Institution: University College London

Unit of Assessment: 1 – Clinical Medicine

Title of case study: Prevention and treatment of childhood obesity

1. Summary of the impact

Clinical research conducted at the UCL Institute of Child Health between 1998 and 2011 under the direction of Professors Alan Lucas and Atul Singhal showed that a slower rate of infant weight gain had long-term benefits to reduce the risk of obesity and cardiovascular disease. This contradicted the accepted view, which favoured the promotion of rapid weight gain in infancy. This work has had a significant influence on public health policies and initiatives in the UK and elsewhere. It has changed the way infant formulas are made and used. Two new interventions for overweight children have been developed and are helping families around the world.

2. Underpinning research

This work was initially based on long-term follow-up during the late 1990s of randomised controlled trials which had originally been set up in the 1980s by Lucas to investigate the impact of early nutrition on long-term health, a concept termed programming **[1]**. Although extensive data from animal models and small-scale epidemiological studies in humans had suggested that growth and nutrition in early life could affect, or program, long-term health, the lack of data from experimental studies had prevented a causal interpretation in humans.

Whilst initially studying adolescents born preterm who had been randomised to different diets at birth, Singhal showed for the first time in humans a causal link between infant nutrition and long-term risk of cardiovascular disease and type 2 diabetes **[2-5]**. He noted large benefits for breast-milk feeding in reducing the major risk factors for cardiovascular disease (high blood pressure, risk of obesity, insulin resistance, markers of inflammation, and high cholesterol concentration) and that, contrary to public health and medical opinion at the time, faster weight gain in infancy increased the risk of obesity, insulin resistance, dyslipidaemia, high blood pressure and endothelial dysfunction up to 16 years later **[1-6]**. Together with Lucas, he proposed the 'Growth Acceleration' hypothesis which suggested that the long-term benefits of breast-feeding for obesity and cardiovascular disease were related to slower weight gain in breast-fed compared to formula-fed infants and that faster infant growth had adverse consequences for later health **[3]**.

Subsequently, this hypothesis was confirmed by his team in randomised trials in infants born at term **[7, 8]** and by others in over 50 studies internationally. The proposed impact of infant growth on later health was substantial. Studies at UCL, and elsewhere building on this work, have suggested that nearly a third of the risk of obesity in childhood could be explained by the pattern of infant growth and, on a population basis, lowering diastolic blood pressure by breast-feeding or by slower infant growth could prevent over 100,000 cardiovascular events per year in the US alone (as reviewed **[3]**).

As highlighted by a Cochrane systematic review, while childhood obesity is a major public health problem, there are few evidence-based interventions for its treatment. From 2004, Singhal's team has developed and tested community based interventions for the prevention and treatment of obesity in both preschool and school aged children. 'MEND' (Mind, Exercise, Nutrition, Do it), a family-based, community program for obese children aged 7-13 years, was designed by Singhal and his PhD student, Paul Sacher, as a multi-component, community-based intervention that fulfilled NICE guidelines and included behaviour modification, nutrition education and physical activity components. The group conducted a randomised controlled trial of this intervention and showed it to be suitable for widespread prevention and treatment for paediatric obesity **[9]**. A related programme 'Trim tots' has been introduced for children under the age of 5 years.

3. References to the research

[1] Singhal A, Cole TJ, Lucas A. Early nutrition in preterm infants and later blood pressure: two cohorts after randomised trials. Lancet. 2001 Feb 10;357(9254):413-9. http://doi.org/dmc57r

[2] Singhal A, Fewtrell M, Cole TJ, Lucas A. Low nutrient intake and early growth for later insulin resistance in adolescents born preterm. Lancet. 2003 Mar 29;361(9363):1089-97. http://dx.doi.org/10.1016/S0140-6736(03)12895-4

[3] Singhal A, Lucas A. Early origins of cardiovascular disease: is there a unifying hypothesis? Lancet. 2004 May 15;363(9421):1642-5. http://dx.doi.org/10.1016/S0140-6736(04)16210-7

[4] Singhal A, Cole TJ, Fewtrell M, Deanfield J, Lucas A. Is slower early growth beneficial for long-term cardiovascular health? Circulation. 2004 Mar 9;109(9):1108-13. http://doi.org/b5ckms

[5] Singhal A, Cole TJ, Fewtrell M, Lucas A. Breastmilk feeding and lipoprotein profile in adolescents born preterm: follow-up of a prospective randomised study. Lancet. 2004 May 15;363(9421):1571-8. http://dx.doi.org/10.1016/S0140-6736(04)16198-9

[6] Singhal A, Lanigan J. Breastfeeding, early growth and later obesity. Obes Rev. 2007 Mar;8 Suppl 1:51-4. http://dx.doi.org/10.1111/j.1467-789X.2007.00318.x

[7] Singhal A, Cole TJ, Fewtrell M, Kennedy K, Stephenson T, Elias-Jones A, Lucas A. Promotion of faster weight gain in infants born small for gestational age: is there an adverse effect on later blood pressure? Circulation. 2007 Jan 16;115(2):213-20. http://doi.org/c7nj83

[8] Singhal A, Kennedy K, Lanigan J, Fewtrell M, Cole TJ, Stephenson T, Elias-Jones A, Weaver LT, Ibhanesebhor S, MacDonald PD, Bindels J, Lucas A. Nutrition in infancy and long-term risk of obesity: evidence from 2 randomized controlled trials. Am J Clin Nutr. 2010 Nov;92(5):1133-44. http://dx.doi.org/10.3945/ajcn.2010.29302.

[9] Sacher PM, Kolotourou M, Chadwick PM, Cole TJ, Lawson MS, Lucas A, Singhal A. Randomized controlled trial of the MEND program: a family-based community intervention for childhood obesity. Obesity. 2010 Feb;18 Suppl 1:S62-8. http://doi.org/cmv6xd

Relevant Funding
MRC Programme Grant: 'The early nutritional origins of cardiovascular disease' (PI: Singhal; £1.3m; 2007-12). Funding for commercialisation from Abbott Nutrition Plc: 'Phase three randomised controlled trial to assess the effects of early nutrition on long-term body composition, growth and risk factors for cardiovascular disease (PI: Singhal; £2.6m; 2010-12).

4. Details of the impact

Our research has influenced policies and initiatives to improve nutrition in children, tackling childhood obesity, and improving the long-term health of the population. Our work has benefited children from birth onwards, covering breast feeding, production and use of infant formulas, and novel public health programmes for children of different ages. Our growth acceleration hypothesis and the results of our randomised controlled trials provided firm scientific evidence that slower growth in infancy has long-term benefits for health, which has been used worldwide to bring about a change in policy and practice.

Slow growth and breastfeeding: impacts on national and international policies and initiatives

Contrary to previous public opinion and paediatric clinical practice, a slower rate of weight gain in infancy (as seen in breast-fed compared to formula-fed infants) is now regarded as desirable for long-term health. Such growth patterns are now actively promoted in statements by official bodies. Our work has provided important evidence to support the importance of breast-feeding for long-term as well as short-term health outcomes, and has been widely cited in health and public health policies and initiatives in this area.

In 2006, the World Health Organisation produced revised child growth charts, based on the slower rate of growth of breast-fed infants (previous charts based on faster growing formula-fed infants). Our research provided scientific evidence that a slower pattern of growth had long-term benefits for health, which supported the adoption of these charts in the UK and elsewhere. The Scientific Advisory Committee on Nutrition (SACN) and Royal College of Paediatrics and Child Health joint report on the WHO growth charts cited our work, stating that: '*current evidence suggests that such a (slower) pattern of growth could potentially reduce the later risk of obesity*' **[a]**. These charts have

now been adapted and adopted for use in the UK.

The research above led to the commission of a review for the UK government's Foresight report on 'Tackling Obesities: Future Choices'. This report states that '*Breast-feeding and early growth patterns provide the only period in which there is clear evidence to support the concept of a critical period of development associated with long-term consequences*' and '*while there is less evidence of a direct link between birth weight and obesity, weight gain in early life appears to be critical*'. It adds **'***Breast-fed babies show slower growth rates than formula-fed babies and this may contribute to the reduced risk of obesity later in life shown by breast-fed babies*' **[b]**.

The Scientific Advisory Committee for Nutrition report on the influence of maternal, fetal and child nutrition on the development of chronic disease later in life, cites references 1-3 above and states: '*In particular birthweight and birth size, early feeding, and the rate of growth in early life modify the prevalence of cardiovascular disease and its risk factors (such as blood pressure, adiposity and glucose tolerance) and certain cancers*' **[c]**.

In 2011, the US Institute of Medicine's policy on childhood obesity stated that health care professionals should '*consider the children's rate of weight gain when determining which children are at highest risk of developing obesity*' and they need to '*support breast-feeding to help prevent future obesity*' **[d]**. Michelle Obama's initiative to tackle childhood obesity cites our work on the mechanisms by which breast-feeding is beneficial for later risk of obesity along with reviews directly based on our work and patents **[e]**.

Infant formulas: impacts on their formulation and use.

This research has also led to changes in the nutrition content of infant formula with an emphasis on changes to both infant formula composition (e.g. lowering of protein content) and volume of consumption in order to produce a growth pattern more similar to the breast-fed infant. For example, formula manufacturers SMA have detailed on their website aimed at professionals how our research has influenced their products **[f]**. We have also patented research relating to the composition of infant formula and this intellectual property is currently under licence to Abbott Nutrition PLC who fund a phase 3 clinical trial to develop a new infant formula designed to mimic the growth rate of the breast-fed infant. This trial has so far generated *[Text removed for publication]* in royalty income for MRC/ICH and over £2.8m in research funding **[g]**.

Our evidence that promotion of faster growth may have adverse consequences for long-term health in infants born small for their gestational age (SGA) has led to changes in the management of these infants. Regarding long-term metabolic complications in such infants, a consensus statement by the International Societies of Paediatric Endocrinology and Growth Hormone Research on the management of SGA infants (to which Singhal contributed), advised that: '*obesity and accelerated weight gain are likely to be major risk factors*' and '*calorie dense feeding for SGA infants may not be appropriate*' **[h]**. As a consequence, nutrient-enriched formulas are no longer recommended for use in otherwise healthy infants born low birth weight at term.

The MEND Programme and Trim Tots: lifestyle interventions for children

The first MEND programme was developed at Great Ormond Street Hospital and the UCL Institute of Child Health, and then in 2004, MEND Central Ltd was set up, operating as a social enterprise, to provide the programme more widely. Since that time, more than 55,000 individuals have benefitted from the programme. It is currently running in more than 200 locations across England and Wales, and has been adapted for use in a number of other countries around the world **[i]**. The Greenwich Healthy Living Service, who have been running the MEND programme for four years, report the following case study about one of their participants: "*Since attending the MEND programme at the Waterfront Leisure Centre with her 12 year old daughter Elise, Carmen, a mum from Eltham, has noticed a huge improvement in her daughter's eating habits. Carmen has made healthy changes to the way she cooks and Elise now tries new things and eats a wider range of foods. Carmen and Elise have also been spending time together whilst improving their health: 'We both joined the gym together and we are definitely much more active. The graduate children's exercise sessions were also very encouraging because you don't just finish the programme; you*

have something to do which continues to motivate the children" **[j]**.

We are now piloting a new intervention for younger children, called Trim Tots. This is a 24-week programme for families with under-fives, which teaches the principles of a healthy lifestyle through art and play. One parent who has taken part in this pilot reported: "*The simple fact is, the lessons we learned and knowledge I have passed on to friends and family, has made a big difference to our lives… The Trim Tots programme and support for children and families at this vital age needs to be widespread. It should be available for all parents as they are the building blocks to nurturing a generation of health conscious, educated young people*" **[k]**.

5. Sources to corroborate the impact

[a] Scientific Advisory Committee on Nutrition & Royal College of Paediatrics and Child Health: Application of the WHO growth standards in the UK. 2007. Report prepared by the joint SACN/RCPCH Expert Group on Growth Standards. *Cites ref [3] on p.10* http://www.sacn.gov.uk/reports_position_statements/reports/application_of_the_who_growth_standards_in_the_uk.html

[b] Tackling obesity. Government Office for Science. *See ref 20 to our work.* http://www.bis.gov.uk/assets/foresight/docs/obesity/17.pdf.

[c] Scientific Advisory Committee on Nutrition. 2011. The Influence of maternal, fetal and child nutrition on the development of chronic disease later in life. Section 5: Human Intervention studies. *Cites references [1-3].* http://www.sacn.gov.uk/reports_position_statements/reports/the_influence_of_maternal_fetal_and_child_nutrition_on_the_development_of_chronic_disease_in_later_life.html

[d] National Institute of Medicine. Early Childhood Obesity Prevention Policies Report: 23 June 2011. http://www.iom.edu/Reports/2011/Early-Childhood-Obesity-Prevention-Policies.aspx *This document cites reviews from the US, all of which include our work..*

[e] Solving the problem of childhood obesity within a generation. White House Task Force on Childhood Obesity Report to the President. May 2010. *Cites our work on early nutrition and leptin concentrations in later life (as reviewed in [3] above).* http://www.letsmove.gov/sites/letsmove.gov/files/TaskForce_on_Childhood_Obesity_May2010_FullReport.pdf

[f] SMA resource for healthcare professionals detailing how Lucas and Singhal's work underpins the composition of their formula milk: http://www.smahcp.co.uk/professional-know-how/nutrition-for-babies/early-nutrition-and-health/information-945.aspx?catid=26

[g] Patent number 0304482.3. Details can be verified by UCL Business. Contact details provided.

[h] Clayton PE, Cianfarani S, Czernichow P, et al: Consensus statement: management of the child born small for gestational age through to adulthood: a consensus statement of the International societies of pediatric endocrinology and the growth hormone research society. J Clin Endocrinol Metab 2007;92:804-10. *Makes the recommendation that "calorie-dense feeding for SGA infants may not be appropriate", referencing a number of papers (e.g. refs 12, 14 and 16) which build on our earlier work in this area.* http://www.ghresearchsociety.org/files/2007_Consensus_SGA.pdf

[i] All details taken from the MEND website (1Sep 2013). http://www.mendprogramme.org/

[j] http://greenwichhealthyliving.nhs.uk/510/healthy-lifestyle-programme-for-children-and-their-families-3/

[k] http://blog.gosh.org/research/trim-tots-improving-child-health/ And see bottom of this page for 'Lennon's Story' of being in Trim Tots: http://www.gosh.nhs.uk/research-and-innovation/our-research-themes/patient-stories/