 26.22% of total variance in IQ, $p < .001$
	Cognitive	91.9(8.6)	86.8(7.7)	95.5(7.9)		
	Motor coordination	1.13(.22)	0.97(.27)	1.16(.19)	Developmental Quotient calculated for Binet Kulshrestha intelligence subsets	
	Language	0.85(.14)	0.78(.11)	0.90(.14)		
	Concept formation	1.32(.43)	1.07(.54)	1.38(.37)		
	Reasoning	1.15(.79)	0.75(.79)	1.43(.89)	Caldwell Inventory	

Evidence table 8. Studies associating cognitive & neurological development with malnourished patients compared to well-nourished control subjects in developing countries

Part II

Author, Year		Development measures			Instrument	Associations found
		Gp1	Gp2	Ctrl		
Drewett, 2001 21174599	Psychomotor	6.6*(4.2)	8.5*(4.3)	10.2(3.7)	Bayley PDI & MDI – nonstandard scoring based on number of items passed	Group status was correlated to psychomotor development ($F = 9.3$, $p < .001$; Gp1&Gp2 vs. Ctrl, $t = 3.8$, $p < .001$; Gp1 vs .Gp2, $t = 2.0$, $p < .05$) with early growth faltering group scoring lower than the late growth faltering group who in turn scored lower than the controls. Similar pattern for mental development scores (Group effect, $F = 12.7$, $p < .001$; Gp1 vs. Gp2, $t = 4.0$, $p < .01$; Gp1 vs. Gp2, $t = 3.0$, $p < .01$). Child's wt at 2 years was related to both scores (PDI: $r = .53$, MDI: $r = .49$, $p < .001$), & maternal education related to mental development (MDI: $t = 2.1$, $p < .05$). No relationship between households with greater than 2 key possessions and psychomotor &mental scores. The difference in initial weights of the 3 groups were statistically significant ($F = 21.4$, $p < .01$).
	Mental	22.6(6.2)	26.6(6.1)	28.9(5.8)		
	Initial wt (g)	2819(323)	3141(351)	3368(430)		
	* Gp1 n= 25, Gp2 n=66					

Evidence table 8. Studies associating cognitive & neurological development with malnourished patients compared to well-nourished control subjects in developing countries

Part III

uthor, Year	Potential biases	Comments
Bartel, 1978, 1979 78180773 79162492	No data on difference of number of children between two reports	Single tester blinded to child's group assignment for Bartel 1978; partially funded by African Medical Research Council
Evans, 1980 81008912	1 child died in each of the controls, sex unkn	Gp1 received supplements until mean 28 months, one examiner blinded to subject's group status, testing 6-7 years after cessation of supplements; US government & South African Medical Research Council
Galler, 1983a, 1985b 83136873 85241833	Withdraws/non-participation – 4 refused consent, 7 LTF, 1 cerebral palsy; Severe PEM	Relevant WISC subtests utilized & some items altered for cultural setting; findings of dominant hand performance of fine motor skill tasks deficient in formerly malnourished children correlates or co-varies with IQ & other soft neurologic signs; private & hospital funded
Grantham-McGregor, 1987, 1978, 1980, 1982, 1983 87117313 79086701 81051042 82236679 83246270	Controls had better housing than other 2 groups in spite of attempts to match; 2 died & 1 WD from intervention group, 1 from nonintervention moved & 1 was adopted by middle-class family, 1 from control WD; 10 of 21 Gp1 had edema, 4 of 18 in Gp2, & none in the control group	Tester blinded to subjects' group, controls hospitalized mainly for gastroenteritis & respiratory infections; government & private funding
Agarwal, 1992 92372206	ND on 17 of 650 in cohort; 5.5% of population were normal for growth at 24 months corresponding to 5.9% for 1989-90.	Funded by Indian Council of Medical Research
Drewett, 2001 21174599	Initial weight a proxy for birth weight as most births at home; 27 of 40 early wt faltering group recruited & tested; significant higher proportion of males in Gp2 vs. Gp1, $\chi^2 = 5.56$, $p < .05$; 6 cases (Gp1-2 & Gp2-4) with lower limb disabilities could not participate in psychomotor test	Sample subset of Jimma Birth Cohort study; Gp2 & Controls selected at random from sampling frame; systematic method for selection of broad comparisons for Control group; testers blinded to child's status; Private & hospital funded

Evidence Table 9. Studies associating other correlates / outcomes with Failure to Thrive patients compared to healthy control subjects in developed countries

Part I

Author, Year, UI	Demographics	Maternal / household demographics	Inclusion criteria	Exclusion criteria	Definition of FTT	Study design
Pollitt, 1976 76109110	Country: US Setting: Outpatient FTT Ctrl Mean age(SD)* Male 33(14) 34(13) Female 39(14) 39(15) Mean ht† Male 93(2) 101(1) Female 90(2) 102(3) Enrolled/Eval 19 19 % Male 47 47 Race: ND * months, † centimeters	FTT Ctrl Maternal educ 11 (2) 12 (1) Income Gross annual 6943 (3444) 9541 (4768) Per capita 1557 (725) 2648 (1517) Health Insur: ND	Outpatient clinic, 12-60 mo, ht & wt < 3%, bw = 2500 gm, GA = 36 wks, nl birth, nonorganic, singleton, maternal ht = 154.5 cm & English-speaking ability Controls matched for age (± 3 mo), sex, race, ht & wt = 25%	Birth complications, physical disability, genetic or organic retardation, brain damage, organic growth retardation	Boston Growth Standards – ht & wt = 3rd percentile	Prospective cross-sectional Weekly interviews for 7-11 sessions
Mitchell, 1980 80166667	Country: US Setting: Outpatient clinic FTT Ctrl Age(y) 2-5 2-5 Wt/age ND ND Ht/length ND ND Enrolled : cohort of 312 Evaluated 30 282 % Male 36.7 51.8 % Black 70 70	Maternal educ: ND Income: ND Health insur: FTT-53% Medicaid Ctrl-49% Medicaid	See Definition of FTT Controls: wt = 80% of nl, matched for age, sex, mother's age / marital status & family problems	Organic cause of FTT, single anomalous low wt recorded, clinic registration by age 6 mo, < 3 visits	Wt for age < 80% of nl up to age 24 mo	Ambidirectional longitudinal 1 fwup at age 3 – 6 y

Evidence Table 9. Studies associating other correlates / outcomes with Failure to Thrive patients compared to healthy control subjects in developed countries

Part I

Author, Year, UI	Demographics	Maternal / household demographics	Inclusion criteria	Exclusion criteria	Definition of FTT	Study design
Hack, 1982 82227864	Country: US Setting-Recruitment: Hospital Follow-up: hospital/clinic Gp1* Gp2† Mean age‡ 32(2.8) 29(1.9) Wt/age(g) 1141(285) 1197(206) Length(cm) 37.9(3.8) 38(2.7) Enrolled|| ND ND Evaluated 38 154 % Male 47 47 % Black 52 63 * SGA, † AGA, ‡ wks gestation, || n = 204	Gp1 Gp2 Maternal educ <HS 12 32 Income* 28 99 Health Insur ND ND * Hollingshead Social Class 4 & 5	VLBW, < 1500g, divided into two groups: SGA < 2 SD or AGA	ND	Wt < 2 SD below mean for age @ term and/or @ 8 mo of age	Prospective longitudinal Assessments at age 40 wk & 8 mo
Haynes, 1984 84233543	Country: US Setting: In & Out-patient Age: ND Wt/age: ND Ht/length: ND FTT1* FTT2† Ctrl Enrolled/Eval 25 25 25 % Race Sp-Am? 44 44 44 Sp-Am? 40 52 52 White? 36 44 36 White? 36 24 28 Black? 20 12 20 Black? 24 24 20 % Male: ND * std care & lay health visitor intervention, † std care only	Maternal educ Income* Gp1 10 379(0-750) Gp2 11 372(0-950) Ctrl 10 362(0-1100) Health insur: ND * @ mo	Consecutive admissions for NOFTT Controls - thriving non-hospitalized patients matched for age, sex, birth wt, & mother's age, ethnicity, number of living children	ND	< 5 percentile or significant decline from birth wt percentiles	Prospective longitudinal 1 assessment 6 mo after intake

Evidence Table 9. Studies associating other correlates / outcomes with Failure to Thrive patients compared to healthy control subjects in developed countries

Part I

Author, Year, UI	Demographics	Maternal / household demographics	Inclusion criteria	Exclusion criteria	Definition of FTT	Study design
Sherrod, 1984 85026403	Country: US Setting-Recruitment: Prenatal clinic Follow-up: Pediatric clinic NOFTT Ctrl Birthwt(g) 3031 3054 Enrolled/ Eval* 31 24 Race-White 10 ND Black 21 ND % Male: ND * 4 arm study – Data for FTT & Ctrl only; abused or neglected cases excluded	NOFTT Ctrl Maternal educ 10.3 11.2 Income* 13 13 Health Insur† ND ND * # employed, † p < .05, ‡ p < .01	NOFTT, abused, or neglected Controls – no hx of abuse, FTT, or neglect	ND	Wt gain fallen below 2/3 of Harvard 50th percentile on growth curve	Retrospective longitudinal 3 annual assessments
Casey, 1985 84206364	Country: US Setting: Outpatient clinic or home FTT Ctrl Age(mo)* 16.4 16.9 Wt/age* 72.5% 94.5% Ht/length* 93.9% 98.5% Enrolled/Eval 23 23 % Male 57 57 Race: % White 26 26 * At diagnosis	FTT Ctrl Maternal educ 11.3 10.9 Income 5,451 6,188 Health insur: ND	All pts referred for FTT evaluation, > 12 wks age, FTT as defined or wt % decreased > 2 SD over time, residence ≤ 30 miles of clinic Control with normal growth, matched for age, race, sex, maternal education, household income, marital status, & crowdedness	Organic illness	Weight < 3rd percentile for corrected age	Prospective cross-sectional 3 wk assessment from time of diagnosis

Evidence Table 9. Studies associating other correlates / outcomes with Failure to Thrive patients compared to healthy control subjects in developed countries

Part I

Author, Year, UI	Demographics	Maternal / household demographics	Inclusion criteria	Exclusion criteria	Definition of FTT	Study design
Hutcheson, 1993 94015754	Country: US Setting: Primary care clinic FTT Ctrl Age(mo) 15.1(5.2) 14.9(5.1) Wt/age 2.83 63.17 Ht/age 23 63 Enrolled/Eval 34 34 % Male 62 62 Race: Black 32 32	FTT Ctrl Maternal educ* 38 70 Income† 64 70 Health insur ND ND * % HS graduate † % receiving AFDC	Age 8 – 24 mo, NOFTT Controls matched for age, sex, race	Congenital disorder, chronic disease, < 37 wk gestation, SGA	Wt for age ≤ 5th percentile, or wt for ht ≤ 10th percentile, based on NCHS	Prospective cross-sectional
Kelleher, 1993 93234174	Country: US Setting: Primary care clinic FTT Ctrl GA(wk)* 33.0 33.1 Wt(g)* 1679 1845 Enrolled: 842* Evaluated 180 591 % Male 52.2 47.9 Race: % Black 50 53.8 * At birth	FTT Ctrl Maternal educ* <HS 40.6 38.1 HS 30.0 29.3 Some col 14.4 20.8 ≥col grad 15.0 11.8 Income <10K 38.6 34.5 10-20K 19.9 23.9 >20K 38.1 37.4 Health insur ND ND * % HS graduate	Gestation age ≤ 37 wks, birth wt ≤ 2500 g, FTT Controls matched for – birth wt +/- 250 g, maternal education, maternal race, & infant sex	Live outside catchment area, D/C outside recruitment period, D/C or died within 48 hr, hospitalized > 60 d, oxygen support > 90 d, twin, triplet or quadruplet of ineligible child, maternal drug/ alcohol abuse, insufficient Eng skills, psychiatric hosp	< 5th percentile for gestation corrected age based on NCHS, growth status on "wt curve below that recorded at last regular assessment visit."	Prospective longitudinal Fwup at ages 12, 24, 36 mo

Evidence Table 9. Studies associating other correlates / outcomes with Failure to Thrive patients compared to healthy control subjects in developed countries

Part I

Author, Year, UI	Demographics	Maternal / household demographics	Inclusion criteria	Exclusion criteria	Definition of FTT	Study design
Drotar, 1994 94308313	Country: US Setting: Inpatient with outpatient follow-up FTT / Ctrl Age(mo)* 4.7(2.8) / 5.0(2.7) Wt/age: ND / ND Ht/length: ND / ND Enrolled 48 / 52 Evaluated 31 / 39 Male 23(74%) / 25(64%) Race: Black 17(55%) / 28(72%) White 14(45%) / 11(28%) *Mean (SD), at enrollment	FTT / Ctrl Maternal educ 10.9 (2.0) / 11.3 (1.4) Income 6414 (6669) / 7495 (10721) Health insur: ND Mean (SD)	Hospitalized for NOFTT, ages 1-9 m Controls matched for age at intake, sex, race, birth order, gestational age, maternal educ & age, family income & size	Physical abuse, residence > 1 hr from hospital, bw < 1500 gm	Wt = 5th percentile based on NCHS, absence of disease, wt gain with inpatient tx, poor wt velocity	Prospective longitudinal 1 follow-up at 3 yrs
Skuse, 1994, 1995 94253258 96091265	Country: UK Setting: Outpatient FTT / Ctrl Mean age(SD)* 14.6(1.4) / 14.2(1.4) Wt/age† -2.07(.44) / .10(.96) Ht/length† -1.27(.94) / .18(.73) Enrolled 49 / 50 Evaluated 47 / 47 % Male 49 / 49 % Non-white 43 / 34 * Age in months † z score, p < .001	Maternal education: ND Income: income/welfare support FTT-16, Ctrl-11 Health insur: National healthcare	District-centered until 12 mo of age, singleton deliveries of 38-41 wks gestation Control matched for sex, age, ethnic origin, bw within 300 g, ordinal position, SES	≤ 3rd centile, no wt data	Wt for age ≥ -1.88 by 12 mo of age & sustained 3 mo (based on NCHS)	Prospective longitudinal Assessments at age 15 mo & 4y

Evidence Table 9. Studies associating other correlates / outcomes with Failure to Thrive patients compared to healthy control subjects in developed countries

Part I

Author, Year, UI	Demographics	Maternal / household demographics	Inclusion criteria	Exclusion criteria	Definition of FTT	Study design
Puckering, 1995 95378341	Country: UK Setting: Outpatient FTT / Ctrl Age(mo) 48.9(1.8) / 48.2(0.8) Wt/age* -2.01(0.6) / -0.32(1.1) Ht/length* -2.24(0.5) / -0.6(0.9) Enrolled/Eval 23 / 23 % Male 48 / 48 Race: 100% White * SDS, based on NCHS, p < .001	FTT / Ctrl Maternal educ* 15.6 (1.4) / 15.6 (1.4) Income† 11 / 7 48% / 30% Health insur: Socialized medicine * Age leaving full-time education † Income support/welfare	From inner city population sample - Caucasian born in 1980 with longitudinal growth data from birth to 4 years Controls matched for sex, gestational age ≥ 38 wks, & ethnic origin	Prematurity, congenital defects/ diseases affecting growth, no perinatal insults	Ht & wt < 10% based on Tanner & Whitehouse growth charts	Ambidirectional cross-sectional
Wilensky, 1996 97022837	Country: Israel Setting: Community pediatric clinic FTT / Ctrl Mean age(mo)* 15/20 / 15/20 Wt/age ND / ND Ht/length ND / ND Enrolled† 55 / 1352 Evaluated 50 / 50 % Male ND / ND Race: ND; Maternal country of birth – 68% Israel, 25% Europe/America, 5% N Africa, 2% Asia * At entry / assessment	FTT / Ctrl Maternal educ* 13.8 (1.62) / 13.4 (1.44) Income: AFDC 76% Health insur: ND * Mean (SD), based on record review of potential subjects	FTT infants by review of records who have reached 15 months born in 1991 Controls from same maternal & child health clinic matched for birth month, maternal educ, maternal age, parity, and infants' birth wt	Birth wt < 2500 gm, < 37 weeks, wt/ht ratio > 10 %, organic cause of FTT	Wt < 3% by NCHS for = 3 months prior to age 15 months	Ambidirectional cross-sectional

Evidence Table 9. Studies associating other correlates / outcomes with Failure to Thrive patients compared to healthy control subjects in developed countries

Part I

Author, Year, UI	Demographics	Maternal / household demographics	Inclusion criteria	Exclusion criteria	Definition of FTT	Study design
Drewett, 1999 99284054	Country: UK Setting: Clinic / home visits FTT Ctrl Age(y) 8.12(0.62) 8.10(0.57) Wt(kg)* 23.8 27.9 BMI* 14.9 16.3 Enrolled 136 136 Evaluated† 107/111 117/122 % Male‡ 40 38 %White‡ 91 91 * Median, † Psychological / anthropometric evaluation, ‡ FTT = 107, Ctrl = 117	FTT Ctrl Maternal educ* 72 66 Income: NA Health insur: National healthcare * % left school at 16 y	At least 1 wt at age 0-2 mo & 2 subsequent wts, thrive index < 5th centile = 2 occasions between 3-18 mo Controls - at least 1 wt at age 0–2 mo & 2 subsequent wts, no thrive index < 10th centile, age ± 1 mo, similar/same residential area or GP practice	ND	Lowest 5% for change of SD score; avg taken of SD scores for all wt bet 0-2 mo, expected wt from 3-18 mo calculated for "thrive index"	Ambidirectional longitudinal Five years from enrollment of 1 y old cases
Wright, 2000 20161504	Country: UK Setting: Outpatient FTT Ctrl Median age* 15.1 ND range (7-28 m) (16-18 m) Wt/age -2.00(.93) ND Ht/length -1.06(.96) ND Enrolled 120 40 Evaluated 97 28 % Male 54 61 % Nonwhite 9 0	Maternal educ: ND Income: ND FTT* Ctrl* Unemployed parent 39 13 Nonhome-owner 54.7 53.6 No car 48.3 50 Health insur: National healthcare * Percent	Baseline wt at 6-8 wk & 2nd wt at 9-18 mo Controls from 3 "generally representative" of Newcastle	2nd twin sibling	Weight decline of 1.26 SD from age 6-8 wks to 2nd weighing at 9-18 months	Prospective cross-sectional

Evidence Table 9. Studies associating other correlates / outcomes with Failure to Thrive patients compared to healthy control subjects in developed countries

Part II

Author, Year	Correlates / outcomes & measures			Associations found	Potential biases	Comments
Pollitt, 1976 76109110		FTT*	Ctrl*	The FTT mothers had less education (t = 1.88, p = 0.05) and the FTT household per capita income levels were also lower than the controls' (t = 2.77, p = .01).	4 cases with FTT hx within ht 3rd & 10th percentiles included in study	Government & privately funded
	Maternal educ	11(2) y	12(1) y			
	Income					
	Gross annual	6943(3444)	9541(4768)			
	Per capita	1557(725)	2648(1517)			
	* Mean (SD)					
Mitchell, 1980 80166667		FTT(%)	Ctrl(%)	The FTT had significantly more neonatal problems (p < .05) such as jaundice, poor suckling, & possible sepsis, and family problems (p < .01) compared to controls. NS but FTT group had higher incidence of prematurity and physical abuse. There were no differences in occurrences of illness, or "problems noted on physical examination".	Physical exams & growth status by PI not blinded; significantly fewer cases had completed immunizations, p < .01	Government & privately funded
	Neonatal abnormalities	30	15			
	Prematurity (<37 wk)	16.7	9.2			
	Family problems	36.7	11			
	Physical abuse	3.3	2.1			
	Acute or chronic illness	ND	ND			
Hack, 1982 82227864	Neonatal risk score Extended hospital stay Chronic disease			Subnormal wts at 8 months experienced by subset of both groups is associated with lower neonatal period (r = 0.28, p < .001), extended hospital stay (r = 0.30, p < .001) and increased illness severity (r = 0.32, p < .005).	8 LTF, 4 incomplete data	SGA mothers incr % pregnancy HTN (p < .05) & multiple births (p < .05) than AGA, also incr antepartum risk score (p < .005) & greater gestational age (p < .005); privately funded

Evidence Table 9. Studies associating other correlates / outcomes with Failure to Thrive patients compared to healthy control subjects in developed countries

Part II

Author, Year	Correlates / outcomes & measures	Associations found	Potential biases	Comments
Haynes, 1984 84233543	Catch-up growth ADL FTT(%)* Ctrl(%) Prematurity 13(26) 5(20) LBW 11(22) 5(20) Re-hospitalization 13(26) 0 * intervention & non-intervention combined	All FTT had some wt gain during hospitalization, at reeval-some minor wt gain, 8 FTT gain > 20 percentile pts or within 5 percentile of birth wt percentile At reeval, only minor improvement in mother's response to child's needs, majority of mothers hostile or incoordination Though NS as a risk factor, FTT had higher trend for prematurity and LBW 26% of FTT were re-hospitalized, 0% for Ctrl	"…because of scheduling, few admissions were not evaluated", 2 refused participation; 10 Gp1 & 3 Gp2 premature – overall similar from FTT vs. Ctrl; at 6 mo fwup: for FTT1 & FTT2 each-3 cases refused reevaluation & from1 dissolution of pair, 1Gp1 died SIDS, 1 Gp2 mother gave up child	Block assignment to Gp1 & Gp2 for hospital convenience & case load requirements; government funded
Sherrod, 1985 85026403	Anatomical defects – FTT Ctrl 1y .13 .08 2y .06 .04 3y .13 .00 Family dysfunction (ND due to low frequencies)	Compared to controls, NOFTT group revealed more anatomical abnormalities such as hernias and heart disease during the 1st year ($\chi^2 = 4.23$, $p < .05$) and during all 3 years ($\chi^2 = 5.44$, $p < .025$); and more family dysfunction during the 1st year or during all 3 years ($\chi^2 = 9.29$, $p < .01$; $\chi^2 = 5.32$, $p < .025$) accounting for clinic visits or identified at clinic visits.	Attending physicians alerted to give special treatment to children suffering from maltreatment, analysis showed no increase in outcome variability; study design to identify relationship of illness to abuse, not NOFTT to illness	Data collectors blind to child group assignment; government & privately funded

Evidence Table 9. Studies associating other correlates / outcomes with Failure to Thrive patients compared to healthy control subjects in developed countries

Part II

Author, Year	Correlates / outcomes & measures	Associations found	Potential biases	Comments
Casey, 1985 84206364	HOME environment FTT Ctrl Total score 29.2(7.7) 33.0(6.1) Maternal responsivity 7.7(2.3) 8.9(1.9) Maternal acceptance 5.1(1.6) 6.2(1.1) Organization of environment 4.7(1.2) 5.3(0.7)	There is an association between the lower HOME total ($p < .04$)& subset scores in maternal responsiveness ($p < .03$), maternal acceptance ($p < .01$), home organization $p < .02$), and FTT group. Coddington Life Events showed no difference between groups.	---	All FTT pts referred to Growth & Development Clinic at hospital, all SES represented-majority low SES, assessor blinded to subject's group; government & privately funded
Hutcheson, 1993 94015754	FTT1* FTT2† Ctrl1* Ctrl2† Maternal psychological functioning - Negativity affectivity 0.38 0.20 0.28 -0.11 Family stress/support - • Parenting stress 0.53 0.57 0.70 0.67 • Informal support 1.12 1.19 1.26 1.46 • Life events 11.29 7.32 9.31 10.13 Mother-child interaction – Maternal affective tone 4.26 3.51 3.96 4.05 Z scores given * Infants: 8 – 13.4 m † Toddlers: 13.5 – 24 m	Though there were no age or group differences found on perceived life stresses, parenting stresses, informal support, and negative affectivity, the FTT infants had fewer life events than FTT toddlers, whereas the reverse was true for the comparison group. Controlling for maternal education, wt for age, & ht for age - significant group by age interaction for maternal factors ($F=4.98$, $p = 0.02$) due to maternal affective tone ($F=9.33$, $p = 0.005$). The maternal affect was less positive toward FTT toddlers than FTT infants.	76% of index group met both criteria for NOFTT (wt for age, & ht for age), 24% met one criterion; unknown n for age by group comparisons	Government & privately funded

Evidence Table 9. Studies associating other correlates / outcomes with Failure to Thrive patients compared to healthy control subjects in developed countries

Part II

Author, Year	Correlates / outcomes & measures			Associations found	Potential biases	Comments
Kelleher, 1993 93234174		FTT(%)	Ctrl(%)	Sample of LBW or premature infants were followed. Infants who developed FTT were more likely to have congenital heart disease, bronchopulmonary dysplasia, and cerebral palsy. General health status was lower for FTT as measured by Stein Total health Score ($p < .003$) and by the Rand General Health Ratings ($p < .0001$). For GI disorders, NS for vomiting & diarrhea. There were significant differences in environmental variables between the two gps ($p < 0.03$).	Of 985 enrolled, 71 LTF, 12%(20) OFTT, 16%(28) were both OFTT & NOFTT	21% of babies develop FTT by 36 wks; ND on funding source
	Prematurity	100	100			
	LBW	100	100			
	Bronchopulmonary dysplasia	13.9	9.6			
	Congenital heart disease	7.2	.3			
	Neurological – cerebral palsy	8.9	4.6			
	Environmental variables*	32.6	33.9			
	General health ratings	ND	ND			
	Gastrointestinal disorders	ND	ND			
	* HOME Inventory - total score					
Drotar, 1994 94308313	Family Relationship Index	FTT	Ctrl	Patients with NOFTT had poor family relationships at time of diagnosis which persisted for 3.6 years despite various interventions compared to the control group ($F = 8.11$, $p < .01$). There was an effect of time in the scores for both groups ($F = 5.13$, $p < .05$).	---	Government & privately funded
	Intake	47.9 (0.8)	53.7 (5.6)			
	Follow-up	51.2 (8.2)	56.0 (9.4)			
Skuse, 1994, 1995 94253258 96091265	15 month assessment –	FTT	Ctrl	At 15 month assessment, NS but the cases had a trend for anemia & lower maternal IQ. At 4 year fwup, FTT at high risk for child abuse or neglect (RR = 4.43).	1994: 2 cases & 3 controls didn't complete assessments & were excluded from analyses, 1 case had microcephaly, hypotonia, & an action tremor or ataxia of unknown origin	Researchers blinded to patient's status in measures except anthropometry, 1994 noted 1554 potential subjects in population sample vs. 2609 in 1995; privately funded
	Mother's IQ	83.4(17.1)	86.4(16.2)			
	Maternal/child interaction	ND	ND			
	Oral-motor function	ND	ND			
	Anemia	25.5%	23.9%			
	Abuse/neglect - 6 FTT & 90 nonFTT from sampling frame 2609					

Evidence Table 9. Studies associating other correlates / outcomes with Failure to Thrive patients compared to healthy control subjects in developed countries

Part II

Author, Year	Correlates / outcomes & measures			Associations found	Potential biases	Comments
Puckering, 1995 95378341	Maternal interactions Positive – Unconditional Conditional Negative – Unconditional Conditional	FTT -1.37 -0.16 1.16 0.04	Ctrl 1.37 0.16 -1.16 -0.12	FTT signf less positive mother-child interactions compared to Ctrls dyads (combined unconditional measures, t = -2.69, p = .01); FTT signf less positive interactions (combined conditional measures), t = -0.88, p = 0.4 NS but trend for more negative mother-child interactions (combined unconditional measures, t = 1.22, p = 0.2) NS (combined conditional measures), t = 0.12, p = 0.8	---	Other than clinic anthropometric measures, home visits by assessors blinded to child's group status; The FTT children were significantly smaller than the controls; government funded
Wilensky, 1996 97022837	Birthweight* Hypotonia* Hospitalization HOME environment • Active stimulation • Family encouraging development • Verbal & emotional reactivity * Record review of 55 FTT & 1352 Ctrl	FTT 3074 7.27% 33.9% .84 (.17) .55 (.31) .85 (.20)	Ctrl 3230 2.27% 16.9% .92 (.11) .71 (.24) .93 (.14)	The FTT group was found to have lower birth weight ($p < .05$), and were more likely to be hypotonic than the control population ($p < .05$). They were twice as likely to be admitted in the hospital during their first year ($\chi^2 = 5.10$, $p < .05$). In addition, an assessment showed the home environment to be less stimulating ($p < .05$).	Feeding behaviors and HOME environment are causal factors given time dissociation as FTT was established at 15 months, where as, maternal interview/home assessment at 25 months.	2/5th of infants diagnosed as FTT no longer fit the criteria at 20-month follow-up, yet had positive association on Bayley MDI. Reported associations for FTT without specific data: paternal age ($p<.01$), maternal education, & behavioral observations of lower sociability ($p<.05$) & fear of examiner ($p<.05$); ND on funding source

Evidence Table 9. Studies associating other correlates / outcomes with Failure to Thrive patients compared to healthy control subjects in developed countries

Part II

Author, Year	Correlates / outcomes & measures			Associations found	Potential biases	Comments
Drewett, 1999 99284054		FTT	Ctrl	FTT children were significantly more likely to visit the hospital or outpatient clinic than the controls ($\chi^2 = 4.54$, $p = .033$). Paternal ht of FTT were significantly shorter than controls ($t = 2.69$, $p < .01$). 9% of cases vs. 3% of controls had relevant medical conditions that may have affected growth. FTT children had significantly more feeding problems than the controls ($\chi^2 = 12.1$, $p < .01$)	Of 136 cases, 1 died, 9 LTF, 15 declined psychological testing, 4 moved; of 136 controls, 2 were preterm, 5 LTF, 12 declined psychological testing, 14 moved & were replaced. 2 FTT cases & 1 control with medical condition affecting growth, & 9 FTT cases & 2 controls with possible medical conditions	Testers blinded to child's status; privately funded
	Hx hospital admission / hospital outpatient clinic	66(62%)	56(48%)			
	Father's height	174.2(7.8)	177.0(7.2)			
	Medical condition affecting growth – "definitely" / "possibly"	2/9	½			
	Feeding problems	49(46%)	28(24%)			
Wright, 2000 20161504		FTT	Ctrl	22% of cases received social work input of which 4% were registered as at risk for abuse or neglect vs. none for the controls. 3 or 4 FTT registered placed in foster care. FTT significantly later start in eating solids ($p = .003$) & finger foods ($p = .005$) compared to control group.	Of 120 cases, 23 recovered above screening threshold & had no subsequent data, 21 families received social work input of which, 4 cases registered at risk of abuse or neglect, 17 cases had "relevant organic conditions"…but only 4 said to be main explanation for their FTT", age difference between groups	Government & privately funded
	Social work input	21/97	0/28			
	Abuse/neglect risk	4/97	0/28			
	Started solids*	3.89	3.04			
	Started finger foods*	7.15	6.14			
	* age (mo)					
	(Belongs in Developmental table)					

Evidence Table 10. Studies associating other correlates / outcomes with malnourished patients compared to well-nourished control subjects in developing countries

Part I

Author, Year	Demographics	Maternal / household demographics	Inclusion criteria	Exclusion criteria	Definition of malnutrition	Study design
Ghosh, 1979 80028795	Country: India Setting: Inpatient Gp1* Gp2† Ctrl Age(mo) 6-36 6-48 6-48 Wt/age ND ND ND Ht/age ND ND ND Enrolled/Eval 28 39 60 % Male 64 54 67 Race: ND (assumed Indians) * Mild-moderately malnourished, † Severe malnutrition	ND	6 – 48 months, children with PEM, see Definition of FTT Control matched for age, > 80% of 50% weight for age	ND	Based on 50th percentile by Harvard scale: Grade 1-mild 71-80%, Grade 2-malnutrition 61-70%, Grades 3 & 4 severe ≤ 60%	Prospective cross-sectional
Bartel, 1978, 1979 78180773 79162492	Country: South Africa Setting: Outpatient Age: ND Wt/age: ND Ht/length: ND Enrolled* Eval* Race Gp 31/30 31/30 Black Ctrll1 31/30 31/30 Black Ctrll2 31/30 31/30 Black Ctrll3† 90 90 White % Male: ND * Bartel 1978 / Bartel 1979, † reported in Bartel 1979	ND	Bk 6 – 12 yr olds hospitalized during first 27 months of life for kwashiorkor, 5 – 10 yrs prior to commencement of study Controls close in age, no hx of PCM: Ctrl1-Siblings close in age Ctrl2-Yardmates of FTT Ctrl3-High SES Whites	Neurological involvement, brain damage, fits, birth trauma, hospital coma, hypoglycemia	Wellcome criteria for kwashiorkor: <3rd percentile, edematous, and dermatitis and/or nutritional hair changes	Ambidirectional longitudinal Assessment at 4 – 12 y after hospitalization

Evidence Table 10. Studies associating other correlates / outcomes with malnourished patients compared to well-nourished control subjects in developing countries

Part I

Author, Year	Demographics	Maternal / household demographics	Inclusion criteria	Exclusion criteria	Definition of malnutrition	Study design
Kothari, 1992 92225733	Country: India (Developing) Setting: Inpatient FTT / Ctrl Mean age(y) 2.65±0.88 / ND Enrolled 25 / 26 Evaluated 25* / 26 % Male 52 / 50 Race: ND (assumed Indians) * Marasmus – 15, marasmic kwashiorkor - 10	ND	Ages 1-5 yr with severe PEM Controls matched for age & sex with normal nutritional status	Controls without anemia, infection, or cardiac disease	Grade IV malnutrition < 50th percent of body wt based on 50th percentile by Harvard scale	Prospective cross-sectional
Bénéfice, 1992 92296639	Country: Senegal Setting: Outpatient Age: ND Enrolled: 100 Evaluated: FTT 64, Control 34 % Male: 46 Race: ND	ND	Age 9 – 14 y from 2 villages with per capita caloric intake of 2200 & 2400	Recent serious illness, clinical signs of malnutrition or anemia	Wt/age < -1 SD median WHO/NCHS	Prospective cross-sectional

Evidence Table 10. Studies associating other correlates / outcomes with malnourished patients compared to well-nourished control subjects in developing countries

Part II

Author, Year	Correlates / outcome & measures	Associations found	Potential biases	Comments
Ghosh, 1979 80028795	Nerve conduction – ulnar, median, peroneal nerves	Highly significant results with lower nerve conduction velocities in all age groups in the severe malnutrition group compared to controls ($p < .001$). No difference between mild/moderate group and controls. Specific n not given, however significant delay in nerve conduction in each nerve in infants with onset PEM < 12 mo vs. cases onset > 12 mo, $p < .001$	---	ND on funding source
Bartel, 1978, 1979 78180773 79162492	Cardiovascular – Avg EEG freq • freq-R 8.17 8.63 8.44 8.70 • freq-L 8.19 8.67 8.54 8.75 Incidence of EEG activity of specified freq bands • theta-R 15.59 9.49 11.76 9.12 • alpha-R 43.96 55.54 51.78 56.41 Mean(SD), * Dominant hand scores	EEG frequency results were significant for group effect for both hemisphere ($p < 0.01$). Also there was group effect for the incidence of a & d bands in the right & a, d, & ? in the left hemisphere ($p < 0.01$). The kwashiorkor consistently scored higher in the d and lower in the a bands vs. the other groups ($p < 0.05$).	No data on difference of number of children between two reports	Single tester blinded to child's group assignment for Bartel 1978; partially funded by African Medical Research Council
Kothari, 1992 92225733	Cases Ctrl Left ventricular mass 25.75(8.09) 32.44(11.64) Left ventricular mass / body wt 4.44(1.45) 2.42(0.87) Cardiac index* 5.95(1.95) 4.97(1.41) Ejection fraction 62.4(10.7) 67.0(7.8) Anemia – Mean hemoglobin – 7.16±1.78 g/dl * l/min/m^2	Left ventricular mass was less in the cases vs controls ($p < 0.05$, CI 2.08-11.30), but left ventricular mass/body wt was higher in the cases ($p < 0.001$, CI 1.28-2.76) which is associated with poorer prognosis. Cardiac index increased in the cases vs. controls ($p < 0.05$, 0.04-1.92) Relative cardiac sparing in most cases, although there was atrophy. No difference between groups in EJ, but there were EF < 50% in 5 cases, 2 of 5 died within 3 wks.	---	ND on funding source

Evidence Table 10. Studies associating other correlates / outcomes with malnourished patients compared to well-nourished control subjects in developing countries

Part II

Author, Year	Correlates / outcome & measures			Associations found	Potential biases	Comments
Bénéfice, 1992 92296639		FTT	Ctrl	Children with malnutrition scored lower in areas of physical activity ($p < .05$), had less work capacity ($t = 3.2$, $p < .001$), had lower pulmonary function ($p < .001$), arm muscle compared to nourished controls. There was no difference in HR ($t = 0.37$) or level of physical activity.	Child's age determined by recall, no records available; no explanation on missing case from each group not in analyses	ND on funding source
	Power work capacity	60.9(2.8)	75.1(4.4)			
	FVC, < 132 months	1.33(0.04)	1.61(0.04)			
	FVC, > 132 months	1.73(0.03)	2.23(0.09)			
	33 m dash (sec)	7.22(0.10)	6.60(0.15)			
	Jumping (m)	1.34(0.02)	1.43(0.03)			
	Throwing (m)	13.4(0.4)	15.7(0.6)			
	Hand grip (kPa)	47.5(2.0)	54.6(2.9)			
	HR (%) > 125	8.85(1.45)	7.85(2.06)			
	Adjusted mean (SD)					

Appendix A. Literature Search Strategies

Search #1

1. follow-up studies/
2. follow-up.tw.
3. exp Case-Control Studies/
4. case-control.tw.
5. exp Longitudinal Studies/
6. longitudinal.tw.
7. exp Cohort Studies/
8. cohort.tw.
9. (random$ or rct).tw.
10. exp Randomized Controlled Trials/
11. exp random allocation/
12. exp Double-Blind Method/
13. exp Single-Blind Method/
14. randomized controlled trial.pt.
15. clinical trial.pt.
16. (clin$ adj trial$).tw.
17. ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw.
18. exp PLACEBOS/
19. placebo$.tw.
20. exp Research Design/
21. Comparative Study/
22. exp Evaluation Studies/
23. exp Prospective Studies/
24. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25. disab$.af.
26. limitation$.af.
27. handicap$.af.
28. impair$.af.
29. 25 or 26 or 27 or 28
30. exp growth disorders/ or failure to thrive/
31. exp Nutrition Disorders/
32. failure to thrive.af.
33. 30 or 31
34. 24 and 29 and 33
35. limit 34 to human
36. limit 35 to english language
37. limit 36 to (newborn infant or infant <1 to 23 months> or preschool child <2 to 5 years> or child <6 to 12 years> or adolescence <13 to 18 years>)
38. 36 not 37
39. limit 38 to (adult <19 to 44 years> or middle age <45 to 64 years> or "aged <65 and over>"

or "aged, <80 and over>")
40. 36 not 39
41. 24 and 32
42. limit 41 to (newborn infant or infant <1 to 23 months> or preschool child <2 to 5 years> or child <6 to 12 years> or adolescence <13 to 18 years>)
43. 41 not 42
44. limit 43 to (adult <19 to 44 years> or middle age <45 to 64 years> or "aged <65 and over>" or "aged, <80 and over>")
45. 41 not 44
46. limit 45 to human
47. limit 46 to english language
48. 40 not 47
49. 47 or 48
50. exp Body Weight/
51. 24 and 29 and 50
52. limit 51 to human
53. limit 52 to (newborn infant or infant <1 to 23 months> or preschool child <2 to 5 years> or child <6 to 12 years> or adolescence <13 to 18 years>)
54. 52 not 53
55. limit 54 to (adult <19 to 44 years> or middle age <45 to 64 years> or "aged <65 and over>" or "aged, <80 and over>")
56. 52 not 55
57. limit 56 to english language
58. 49 or 57

Search #2

1. exp Failure to thrive/
2. exp Infant nutrition disorders/
3. exp Nutrition disorders/
4. exp failure to thrive/ or exp growth/
5. exp Growth/
6. exp Growth disorders/
7. exp Nutrition disorders/
8. exp Protein-energy malnutrition/
9. exp Child nutrition disorders/
10. exp Child nutrition/
11. exp Infant nutrition disorders/
12. exp Body weight/
13. exp Growth/
14. exp Protein-energy malnutrition/
15. exp Growth disorders/
16. exp Body height/
17. exp Dwarfism, pituitary/
18. exp Dwarfism, pituitary/

19. exp Psychosocial deprivation/
20. exp Dwarfism/
21. exp Stress, psychological/
22. exp Stress, psychological/
23. exp Psychophysiologic disorders/
24. exp Hyperphagia/
25. exp Child behavior/
26. exp Child abuse/
27. FAILURE TO THRIVE.mp.
28. childhood malnutriton.mp. [mp=title, abstract, registry number word, mesh subject heading]
29. failure to thrive.mp. [mp=title, abstract, registry number word, mesh subject heading]
30. protein energy malnutrition.mp. [mp=title, abstract, registry number word, mesh subject heading]
31. growht failure.mp. [mp=title, abstract, registry number word, mesh subject heading]
32. growth failure.mp. [mp=title, abstract, registry number word, mesh subject heading]
33. failure to grow.mp. [mp=title, abstract, registry number word, mesh subject heading]
34. pshchosocial dwarfism.mp. [mp=title, abstract, registry number word, mesh subject heading]
35. psychosocial dwarfism.mp. [mp=title, abstract, registry number word, mesh subject heading]
36. hyperphagic short stature.mp. [mp=title, abstract, registry number word, mesh subject heading]
37. childhood neglect.mp. [mp=title, abstract, registry number word, mesh subject heading]
38. childhood neglect.mp. [mp=title, abstract, registry number word, mesh subject heading]

Search #3

1 thriv$.af.
2 follow-up studies/
3 follow-up.tw.
4 exp Case-Control Studies/
5 case-control.tw.
6 exp Longitudinal Studies/
7 longitudinal.tw.
8 exp Cohort Studies/
9 cohort.tw.
10 (random$ or rct).tw.
11 exp Randomized Controlled Trials/
12 exp random allocation/
13 exp Double-Blind Method/
14 exp Single-Blind Method/
15 randomized controlled trial.pt.
16 clinical trial.pt.
17 (clin$ adj trial$).tw.
18 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw.
19 exp PLACEBOS/
20 placebo$.tw.

21 exp Research Design/
22 Comparative Study/
23 exp Evaluation Studies/
24 exp Prospective Studies/
25 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26 1 and 25
27 limit 26 to human
28 limit 27 to english language

Appendix B. Data Abstraction Form

FAILURE TO THRIVE Association with Disability

Instructions: Check or fill-in where appropriate. Only one answer except where indicated by an *

Reviewer: **Review date**: / / **First author**: **Year**: **UI**:

Is there a Non-FTT comparison group? ☐ Yes ☐ No **IF NOT, DO NOT DATA EXTRACT!**
Other reason(s) for rejection (no data reported, wrong population, etc)**:**

STUDY CHARACTERISTICS
***Name of Country(s):** _____ ☐ Developed ☐ Developing ☐ ND
Number of Sites: _____ ☐ ND
***Study setting during recruitment :** _____ ***Study setting at follow-up:**

Duration of Study: ☐ ND _____ to _____ Other
Funding source: ☐ Government ☐ Pharmaceutical ☐ Private ☐ Hospital ☐ ND

METHODS
Study Design: (CHOOSE ONE): ☐ Longitudinal ☐ Cross-sectional
(CHOOSE ONE): ☐ Prospective ☐ Retrospective ☐ Unclear
(CHOOSE ONE-(PI'S INTENTION)): ☐ RCT ☐ Cross-over ☐ Case-Control ☐ Other _____
Definition (or categories) of Failure to Thrive (as defined by authors): ☐ ND

STUDY POPULATION
Inclusion criteria for FTT:
_____Inclusion criteria for Control:
_____Exclusion criteria for FTT:

Exclusion criteria for Control:

Total number of subjects enrolled - FTT _____ Control _____ ☐ ND
If longitudinal study - # follow-up visits: _____ Follow-up intervals:
Number of subjects evaluated (Final sample size) - FTT _____ Control _____ ☐ ND
Number of subjects who died prior to evaluation - FTT _____ Control _____ ☐ ND
Other reasons for withdrawals/non-participation (by group):
Applicability to question of interest:
How representative was FTT study population to the US FTT population? ☐ Excellent ☐ Good ☐ Fair ☐ Poor

Appendix B. Data Abstraction Form

Appendix B. Data Abstraction Form (continued)

DEMOGRAPHICS OF INITIAL POPULATION (if no data – write ND in the box)

Brief Description of groups ? Circle mean or median ?	**Group 1** (eg. FTT tx)	**Group 2** (eg. FTT placebo)	**Group 3**	**Group 4 Non FTT** (eg. Control)
Sample size evaluated				
Mean/median age at entry (range)				
Mean/median weight for age				
Mean/median ht/ length				
Race- Incl # eg. 5 bk 10 wh 7 asian 2 Nat Amer				
# Males				
Maternal educ level (range)				
Income level (range)				
Health insur type				

Additional SES:

Appendix B. Data Abstraction Form (continued)

***VARIABLES (predictors or outcome) WITH DISABILITY EXAMINED – Fill in 1st column (Variables) with codes listed below**

1 – PERINATAL	2 – DEMOGRAPHIC	3 – ANTHROPOMETRIC	4 - ORGANIC ILLNESS	5 – DEVELOPMENTAL MARKERS
a. tobacco	a. education	a. weight	a. congenital h. Immunologic	a. Cognitive development
b. alcohol	b. income	b. weight for age	b. pulmonary i. Infectious	b. Behavioral disorder
c. cocaine	c. health coverage	c. height	d. cardiovascular j. endocrine (incl precocious puberty)	c. ADHD
d. infection	d. maternal IQ	d. height for age	e. gastrointestinal k. other	d. Learning disability
e. prematurity	e. quality of HOME Envirmnt	e. head circumference	f. renal	e. Speech/lang/communication disorder
f. LBW	f. age f. wt for ht		g. neurological (incl oral-motor dysf)	f. Activities of daily living
g. other	g. gender	g. other		g. School performance
	i. other			h. other

Appendix B. Data Abstraction Form (continued)

Variables (outcome or predictors)	**Time to f/u**	**N** (total # eval by Gp)	**Measurement tool** (eg. Child Behavior Checklist)	**Statistical methods**	**Tool appro-priate?**	**Criteria / cut-point** (text description and/or cut-point value for test ⊕ or test T)	**Outcome values/measures** (by Gp)	**Results** (incl p-value)
eg. 2g (maternal edu)	NA	FTT-19 Cntl-19	Questionnaire	One-tail t test	Y	NA	FTT – 11 yr (SD = 2) Control – 12 yr (SD = 1)	There was a difference between the two groups in maternal educ. ($p < 0.05$)

Appendix B. Data Abstraction Form (continued)

Other findings/Results/Conclusions of interest:

BIAS/LIMITATIONS

Eligibility criteria: ☐ Explicit & appropriate ☐ No

Sample size: ☐ Sufficient ☐ Small

Funding source: ☐ Not of concern ☐ Of concern ☐ No data

Dropout rate/reasons: ☐ Not of concern ☐ Of concern ☐ No data

Predictors & outcomes: ☐ Relevant ☐ Not relevant

Follow-up duration: ☐ Adequate ☐ Inadequate ☐ Cross-sectional

Methodology: ☐ Adequate ☐ Inadequate ☐ Unsure

Statistical analysis: ☐ Adequate ☐ Inadequate ☐ Unsure

Control group: ☐ Appropriate ☐ Inappropriate ☐ No control group

Sample representative of inclusion criteria: ☐ Yes ☐ No

Post hoc analyses: ☐ All ☐ Some ☐ None ☐ Unsure

Other:

Internal Validity (Quality of Methods)

☐ **A** Prospective (Not Retrospective). Complete reporting of methods and results (incl. inclusion/exclusion criteria, "Table 1 data,") proper reference ("gold") standard, correct analyses performed (No data inconsistency and discrepancy).

☐ **B** Prospective or Retrospective. Not all criteria of A. Some deficiencies, however, unlikely to cause major bias

☐ **C** Prospective or Retrospective. Significant design or reporting errors, large amount of missing information or bias. No reference standard provided or use of inappropriate reference standard.

If B or C: **Deficiency:**

Study Summary – (A brief paragraph for the Results section of the report including the basic methodology, population, outcomes, stats & results and biases)

Appendix C. Acknowledgments

The Evidence-based Practice Center staff acknowledges the collaboration of the clinical experts who served on the EPC Technical Expert Panel. The EPC also acknowledges the contributions by those who acted as peer reviewers for the evidence report.

New England Medical Center EPC Project Staff

Joseph Lau, MD; EPC/Project Director
Ethan Balk, MD, MPH, Assistant Project Director and Project Leader, Short Stature
Cynthia Cole, MD, MPH, Coordinating Team Leader
Deirdre DeVine, M Litt, Project Manager
Priscilla Chew, MPH, Project Leader, Failure to Thrive
Kimberly Miller, BA, Research Assistant
Chenchen Wang, MD, MSc, Project Leader, Low Birth Weight

Technical Expert Panel

Evidence Review Teams, Tufts New England Medical Center

Very Low Birth Weight

Dr. Cynthia Cole, Project Coordinator and Team Leader
Drs. Geoffrey Binney, John Fiascone, James Hagadorn, and Chiwan Kim
Patricia Casey, NNP

Short Stature

Dr. Patricia Wheeler, Team Leader
Drs. Barbara Shephard and Karen Bresnahan

Failure To Thrive

Dr. Ellen Perrin, Team Leader
Drs. Stephan Glicken, Nicholas Guerina, Kevin Petit, Robert Sege, MaryAnn Volpe, and Deborah Frank
James Perrin, MD, Pediatric Consultant to the EPC

Social Security Administration

Science Partner: Dr. Paul Burgan, MD, PhD; Regina Connell, MS

Agency for Healthcare Research and Quality (AHRQ)

Marian James, PhD, Task Order Officer

American Academy of Pediatrics

Marilee Allen, MD (Very Low Birth Weight)
Professor
Neonatology, Department of Pediatrics
Johns Hopkins University
Baltimore, Maryland

Joseph Hersh, MD (Short Stature)
Louisville, Kentucky

Michael Farrell, MD (Failure to Thrive)
Chief of Staff
Childrens' Hospital Medical Center
Cincinnati, Ohio

Carla Herrerias, BS, MPH
Senior Health Policy Analyst
Department of Practice and Research
American Academy of Pediatrics
Elk Grove Village, Illinois

Disability Law Center, Inc.

Linda Landry, Esq.

Peer Reviewers

American Academy of Pediatrics

Very Low Birth Weight

Deborah Campbell, MD
Hartsdale, New York

Warren N. Rosenfeld, MD
Department of Pediatrics
Winthrop University Hospital
Mineola, New York

Short Stature

Susan Rose, MD
Department of Endocrinology
Childrens' Hospital Medical Center of Cincinnati
Cincinnati, Ohio

Failure to Thrive

William Cochran, MD

Department of Pediatric GI/Nutrition
Geisinger Health System
Danville, Pennsylvania

American Association of Clinical Endocrinologists

A. Jay Cohen, MD
The Endocrine Clinic, PC
Memphis, Tennessee

Lawson Wilkins Pediatric Endocrine Society

David M. Brown, MD
Professor of Pediatrics
University of Minnesota
Minneapolis, Minnesota

National Institute of Child Health and Human Development

Gilman Grave, MD
Chief, Endocrinology, Nutrition and Growth Branch
Center for Research for Mothers and Children
Bethesda, Maryland

Catherine Y. Spong, MD (for VLBW and Failure to Thrive)
Chief, Pregnancy and Perinatology Branch
Center for Research for Mothers and Children
Bethesda, Maryland

Tonse Raju, MD (for VLBW and Failure to Thrive)
Pregnancy and Perinatology Branch
Center for Research for Mothers and Children
Bethesda, Maryland

Society for Developmental and Behavioral Pediatrics

Denis Drotar, MD
Professor and Chief
Division of Behavioral Pediatrics and Psychology
Rainbow Babies and Childrens' Hospital
Cleveland, Ohio

Daniel Kessler, MD
Phoenix, Arizona

Appendix D: Acronyms/Abbreviations

ADHD	Attention deficit hyperactivity disorders
ADL	Activities of daily living
AFDC	Aid to Families with Dependent Children
AGA	appropriate for gestational age
ALRI	acute lower respiratory infections
ANCOVA	analyses of covariance
ARI	acute respiratory infections
BGS	Boston Growth Standard
BMI	body mass index
CBCL	Child Behavior Checklist
Ctrl	control
D	day(s)
D/C	discharge
FU	follow-up
FVC	forced vital capacity
GCI	general cognitive index
GA	gestational age
Gp	group
HC	head circumference
HOME	Home Observation for Measurement of the Environment
HR	heart rate
HS	high school
Ht	height
Hx	history
Incr	increase(d)
LBW	low birth weight
LOMDS	Lincoln-Oseretsky motor development scale
MANCOVA	multivariate of analyses of covariance
Mo	month(s)
MDI	mental development index
ND	no data
Nl	normal
NOFTT	non-organic failure to thrive
NS	not significant
NCHS	National Center for Health Statistics
Nonsignf	nonsignificant
OFTT	organic failure to thrive
PCERA	Parent-Child Early Relational Assessment scale
PCM	protein-calorie malnutrition
PDI	psychomotor development index
PEM	protein-energy malnutrition
PHA	phytohemagglutinin
PPVT	Peabody Picture Vocabulary Test

RFC	rosette forming cells
RR	relative risk
SD	standard deviation
SDS	standard deviation score
SES	social-economic status
SGA	small for gestational age
Signf	significant
SK-SD	streptokinase-streptodornase
Std	standard
SOMA	Schedule for Oral Motor Assessment
SWFA	standard weight for age
THE	tetrahydrocortisol
THF	tetrahydrocortisone
TRIB	Tester's Rating of Infant Behaviour
UI	Medline unique indentifer
WAIS	Wechsler Adult Intelligence Scale
WD	withdrawn
WPPSI / WPPSI-R	Wechsler Pre-school and Primary Scale of Intelligence
WISC	Wechsler Intelligence Scale for Children
WORD test	Wechsler Objective Reading Dimensions manual
Wt	weight