Outcomes 8 years after preterm birth

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Chapter 2

Aim, design and outline of this thesis

AIM

Survival of (extremely) preterm infants has increased dramatically and, as a consequence, neonatal and long-term morbidity numbers remained stable or even increased. Early nutrition is considered a key factor in an attempt to optimize later outcomes of preterm-born children. Long-term follow-up of nutritional intervention studies in preterm infants, however, is scarce.

The primary aim of this thesis is to describe the follow-up at age 8 years of preterm-born children who originally participated in the nutritional RCT called 'Study Towards the Effects of Postdischarge nutrition' (STEP). The secondary aim is to explore the influence of early-life growth and nutrition on various outcomes including growth, body composition, neurodevelopment, and endocrine variables.

DESIGN

Original study

A total of 152 infants born very preterm (gestational age of ≤ 32 weeks) and/or with a very low birth weight (≤ 1500 g) were included in the STEP between January 2003 and March 2006. At term age, 102 infants were randomly assigned to receive either an isocaloric protein- and mineral-enriched (postdischarge) formula (PDF) or a standard term formula (TF) until 6 months corrected age (CA). In addition, 50 infants who were fed predominantly (> 80%) human milk (HM) at term age were included as a control group (**Figure 2.1**). If HM was insufficiently available during the first 6 months after term age, TF was given in addition. At term age and at 3, 6, 12, and 24 months CA children visited the outpatient clinic (**Figure 2.2**).

Main results of the STEP until 6 months CA

No differences in weight, length, head circumference, and body composition were found between the PDF and TF groups at birth or at term age. At 6 months CA, the PDF group had gained more lean mass and less fat mass compared with the TF group, while weight, length and head circumference SDS were similar.[1] In addition, infants fed PDF showed enhanced gain in bone mineral content from term age until 6 months CA, which could in part be attributed to higher intake of vitamin D and a greater increase in serum 25(OH)D concentration.[2,3] On the other hand, infants born SGA showed a lower gain in bone mass, independent of body size.[4]

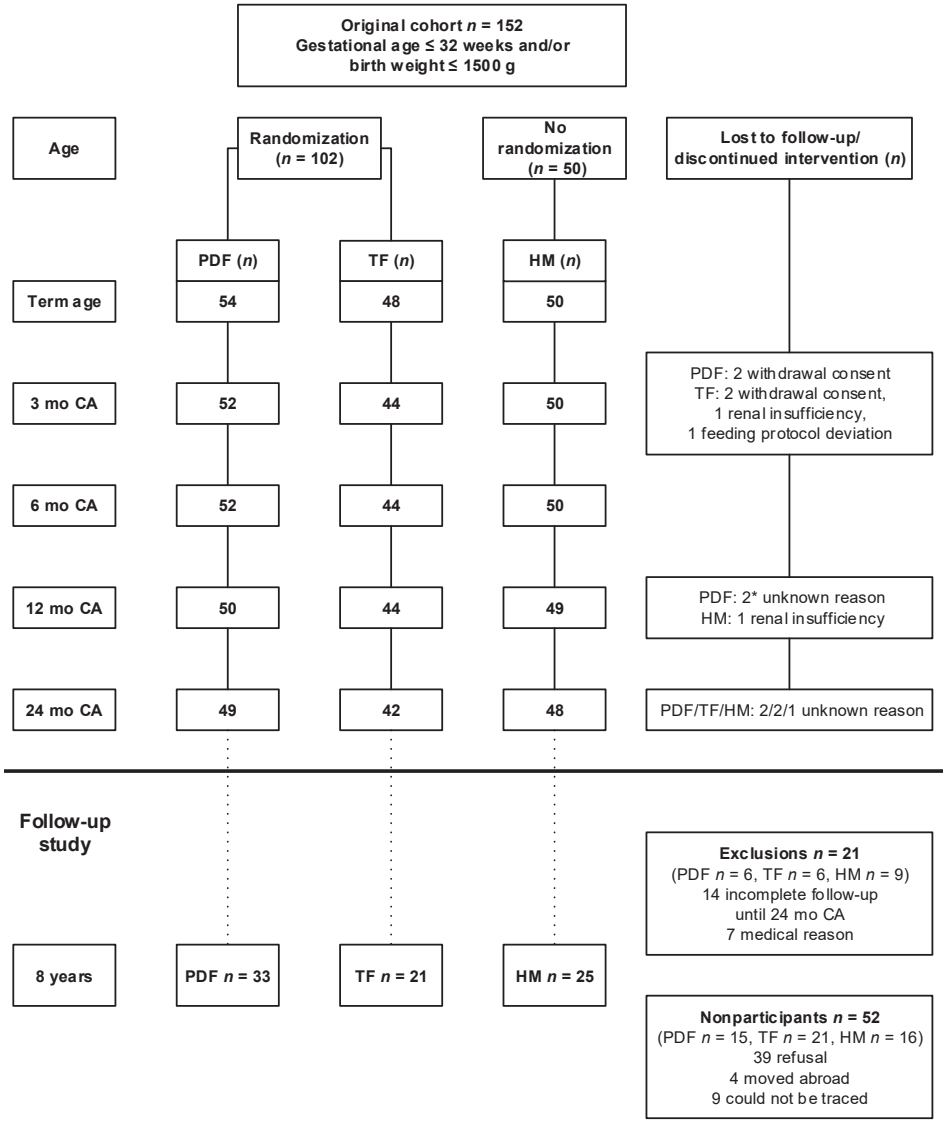

Figure 2.1. Flowchart of the study population.
* 1 PDF participant only no show at 12 months corrected age (CA). HM, human milk; PDF, postdischarge formula; TF, term formula.

Furthermore, growth regulation in the first 6 months after term age was associated with insulin-like growth factor 1 (IGF-1) and insulin.[5]

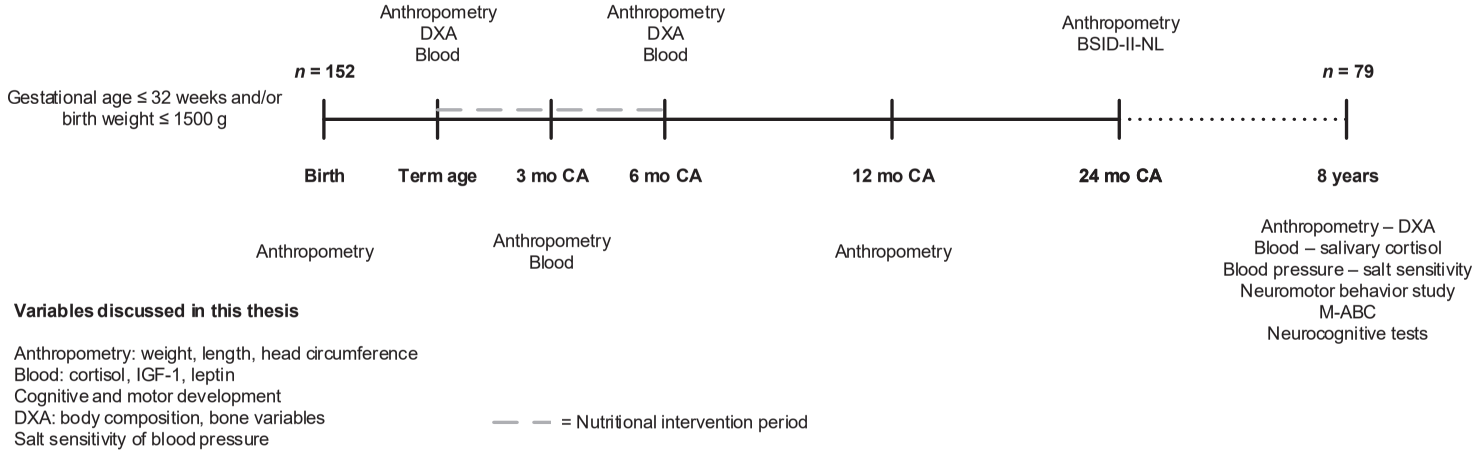

Figure 2.2. Overview of study procedures during the STEP(2).
BSID-II-NL, Bayley Scales of Infant Development, Dutch second version; CA, corrected age; DXA, dual-energy X-ray absorptiometry; IGF-1, insulin-like growth factor 1; M-ABC, Movement Assessment Battery for Children.

Follow-up at age 8 years

At age 8 years, 21 children were excluded for participation in the follow-up study (STEP-2): 14 had an incomplete follow-up until 24 months CA and 7 were excluded for medical reasons (3 severe cerebral palsy, 2 tuberous sclerosis, 1 renal failure, 1 hydrocephalus). The remaining 139 parents and children were approached to participate in the follow-up. A total of 52 parents and children declined or could not be traced, resulting in 79 participating children (**Figure 2.1**). Children visited the outpatient clinic twice with a median of 4 [IQR 2–7] weeks between the visits. Study procedures were performed as shown in **Table 2.1**.

Table 2.1. Study procedures during follow-up (STEP-2) at age 8 years

	Day 1	Day 2
Anthropometry		
Weight	x	
Height	x	
Head circumference	x	
Hip circumference	x	
Waist circumference	x	
Skinfolds	x	
Blood pressure, 6 measurements in 30 min	x	x*
Blood draw after overnight fast	x	x
Salivary cortisol	x	
DXA	x	
Neurocognitive tests		x
Neuromotor tests	x	

* After high salt diet.

THESIS OUTLINE

Part I. Follow-up of the nutritional RCT at age 8 years

Chapter 3 reports the primary and secondary outcomes of the follow-up study of the original nutritional RCT. The feeding groups are compared on anthropometric variables, body composition, bone mineralization, and metabolic health variables.

Part II. Neurodevelopment of preterm-born children, influences of early nutrition and growth.

As part of long-term health and quality of life, cognitive and motor functioning are considered important outcome parameters. Many interventions have been proposed to

improve these outcomes in preterm-born children. In **Chapter 4**, as a secondary outcome of the RCT, we assess neurodevelopment at 24 months CA and 8 years in relation to type of feeding after discharge. In addition we study the correlation between outcomes at 24 months CA and 8 years, as well as predictors for outcomes at both ages.

Considering the dramatic changes in care for preterm infants, we were curious how this might relate to neurodevelopmental outcomes and the effect of early growth patterns on these outcomes. Therefore, in **Chapter 5** we investigate whether early growth has improved and whether the effect of different early growth patterns on later neurodevelopment has changed with time using two sequential cohorts of preterm-born children.

Part III. Endocrine variables

Early development can be influenced by numerous processes: endocrine regulation is an important contributor. In **Chapter 6** we explore the relation between early growth and HPA-axis development, as represented by its end-product cortisol.

In **Chapter 7** we assess the association of leptin and IGF-1 with body composition and bone mineralization from infancy to 8 years.

Chapter 8 describes a relatively unexplored phenomenon in preterm infants, the salt sensitivity of blood pressure (i.e., the response of blood pressure to variations in salt intake), as a possible explanation for the association between preterm birth and cardiovascular diseases in later life.

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