Energy utilisation of infants in Southern Brazil

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Metabolic programming and obesity
The prevalence of obesity is increasing world-wide. The aetiology is complex: genetic factors, intake of energy dense foods, and lack of physical activity can only partly explain the increased prevalence. Originally, obesity was considered a problem mainly of the higher socio-economic class, but in countries undergoing the transition from a developing to an industrialised society, depending on the stage of transition obesity increasingly occurs in the lower socio-economic classes. An increased prevalence of obesity has also been observed in immigrant populations moving from a developing to an industrialised society.

Recently, much attention has been given to the theory of metabolic programming. This theory proposes that metabolic characteristics are being developed during a critical window of time in early life, and these determine later health outcomes. Initially, the focus was on babies born with low birth weight indicating growth retardation in utero, and the subsequent catch-up growth early in life. More recently however, evidence is increasing that not only rapid growth of low birth weight babies, but also a period of rapid postnatal growth in full-term babies may be a risk factor for the development of glucose intolerance and obesity later in life. It is therefore highly important to monitor growth of infants and young children, and to apply recommendations of energy intake that result in a growth rate consistent with long term health.

Research questions:

1. Are energy intake, components of energy expenditure, anthropometric measures, body composition, and prevalence of obesity different between infants who receive breast milk as the only source of milk, or who also receive cows' milk or formula?

2. Are energy intake, components of energy expenditure, anthropometric measures, body composition, and prevalence of obesity different between infants from low and high socio-economic status?

3. If so, could the difference be explained by nutrition, activity levels, or environmental factors?

Growth charts: the influence of socio-economic status and feeding pattern
Growth charts are widely used throughout the world for monitoring growth of infants and young children. They serve the purpose of a diagnostic tool in public health services. Both periods of rapid growth, and growth retardation (both in weight and length) of an individual relative to the reference can be diagnosed,
and action taken. Comparisons between populations can also be made. Currently used growth reference data (National Center for Health Statistics, NCHS) are based on US infants who were predominantly bottle-fed. Breast-fed infants appear to grow faster during the first 3 months of life, and gain less weight during the second half of infancy (6 to 12 months). The apparent growth faltering of breast-fed infants after 3 months of age relative to the NCHS reference has been thought to be a reason for early introduction of complementary foods. In developing countries, with poor sanitary conditions, this practice is known to increase infant morbidity and mortality, and this has been one of the reasons for the World Health Organisation (WHO) to undertake the construction of new growth reference curves for infants and young children until 71 months of age. The new growth reference curves will be based on breast-fed infants raised under optimal circumstances with no constraints to growth so that the database constructed will be normative (as opposed to descriptive). Pelotas was the first of the 6 sites were the Multicenter Growth Reference Study (MGRS) was implemented in 1998, and the children selected to participate were from high and middle socio-economic groups. Food intake data were also obtained to allow estimations of energy and macronutrient intake that correspond to the new growth curves.

**Energy requirements**

In the past estimations of energy intake have been used by WHO/FAO/UNU as the basis for estimations of energy requirements. However, accurate assessment of food intake is difficult, and, in a review that was published in 1996 as a result of a meeting of the International Dietary and Energy Consultancy Group (IDECG), it was concluded that the 1985 WHO/FAO/UNU recommendations were overestimating metabolic needs by 9-39%. In the light of the increasing prevalence of obesity and associated degenerative diseases, such as non-insulin dependent diabetes, worldwide, this is a matter of growing concern. WHO was advised to modify the recommendations, and to base the estimations of energy requirements on measurements of energy expenditure and an added component for the energy deposited in new tissue.

Energy requirements (ER) of infants and young children are defined as the energy intake (EI) that will balance energy expenditure at a level of physical activity consistent with normal development and allow for deposition of tissues at a rate consistent with health. ER are known to be a function of age, size, gender and feeding mode. Breast-fed infants have lower energy requirements than formula-fed infants, and this appears to be at least partly due to metabolic differences (higher sleeping metabolic rate in the latter). Total energy expenditure (TEE) can be measured using doubly labelled water (H\textsubscript{2}O\textsubscript{18}, DLW), and be used as a basis for calculations of ER. Exclusively breast-fed (EBF) infants are the only group in which energy utilisation can be accurately assessed from
measurements of breast milk intake using the dose-to-the-mother deuterium-oxide ($^2$H$_2$O) turnover method. In combination with breast milk composition data (assuming that this is accurately known), energy intake can then be calculated.

The 1996 review included an update of the estimates of energy requirements for infants based on measurements of TEE using DLW, but data during the second half of infancy were scarce, and an expansion of the database would be needed for WHO to justify a modification of the 1985 WHO/FAO/UNU estimates. Meanwhile additional studies of TEE in infants have been done, and in 2002, the Food and Nutrition Board (FNB) of the U.S. National Academy of Sciences published an update of the 1985-estimated ER, and the WHO/FAO/UNU modification is currently underway.

TEE is made up of basal metabolic rate (BMR), thermal effect of feeding (TEF), thermoregulation, activity energy expenditure (AEE), and energy cost of growth. Measurements of BMR require a high level of standardisation including 12-h fast, measured supine but awake. For obvious reasons, this standardised protocol is not feasible or ethical in infants. Both sleeping metabolic rate (SMR) and minimal observable energy expenditure (MOEE) have been used in infants as estimations of BMR. MOEE is a more standardised entity than is SMR, and in the work described here MOEE has been used as the closest approximation of BMR in infants. AEE is calculated as the difference between TEE and MOEE.

It could be argued that in line with the status of the debate on new growth references, energy requirements should also be derived from breast-fed infants from high and middle socio-economic status (SES). However, 11.6% of the Brazilian population lives in extreme poverty (income < 1 US dollar/day), with a prevalence of malnutrition and common infections such that they can be regarded as part of ordinary life, and this is known to increase ER. A study of the effect of SES on ER would provide insight into the impact of this reality. It has been generally accepted that feeding pattern (breast- versus formula-fed) influences energy utilisation, and modified recommendations of energy intake would take feeding pattern into account, however, no studies have addressed a possible effect of SES on TEE and ER.

**Study groups**

Infants were classified by SES on the basis of maternal education. Low SES was defined as no more than 3 years of maternal education, and high SES included infants whose mothers had completed at least 8 years of education.

A classification by feeding pattern was made on the basis of intake of breast- and formula-feeding. The first category included infants who were receiving breast milk as the only source of milk (BM); the second included infants who were
receiving both breast and cows’ or formula milk (BCFM); and the third included infants who were only receiving cows’ or formula milk (CFM).

Selection of study site
Pelotas, a city of about 330,000 habitants in the extreme south of Brazil was chosen as the research location for the following reasons:
a. Social inequity in Brazil is among the highest in the world, making it a suitable site to study the effect of SES;
b. Babies are breast-fed for a longer period of time, allowing assessment of the effect of breast-feeding pattern;

Pelotas was the first of the 6 study sites where the WHO Multicenter Growth Reference Study (MGRS) was implemented, and the results of the work from study 2 (see below) would contribute to the interpretation of the MGRS data.

Studies
To address the objectives of this thesis, three separate studies were conducted:
Study 1. A secondary analysis was performed using the Pelotas 1993 birth cohort: to investigate the effect of feeding pattern and SES on growth and prevalence of obesity (as assessed by BMI). The Pelotas 1993 birth cohort was the only study including the third feeding group: infants who were receiving only cows’ milk or formula (CFM).
Study 2. A cross-sectional study was carried out to examine the effect of breast-feeding pattern on EI, BMI, and growth in high SES infants aged 4 months of age. All infants were from high SES to constitute a mirror sample of the MGRS. For that reason an effect of SES could not be investigated.
Study 3. A cross-sectional study was carried out to examine the effect of SES and breast-feeding pattern on components of TEE, body composition, and prevalence of obesity in breast-fed infants aged 8 months of age.

The Pelotas 1993 birth cohort served to relate the results obtained from the cross-sectional studies to growth and the prevalence of obesity during the first year of life.

Outline of the thesis
The thesis consists of a synthesis and annexes. The synthesis includes a compilation of the 3 studies described above. In the annexes the studies are described in greater detail. Annex I and II refer to study 2 (assessment of breast milk and energy intake in infants aged 4 months of age), and Annex III and IV refer to study 3 (measurement of components of energy expenditure in infants aged 8 months of age).
Methods
Study 1 included a secondary analysis of the Pelotas 1993 birth cohort. Weight and length were analysed by feeding pattern and socio-economic status, and prevalence of obesity at 12 months was calculated on the basis of BMI Z-scores. Main outcomes of study 2 were breast milk and energy intake, and anthropometric measures. Breast milk intake was measured using the dose-to-the-mother $^{2}$H$_2$O turnover method, and complementary food intake (including intake of cows’ milk) was measured using a frequency questionnaire. Main outcome measures of study 3 were energy intake, components of energy expenditure, anthropometric measures, body composition, and prevalence of obesity. As in study 2 breast milk intake was measured using the dose-to-the-mother $^{2}$H$_2$O turnover method; complementary food intake was measured by 1-day food weighing. The doubly labelled water (DLW) method was used for measurement of TEE. MOEE was measured using respiration calorimetry. AEE was calculated as the difference between TEE and MOEE. ER were calculated from TEE with an added component to account for energy deposited in new tissue. Additional measurements taken of the babies were of weight and length, body composition (from the isotopic data), child development (Bayley Scales of Infant Development). Information on maternal characteristics, indicators of socio-economic status and environmental factors were obtained using a questionnaire.

Results

Effect of breast-feeding pattern
(Study 1). Within the Pelotas 1993 birth cohort (Section 4.1.1), there was no difference in weight between infants who were receiving breast milk as the only source of milk (BM infants), and breast-fed infants who were also receiving cows’ milk or formula (BCFM infants) throughout the whole period of infancy. At birth formula-fed infants or infants receiving cows’ milk (CFM infants) were weighing less as compared to BM and BCFM infants (p=0.043), but at 12 months of age CFM infants were heavier (p=0.008). In contrast, length was similar between BCFM and CFM infants. BM infants were taller at 3 months, but shorter at 12 months as compared to the BCFM and CFM infants. CFM infants gained more weight during the first year than BM and BCFM infants, but the prevalence of obesity or overweight was not different between feeding groups.

(Study 2). BCFM infants aged 4 months of age had an EI that was 18% higher than BM infants (Section 4.1.2 and Annex I). Nutritional status, BMI, and weight gained from birth were not different between the feeding groups.
BCFM infants aged 8 months of age had more fat mass (FM, kg, p=0.016) and a higher fat mass index (FMI, kg/m², p=0.013) as compared to BM infants. The prevalence of overweight or obesity was not different between groups. There were no significant differences in EI, TEE or ER between BM and BCFM infants. However, MOEE (kcal/d) was 11% higher in BCFM infants. TEE also tended to be higher in BCFM infants, but this was not significant. Weight (kg) and protein intake (g/d) mediated the effect of feeding pattern on MOEE, implying that weight and protein intake were an intermediate factor in the causal pathway of the association between feeding group and MOEE. Inclusion of these factors into a model of covariance reduced the difference between feeding groups from –44.6 to –23.8 kcal/d (p=0.059) (Annex III).

Overall it can be concluded that CFM infants are weighing less at birth as compared to BCFM or BM infants, suggesting that a lower birth weight may be a reason for the mother not to breast-feed. At 4 months BCFM infants have a higher EI than BM infants, but no differences in weight or BMI are apparent at that time. However, at 8 months BCFM infants have a higher fat mass, fat mass index and a higher MOEE as compared to BM infants. CFM infants gain weight most during infancy, but at 12 months prevalence of overweight or obesity is not different between BM and BCFM or CFM infants.

**Effect of SES**

(Study 1). Within the Pelotas 1993 birth cohort (Section 4.2.1), infants from high SES were significantly taller and heavier throughout the whole first year of life. High SES infants gained more weight during infancy (p=0.008), but BMI and the prevalence of overweight or obesity were not different between high and low SES infants (BMI, p=0.989; prevalence of overweight or obesity, p=0.881).

(Study 3). In a study of infants aged 8 months of age, there were no significant differences in nutritional status or body composition between high and low SES infants, but high SES infants tended to have higher birth weight (p=0.119), higher weight at 8 months (p=0.123), and be taller at 8 months (p=0.089). The prevalence of overweight or obesity tended to be higher in high SES infants (high SES, 15.4%, low SES, 5.1%, p=0.150). TEE adjusted for ethnicity was 21% higher in low as compared to high SES infants (Section 4.2.2 and Annex IV). As MOEE was the same between the groups, the dissimilarity in TEE was attributed to a difference in activity energy expenditure (AEE), with high values in infants from low SES. Analysis of covariance showed that the effect of SES on AEE was mediated by crowding (number of persons per bedroom). Inclusion of crowding into the model reduced the difference between SES groups to an extent that it was no longer significant. A better motor development in the high SES babies was not associated with AEE.
Overall it can be concluded that infants from low SES are shorter and weigh less throughout the whole first year of life. At 8 months TEE is higher in low SES infants, and this is attributed to a higher AEE as a result of increased crowding in the low SES homes. Overweight or obesity tend to be prevalent more in high SES infants as compared to low SES infants at the age of 8 months, but at 12 months this difference was not found.

Conclusions and implications
Feeding pattern influences EI, body composition, and parameters of energy expenditure. At 4 months (study 2), EI was higher in BCFM as compared to BM infants, with no differences in nutritional status or BMI. This was in accordance with data from the 1993 Pelotas birth cohort, where weight and BMI of BM and BCFM infants were also similar. At 8 months (study 3), MOEE was different between BM and BCFM infants with higher values in the latter group, and BCFM infants were fatter. Protein intake and weight mediated the effect of feeding pattern on MOEE, but could not explain it all, indicating that some factor in cows' milk increases, or alternatively some factor associated with breast milk or breast-feeding, decreases MOEE. At 12 months no difference in the prevalence of overweight or obesity was observed between the feeding groups.

An effect of SES on growth and components of energy expenditure was also observed (1993 cohort and study 3). High SES infants were significantly taller and heavier throughout infancy. At 8 months babies from high SES had lower TEE, but there were no differences in MOEE, thus low AEE in these babies was the reason for their reduced expenditure. The mediation of the effect of SES on AEE by crowding suggests that AEE is related to time spent sleeping. Low SES infants sleep with more people in a room, and are likely to rest or sleep less than high SES infants. Although the difference in weight and length between high and low SES was not significant, there was a tendency towards higher values in the high SES group. In a larger sample, this difference would have probably been significant. Body composition was not different between high and low SES infants aged 8 months of age (study 3), but the prevalence of overweight tended to be higher in high SES infants. At 12 months (study 1) no difference was observed in the prevalence of obesity or overweight between high and low SES infants.
In conclusion:

- The average value for energy requirements of infants from high and low SES is comparable to values recently published by the Food and Nutrition Board of the US National Academy of Sciences and with updated values expected to be published soon by WHO/FAO/UNU;

- The development of universally applicable values for energy requirements based on infants from high SES may not be acceptable;

- Complementary feeding with cows’ milk increases sleeping metabolic rate and fat storage, and tends to result in increased growth rates. This deserves attention in relation to the development of obesity later in life.

Future research

Further studies should address long term effects of early feeding pattern on growth and body composition and their relationship to long-term health outcomes, such as obesity and diabetes. The influence of SES on energy expenditure should be repeated at a later age to determine whether the differences found at 8 months of age are relevant to health outcomes later in life. The cohort of 77 infants that served as the basis for study 3 will therefore be followed up when the children are about 3 and 8 years old.