Institution: University of Nottingham

Unit of Assessment: 6; Agriculture, Veterinary and Food Science

Title of case study: Influencing national and international health policies on early life nutrition.

1. Summary of the impact

Research at the University of Nottingham (UoN) has had influence on development of health policy in the UK and internationally. It is recognised that the risk of diseases related to obesity and insulin resistance, is partly determined by the nutritional environment experienced during early life. Against a background of scepticism researchers at the UoN have generated data that has been critical in demonstrating the biological plausibility of such associations. This has influenced expert panels and non-governmental organisations in framing their current recommendations for nutrition in pregnancy and infancy, which benefit women and children worldwide.

2. Underpinning research

Key researchers:
Professor Simon Langley-Evans; Professor of Human Nutrition (UoN 2001-present)
Dr David Gardner; Associate Professor of Developmental Physiology (UoN 2002-present)
Dr Sarah McMullen; Lecturer in Human Nutrition (UoN 2002-present)
Professor Kevin Sinclair; Professor of Developmental Biology (2003-present)

Two decades of epidemiological and experimental research has shown that risk of disease in adulthood is partly determined by maternal diet during pregnancy and nutrition during early infancy. Investigators based at UoN are world-leaders in this field of the Developmental Origins of Health and Disease (DOHaD). They initiated and subsequently developed the experimental research that confirmed the biological plausibility of DOHaD and offered insight into a mechanistic pathway. The output and impact of their research programme has contributed toward high-profile reviews for dissemination to obstetricians and general practitioners (e.g. in the British Medical Journal, Lancet and New England Journal of Medicine), and also to Government and non-governmental organisations (e.g. WHO) in order to provide nutritional advice offered to women of reproductive age.

Initially, epidemiological studies led by the University of Southampton identified birth weight as an important contributing factor toward an individual's overall health as an adult. An individual born relatively small or relatively large (each a proxy for challenged intrauterine development) has a two- to eight-fold greater risk of dying due to ischaemic heart disease or type 2 diabetes in middle-age. The DOHaD phenomenon therefore has broad implications for public health and the national economic spend on health-related morbidity for generations to come. The epidemiological studies in human populations and their conclusions received heavy criticism for ascribing cause-and-effect by association and inappropriate adjustment for potential confounding factors such as current diet, current weight and ethnicity. Hence, suitable animal models had to be developed to test DOHaD prospectively and in a controlled laboratory environment **[c,d]**. Prof. Langley-Evans developed the first nutrition-related animal model of DOHaD in which pregnant rats fed a low protein diet (commonly associated with low birth weight in populations with a high prevalence of protein-energy malnutrition) gave birth to smaller offspring that developed high blood pressure and an increased propensity to other such non-communicable diseases (e.g. chronic kidney disease, premature aging, glucose intolerance; **[1, 2]**). This rat model represented a paradigm-shift in the nutritional causation of disease and was well-received by the scientific community. Many other groups have since repeated the study and replicated the results around the world and now use the same approach to drive mechanistic studies of DOHaD.

UoN investigators also established large animal models of DOHaD, such as the nutrient restricted sheep **[a, b, e]**, to allow more detailed investigation of the perturbed intrauterine environment arising from maternal nutritional imbalance **[3,4]**. Such work identified the early embryo as being particularly susceptible to low methyl-group availability – one of a number of effects of maternal protein-energy malnutrition. This and related work using rodent models identified a plausible epigenetic mechanism operating during early embryogenesis that may underpin DOHaD. More recent work has moved the research to consider the impact of nutrition in the early postnatal period, in both animals and humans, upon health in adult life. These studies, which have included

a new human pregnancy cohort study and a series of systematic review papers **[5,6]** have demonstrated that the 'window' during which nutritional programming of disease risk occurs is wider than originally suspected.

In summary, Nottingham investigators have generated research that has provided the initial evidence to support a role for nutrition during early life predisposing to a greater susceptibility toward non-communicable disease in adulthood. Having defined the problem and provided insight into the mechanistic basis of DOHaD, their research continues in order to provide novel solutions to the multifactorial paradigm of the early life origins of adult disease.

3. References to the research

1. Bellinger L, Lilley C, **Langley-Evans, SC.** (2004) Prenatal exposure to a maternal low protein diet programmes a preference for high fat foods in the young adult rat. British Journal of Nutrition 92: 513-520. DOI: 10.1079/BJN20041224***.***
2. Jackson, AA; Dunn, RL; Marchand, MC; **Langley-Evans, S.C.** (2002). *Increased systolic blood pressure in rats induced by a maternal low-protein diet is reversed by dietary supplementation with glycine*. Clinical Science 103(6): pp633-639. Available on request. ***Referenced in source 4, section 5 below.***
3. **Sinclair K.D.,** Allegrucci C., Singh R., **Gardner D.S.,** Sebastian S., Bispham J., Thurston A., Huntley J.F., Rees W.D., Maloney C.A., Lea R.G., Craigon J., McEvoy T.G. and Young L.E. (2007). *DNA methylation, insulin resistance, and blood pressure in offspring determined by maternal periconceptional B vitamin and methionine status* Proceedings of the National Academy of Sciences **104(49):** p19351-56. DOI: 10.1073/pnas.0707258104***. Referenced in source 3, section 5 below.***
4. **Gardner, D.S.,** Van Bon, B.W.M., Dandrea, J., Goddard, P., May, S.F., Wilson, V., Stephenson, T. & Symonds, M.E. (2006) *Effect of periconceptional undernutrition and gender on hypothalamic-pituitary-adrenal function in young adult sheep.* Journal of Endocrinology **190(2):** 203-12. DOI: 10.1677/joe.1.06751. ***Referenced in source 1,2; section 5 below.***
5. Pearce, J. and **Langley-Evans, S.C.** (2013). The types of food used in complementary feeding and childhood obesity: a systematic review. *International Journal of Obesity* **37**: 477-485. DOI: 10.1038/ijo.2013.8
6. Lloyd, L.J., **Langley-Evans, S.C.** and **McMullen, S.** 2010, 'Childhood obesity and adults cardiovascular disease risk: systematic review', *International Journal of Obesity*, **34:** 18–28. DOI: 10.1038/ijo.2009.61***. Referenced in source 1,2; section 5 below.***

These papers are a selection of 6 from a total of 120 published by this group since 2007. Evidence of the international quality of this body of work is indicated by the publication of all these papers in intermediate-to-high impact peer-reviewed journals and invitations of the researchers to present the work at international conferences and workshops. The work has received continuous funding since 1994 (UoN since 2001).

Underpinning research projects:

The key researchers have held continuous funding (total value approx. £5m) in this area since 2002, with grants from the BBSRC, MRC, US National Institutes of Health, US Department of Agriculture, British Heart Foundation and other UK health charities:

a. 2005-2010: Animal studies to investigate early nutrition programming. Project title: Farm animal studies to determine the mechanisms of early nutritional programming. Co-P.I.s Prof Langley-Evans, Dr David Gardner (UoN). Funder: European Commission 'EARNEST' programme grant £336,866.
b. 2003-2008: Fetal programming of blood pressure control. Project title: The effects of nutritional manipulation during fetal and/or postnatal development in the sheep on the dynamics of cardiovascular control P.I. Dr David Gardner (UoN). Funder: The British Heart Foundation. £245,475
c. 2008-2011: Mechanisms for nutritional programming of hypertension: identification of gatekeeper genes and proteins. PI Prof Simon Langley-Evans, CoI Dr Sarah McMullen (UoN). BBSRC, £449,713
d. 2009-2012: Progression of renal injury in developmentally programmed hypertension. PI Dr Sarah McMullen. CoI Prof Simon Langley-Evans (UoN). British Heart Foundation, £269,339.

e. 2009-2010: Cardiovascular health of aged adult offspring derived from mothers deficient in B-vitamins during the periconceptional period. PIs Dr David Gardner, Prof. Kevin Sinclair (UoN). British Heart Foundation. £149,092
f. 2002-2007 Oocyte quality and female health - DNA programming by oocyte environment (U01 HD044638-03) P.I. KD Sinclair (UoN), NIH £650,000.

4. Details of the impact

A sustained body of work by the named key researchers spanning 20 years (of which 12 have been at UoN) provided the initial, and strengthened the current, evidence base in favour of developmental programming effects upon adult health and disease. The UoN researchers are among a number of prominent UK groups that take a lead role in studying the early life programming phenomenon and shaping the positions and policies of public health bodies (also Universities of Cambridge, Southampton- where Prof. Langley-Evans initiated this work- and Kings College London). The total body of UK and international work has prompted several expert committees, global organisations and high impact journals (e.g. The New England Journal of Medicine, **Source 1**) to make specific recommendations about maternal and infant health. The British Medical Association published '*Early Life Nutrition and Lifelong Health*' in 2009 as a point of reference with key messages about maternal, fetal and infant nutrition for healthcare professionals to disseminate to the wider public. The approach of the BMA Board of Science is to provide a clear synthesis of the available research, and to develop evidence-based conclusions and recommendations for policy. The BMA report was commissioned after a 2007 debate that called upon the BMA's Board of Science to recognise and promote the importance of fetal and early life nutrition and its relationship to lifelong health. The report stated that, "*compelling evidence supports a role for early life nutrition in setting the risk of other conditions including osteoporosis, asthma, lung disease and some forms of cancer and that evidence is growing that early life nutrition can play a role in behavioural and cognitive problems in children and adolescents, and possibly even in cognitive decline and other aspects of ageing*". UoN research **[4]** contributed evidence to support these assertions **(Source 2)**.

The global company, Nestlé produced a White Paper '*Harnessing the power of epigenetics for targeted nutrition*' **(Source 3)** in which they outlined how they should consider novel approaches for harnessing personalised nutrition for use by their end-users, the general public. The paper referenced the work of UoN researchers **[3]** in order to support their novel, potential nutraceutical epigenetic approach.

The Department of Health (DoH) commissioned the Scientific Advisory Committee on Nutrition (SACN) to review the evidence for an effect of maternal, fetal and child nutrition, including growth and development *in utero* and up to the age of 5 years, on the development of chronic disease in later life in the offspring. Part of the SACN remit was to identify opportunities for nutritional intervention that could influence the risk of chronic disease in later life in the offspring. SACN published their report, 'The influence of maternal, fetal and child nutrition on the development of chronic disease in later life' in 2011 **(Source 4)**. Nottingham researchers contributed evidence e.g. **[1, 2]** among the wider body of evidence which informed this review. In their terms of reference, SACN stated that, '*the evidence associating early life nutrition with later risk of chronic disease is variable in quality*. *Most of the human evidence demonstrates associations that are susceptible to confounding by environmental and behavioural factors at different stages of the life course*'. Hence, they also reviewed the studies in animal models that had contributed invaluable evidence to support the human prospective and retrospective data, stating; '*Experimental interventions, mainly in animal models, help to ascribe mechanisms that may explain the associations observed. As with prospective observational studies, the length of the human lifespan places limitations on most existing intervention studies in humans, although markers of later risk, particularly if validated in animal models, may be useful'.* SACN made 6 public health recommendations to the DoH. These included a recommended strategy to promote, protect and support breastfeeding, to optimise the diets and body composition of young women and a research recommendation supporting the use of animal models as a means of identifying predictive markers of future poor health in humans. In an email to Dr Gardner **(Source 5)**, a team leader for nutrition policy and advice at the UK DoH stated that, "*SACN's report confirmed that maternal diet is an important aspect of fetal and longer term outcomes of pregnancy. This reinforced the basis of current Government advice. … This is*

current Government advice that has been taken as a result of the SACN report".

Following the SACN recommendations and drawing upon the work of UoN researchers, the UK DoH developed websites providing information on healthy eating and on good nutrition before, during and after pregnancy **(Source 6)**. Thus, the scientific context of DOHaD has been encapsulated in advice Government is offering the general public - 'optimising lifelong health is a key element of national health education programmes' through websites such as Change4Life and Start4Life **(Source 6)**. The UK Government is not alone in realising the potential health and economic implications of DoHAD. The World Health Organisation (WHO) invited Prof. Langley-Evans to a workshop event in 2004 **(Source 7)** considering the impact of DOHaD on WHO global strategy and policy for maternal and infant health. The outcomes from this workshop (fed-back to the WHO officer in charge of their Collaborating Centre on Nutrition Changes and Development, Dr Chizuru Nishida, Department of Nutrition, WHO Geneva) made the WHO more aware of the impact of nutritional programming in early life and subsequently in 2012, WHO proposed global targets and recommendations for the nutrition of mothers, infants and young children in order to reduce the prevalence of low birth weight **(Source 8)**. In addition, UoN researchers have contributed evidence **[6]** that has challenged some of the prevalent views about childhood obesity and which has had an international impact. For example, the Australian Government used this evidence in an advisory paper for the Productivity Commission **(**Sep 2010; **Source 9)** on the likely longer-term impact of childhood obesity. This document was used to inform their strategy for economic spend on healthcare. The ultimate beneficiaries of the ongoing UoN contribution to global research in this area, are therefore pregnant women and their children throughout the world, as the research is a springboard for policy changes that will benefit health across the generations.

5. Sources to corroborate the impact

1. Leading edge article in New England Journal of Medicine, "Effect of In Utero and Early-life Conditions on Adult Health and Disease' referencing work from UoN researchers http://www.nejm.org/doi/full/10.1056/NEJMra0708473 2008.
2. British Medical Association Board of Science report on Early Life Nutrition and Lifelong health referencing UoN researchers and being highlighted by UNICEF: (http://www.derbyshirelmc.org.uk/Guidance/Early%20Life%20Nutrition%20and%20Lifelong%20Health.pdf) 2009.
3. Nestle report on 'Harnessing the Power of epigenetics for targeted Nutrition' drawing on UoN work. (http://www.research.nestle.com/resources/downloads/Documents/Nestl%C3%A9%20White%20paper%20Nutrigenomics%20FINAL.pdf) 2009.
4. Scientific Advisory Committee for Nutrition report on the 'Influence of maternal, fetal and child nutrition on the development of chronic disease in later life' for which UoN researchers contributed a significant volume of evidence http://www.sacn.gov.uk/pdfs/sacn_early_nutrition_final_report_20_6_11.pdf. 2011.
5. Corroboration of the impact of the SACN report upon the development of maternal and infant diet components of the Change4Life and Start4Life strategies can be provided by the Team Leader for Nutrition Policy and Advice at the Department of Health.
6. Government websites offering advice on healthy eating during pregnancy and its importance on lifelong health, developed as a direct result of commissioned reports on maternal nutrition, which drew upon the work of UoN researchers http://www.nhs.uk/Change4Life 2012.
7. Corroboration of the impact of this workshop, which led to the following publication (http://www.who.int/nutrition/publications/programming_chronicdisease.pdf) can be provided by Director of WHO Collaborating Centre on Nutrition Changes and Development.
8. World Health Organisation paper on proposed global targets and recommendations for the nutrition of mothers, infants and young children in order to reduce the prevalence of low birth weight, instigated after a Workshop contributed to by Prof Simon Langley-Evans http://www.who.int/nutrition/events/2012_proposed_globaltargets_backgroundpaper.pdf 2012
9. Australian Government report that identifies work from UoN researchers as being opinion making http://www.pc.gov.au/__data/assets/pdf_file/0015/103308/childhood-obesity.pdf 2010