FOOD-CT-2005-007036

EARNEST

EARly Nutrition programming- long term follow up of Efficacy and Safety Trials and integrated epidemiological, genetic, animal, consumer and economic research

Instrument: Integrated Project

Thematic Priority 5.4.3.1: Food Quality and Safety

Final public report on activity 1.2.4

Long term follow up of UK infants born pre term and term and randomised to formulas intended to modify the whole diet or specific nutrients with reference to atherosclerotic cardiovascular disease

Period covered from 15.04.2005 to 14.10.2010

Start date of project: 15.04.2005 Duration: 5,5 Years

Organisation Name of Lead Contractor for this report: UCLON

Final report of data from Activity 1.2.4

Background: Much observational evidence supports the hypothesis that early growth acceleration caused by over-nutrition in infancy has long term effects on cardiovascular disease (CVD) and its risk factors including obesity[1], lipid profiles[2] and high blood pressure[3]. However, there are few examples of this hypothesis being tested experimentally; infants born small for gestational age (SGA) can provide potential populations where the growth acceleration theory can be tested. SGA infants are at increased risk of deficits in stature[4], cognitive and behavioural development[5]; previously to mitigate these risks, strategies that promoted catch-up growth during infancy were employed using enriched formulas that would promote growth during early infancy.

Conversely, it is inappropriate to test this hypothesis using enriched formulas in children who were born appropriate for their gestational age (AGA) this could promote growth unnecessarily; an alternative strategy to investigate this hypothesis in AGA populations would be to use prospective cohort studies where detailed early growth has been monitored and then followed-up into later childhood, this strategy would not only allow the hypothesis to be tested per se but also help identify the period of early life that is sensitive to early growth promotion.

Early infancy could be considered a useful period for an intervention for the prevention of obesity as i) the post-natal period is more amenable to intervention than the ante-natal period, ii) infancy is shorter than other childhood periods, iii) infancy is a period of high contact with health professionals and finally iv) parents have greater control of feeding during infancy than during later childhood.

Objective: The objective of this Activity was to follow-up two cohorts as two tasks; Task 1 was a follow-up of a cohort of formula fed infants born SGA who took part in a randomised controlled of standard term formula versus a nutrient enriched formula designed to promote catch-up growth for the first six months of life. This study was conceived and carried out at a time when it was still considered appropriate to promote early growth in infants who were born SGA. Task 2 was a follow-up of a cohort of term infants (breast, formula and mixed fed) who took part in a large prospective study of early growth for the first two years of life. Cardio-vascular risk factors, particularly the risk of obesity during childhood and adolescence were investigated in both tasks; body composition data were collected to provide 2- and 4 - component models of body composition.

Main tasks:

Task 1 was a follow-up of a cohort of infants born SGA (n=246) in the Glasgow region who had taken part in a randomised controlled trial of nutrient enriched vs standard infant formula for the first 6 months of life, the cohort were 5-7 years old at follow-up (mean 6.3 yrs, SD 0.7), the enriched, trial formula used contained 43% more protein, 12% more energy and higher levels of vitamins and minerals than the control formula. All families who took part in the original study were approached by letter and invited to attend a clinic locally where the child was assessed.
Task 2 was a follow-up of a cohort of young adults (mean age 19 years) born at term and appropriate for gestational age (AGA) who had taken part in an observational

study during the first two years of life when detailed growth measurements and feeding records had been collected from birth every four weeks until two years old. This cohort was recruited from Cambridge, UK during the mid-1980's and had included infants who were exclusively breast-fed, formula fed or mixed fed for the first few months of life. At follow-up, members of the cohort were approached by letter to take part and invited to attend a clinic at the Institute of Child Health in London.

At follow-up, detailed information on body composition was assessed in both studies, in Task 1 deuterium dilution was used to provide estimates of total body water (TBW) and skinfold measurements using the equations of Deurenberg[6] for estimates of fat and fat free mass. To carry out the deuterium dilution, subjects were dosed with a small known quantity of dueterated water, ^2H_2O; urine samples were collected immediately prior to dosing and four hours later. For the calculation of the TBW the ^2H_2O dilution space is assumed to be over-estimated by 1.044, in addition, correction for any fluid intake during the four hours pre- and post-dose sample was collected. Gender and age specific hydration factors were then applied to estimate the fat fee mass of each subject. To calculate body fat mass from skinfold measurements, the equations of Deurenberg require data from four-sites (biceps, triceps, sub-scapular and supra-iliac crest), the sum of these four skinfolds is applied in age and gender specific equations.

In Task 2, in addition to TBW measurements by deuterium, data from dual x-ray absorptiometry (DXA) to estimate bone mineral content and body volume measured using a Bod-pod were collected; this allowed a 4-component model of body composition to be used to estimate fat mass where[7]:

$$\text{FM (kg)} = 2.747\ \text{BV} - 0.710\ \text{TBW} + 1.460\ \text{BMC} - 2.050\ \text{BW}$$

(FM = fat mass, BV = body volume, TBW = total body water, BMC = bone mineral content and BW = body weight)

Background demographic and health data was collected in both studies to be used in adjusted regression models.

Results:
At follow-up, 29% (70/240) of the Task 1 cohort and 21% (52/252) of the older Task 2 cohort were measured. The subjects who took part in the follow up of Task 1 were compared to those who did not; there were no differences between the groups with respect to birthweight, gestation, gender and maternal age however, there were demographic differences, those who were followed-up were more likely to come from non-manual social groups (23% vs 12%, p = 0.03, chi^2) and have mothers who had some formal educational qualifications (11% vs 32%, p = 0.02, chi^2).

In Task 1, comparisons of the fat mass and fat mass index (fat mass/ $height^2$) from deuterium dilution were compared between the two randomised groups; the group randomised to the nutrient enriched formula had 1.2 kg greater fat mass (95% CI: -2.4kg – 0.0kg, p = 0.05) or 18% (95% CI 36% - -0.3%, p = 0.04) than the group on control formula, this effect remained even when the analysis was adjusted for factors that are known to confound fat mass at this age including birthweight z-score, gestation and social class. In a further non-randomised analysis using linear regression there was a significant association of faster weight gain in the first six months of life with increased fat mass at age 6 years but not fat free mass; again this was adjusted for confounders. This effect was shown with both deuterium and skinfold results.

In Task 2, fat and fat free mass, using a four component model, were calculated in these young adults (n= 52, mean age 19 years, range 15-22 years, 21% of original cohort). Compared to the original cohort, subjects who were followed-up were more likely to be female (67% vs 41%), breast-fed (64% vs 44%), have taller mothers (164.2cm vs 162.6cm), be weaned later (14.9 weeks vs 13.7 weeks) and have a higher birth weight (3.47kg vs 3.37kg).

Linear regression alone was carried out as there were no randomised groups. Early growth was divided into the following age categories;birth to 4 weeks, 4 to 24 weeks, 24 to 52 weeks, 52 to 78 weeks and 78 and 104 weeks. Data was collected on CVD related outcomes such as body composition, vascular function and blood pressure. These linear regression analyses examined the relationships between change in weight SD scores from birth to four weeks and i) BMI, ii) fat mass index (FM / Ht ^{2}) and iii) fat free mass index (FFM / Ht ^{2}) at 19 years. There was a significant and positive relationship with an increase in weight SDs birth to 4 weeks and higher BMI, fat mass and fat free mass indices at 19 years. These effects remained even after adjusting for factors likely to effect current body composition such as social class, maternal education, and parental anthropometry, mode of infant feeding and present levels of activity of the subject. In the case of fat mass index, the effect increased most noticeably from $p = 0.04$ to $p = 0.01$. These analyses were repeated for the following periods (4 – 24 weeks, 6 – 12 months, 12 – 18 months and 18 – 24 months) but no further significant effects were seen.

Discussion:

In Task 1 we found that use of a nutrient enriched formula for the first 6 months of life designed to promote faste infant weight gain resulted in increased body fatness by mid-childhood. This effect was demonstrated using 2 different techniques and was independent of sex, height in childhood, birth-weight z score, gestational age, socioeconomic status, and maternal BMI. These experimental data suggest that the association between infant growth and nutrition and the long-term risk of obesity is independent of genetic or environmental confounding factors that influence early growth and later adiposity. Therefore, our findings support, for the first time to our knowledge, the hypothesis that there is at least a partially causal link between early nutrition and long-term adiposity. Early weight gain in SGA cohorts has previously been reported; Ibanez[8] found that rapid weight gain from birth to 2 years led to increased levels of abdominal fat by 4 years. These data have important implications for the management of infants born SGA and suggest that the primary prevention of obesity could begin in infancy with major benefits for obesity and later CVD risk.

The follow-up in Task 2 has allowed us to identify a four week period (birth to 4 weeks) of rapid growth that appears to be critical to the development of increased BMI, fat and fat free mass at 19 years, with the strongest effect being seen with fat mass index. These data add to the body of already published data suggesting rapid early post-natal growth may have long term risk of obesity and greater fat mass by early adulthood; however few authors have been able to reduce the window to such a short period. In term cohorts, Ekelund[9] found that rapid growth in the first 6 months of life is associated with increased BMI and fat mass at 17 years and

Karaolis[10] reported that rapid growth from birth to 6 months is associated with increased BMI, % fat mass and risk of being overweight by 7 years. These earlier reports have previously been limited by data with relatively long time periods between individual measurements of growth; some of these prospective cohorts were created before the 'rapid growth hypothesis' was suggested.

Our data here did not show any effects of rapid growth after the age of four weeks, there is some literature to suggest that rapid growth after 3 months of age may also be important. In 11 year old children in the UK who were born at term, Chomtho[7] found changes in weight gain between 0 - 3 months and 3 - 6 months were associated with increased FM and FFM but between the period of 3 - 6 months the effects were greater in the FM gain, which contrasts with our data here that suggests weight gain between birth to 4 weeks has the highest impact on FM. These data are not yet conclusive and further work, preferably in prospective cohorts need to be designed to elucidate the timing of rapid growth and later obesity.

We encountered particular problems in following up subjects in this age group; many had left home and were either working or at college in different parts of the UK making them reluctant to take time out to take part in a study based in London, rather than Cambridge where many of them still had family.

Cohort attrition was a limitation of both studies; for the younger study only 29% of subjects agree to take part. This was a cohort of formula feeding mothers and the attrition rate would be expected to be greater than a cohort that also had breast-feeding mothers reflecting the social and education status of the mothers. For the older cohort of Task 2 many of the subjects were now students or working and no longer dependents of the parents; only 21% of the original cohort took part. We have recently tried to address the problems of cohort attrition in both RCTs and observational follow-ups as reported here, in a discussion paper published in 2008. A reduced sample size increases the risk of missing an effect and may result in bias; our results from Task 1 here appear to represent a strong and consistent effect of rapid growth in the first four weeks of life, which despite a small sample size remained significant even when adjusted for factors know to effect outcomes. We also acknowledge that our cohort here represents a group of children who were born 6-7 years earlier and a group of young adults who were born around 20 years ago and particularly for the older formula fed infants, there may be significant differences in formula currently used, however, as this effect is primarily one of growth per se rather than early diet we feel that this effect is generalisable to current populations.

Conclusions. Task 1: by using an RCT, designed to compare an enriched infant formula to promote growth with a control infant formula we have shown that rapid growth in first 6 months of life is associated with increased fat mas at 6 years.
Task 2: Accelerated growth in the first four weeks of life has a strong effect on components of body composition, with the strongest effect seen on fat mass index at 19 years.

Dissemination:

The results of the Task 2 study have recently been published in American Journal of Clinical Nutrition

1. Singhal A, Kennedy K, Lanigan J, Fewtrell MS et al. Nutrition in infancy and long-term risk of obesity: evidence from 2 randomised controlled trials. AJCN doi:10.3945/ajcn2010.29302

The published discussion paper investigating the effects of cohort attrition in long-term follow-ups is:

2. Fewtrell MS, Kennedy K, Singhal A, Martin RM, Ness A, Hadders-Algra M, Koletzko B, Lucas A. How much loss to follow-up is acceptable in long-term randomised trials and prospective studies? Arch Dis Child 2008; 93: 458-61.

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1. Owen CG et al. Effect of infant feeding on the risk of obesity across the life course: a quantitative review of published evidence. Pediatrics 2005; 115: 1367–1377.
2. Singhal A et al. Breast milk feeding and lipoprotein profile in adolescents born preterm: follow-up of a prospective randomised study. Lancet 2004; 363: 1571-8
3. Singhal A et al. Promotion of faster weight gain in infants born small for gestational age; is there an adverse effect on later blood pressure? Circulation 2007; 115: 213–220.
4. Leger J et al. Reduced final height and indications for early development of insulin resistance in a 20 year old population born SGA. BMJ 1997; 315: 341-7.
5. Lundgren EM et al. Intellectural and psychological performance in males born with and without catch-up growth. Pedriat Res 2001; 50: 91-96.
6. Deurenberg P, Pieters JJL, Hautvist JGAJ. The assessment of body fat percentage by skinfold thickness measurement in children and young adolescence. Brit J Nutr 1990; 63: 293-303.
7. Chomtho S et al. Association between birth weight and later body composition: evidence from a 4-component model. Am J Clin Nutr 2008; 88: 1040-8.
8. Ibanez L et al. Early development of adiposity and insulin resistance after catch-up weight gain in small for gestational age. J Clin Endocrinol Metab 2006; 91: 2153-8.
9. Ekelund U, Ong K, Linne Y et al. Upward weight percentile crossing in infancy and early childhood independently predicts fat mass in young adults: the Stockholm Weight Developmetn Study (SWEDES). Am J Clin Nutr 2006; 83: 324-330.
10. Karaolis-Danckert N et al. Rapid growth among term children whose birthweight was appropriate ofr gestational age has a longer lasting effect on percentage body fat than BMI. Am J Clin Nutr 2006; 84: 1449-55.