

Institution: University of Southampton
Unit of Assessment: 01 Clinical Medicine
Title of case study: 01-05 Nutrition, developmental epigenetics and lifelong health
<p>1. Summary of the impact</p> <p>The University of Southampton's lifecourse cohort studies have led to a paradigm shift in the medical approach to obesity and non-communicable diseases. Research linking maternal pre-conception and early years nutrition with health outcomes for later life has directly influenced public healthcare policy at international (United Nations), national (Scientific Advisory Committee on Nutrition) and local (Southampton City) levels. Dissemination through medical practice and Southampton-designed public education programmes such as <i>LifeLab</i> means this research has already led to health benefits for tens of thousands of people, providing them with the information and tools to help prevent themselves and their children from succumbing to a non-communicable disease.</p>
<p>2. Underpinning research</p> <p>While scientists have long known that chromosomes passed from parent to child form a genetic blueprint for development, they've come to realise more recently that genes are not a fixed predetermined programme. Instead, they can be turned on and off by experiences and environment. It is this science of 'epigenetics', particularly how nutritional influences during development affect later risk of obesity and chronic non-communicable diseases (NCDs) that has been the focus of research at the University of Southampton's Medical Research Council (MRC) Lifecourse Epidemiology Unit (LEU), led by Professor Cyrus Cooper, LEU Director (joined Southampton 1992), Keith Godfrey, Professor of Epidemiology and Human Development (joined 1999), Hazel Inskip, Deputy Director LEU (joined 1991), David Barker, Professor of Clinical Epidemiology (joined 1972) and Mark Hanson, Director, Institute of Developmental Studies (since 2000).</p> <p>This research is framed by two ongoing projects: the Hertfordshire Cohort Study (since 1989) and the Southampton Women's Survey (since 1998).</p> <p>The Hertfordshire Cohort Study (HCS) comprises 3000 people born 1931-1939. Its principal objective has been to evaluate the relationship between early growth, genetic influences, adult lifestyle and the risk of common age-related disorders such as osteoporosis, osteoarthritis, sarcopenia, type 2 diabetes and cardiovascular disease. Since 1993 researchers focusing on NCDs have undertaken detailed cardiovascular phenotyping of 1000s of participants during the seventh and eighth decade of life, and, using historical data (e.g. birthweight, weight at age one year, method of infant feeding, childhood illnesses) linked these to poor growth in utero and during infancy [3.1]. Additional key findings included the insight that elements of the heritable/familial component of susceptibility to cardiovascular disease, obesity and other NCDs can be transmitted across generations by non-genomic means [3.2].</p> <p>The Southampton Women's Survey (SWS) is the only European study of women and their children for which maternal data and samples were collected before conception. Between 1998 and 2002, SWS researchers interviewed 12,583 women aged 20-34 years. Those who became pregnant afterwards were invited to take part in the pregnancy phase of the survey. Participants received ultrasound scans at 11, 19 and 34 weeks of pregnancy, and their babies (3156 between 1998 and 2007) were measured soon after birth. Offspring were further assessed during home visits at 6, 12, 24 and 36 months. Some attended follow-up clinics to assess bone density (745 children), heart rate (414 mother/child pairs) and brain development (269 mother/child pairs) at ages four, six and ten/eleven years. Dietary information was also collected. Researchers found that patterns of diet, health behaviours and lifestyle were set before pregnancy and that maternal pre-pregnancy quality of diet was the strongest predictor of the quality of her infant's diet, which in turn</p>

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is positively associated with later outcomes [3.3], particularly lean mass [3.4] and cognitive function. Researchers also found that pre-pregnancy adiposity and excessive weight gain during pregnancy were associated with increased risk of childhood obesity [3.5]. Epigenetic markers identified from umbilical cord samples were strongly associated with childhood total and central body fat at age 6 years [3.6].

3. References to the research

3.1 Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of in utero and early-life conditions on adult health and disease. *New England Journal of Medicine* 2008; 359:61-73 [844 cites]

3.2 Godfrey KM, Lillycrop KA, Burdge GC, Gluckman PD, Hanson MA. Epigenetic mechanisms and the mismatch concept of the developmental origins of health and disease. *Pediatr Res* 2007; 61:5R-10R. [177 cites]

3.3 Robinson S, Marriott L, Poole J, Crozier S, Borland S, Lawrence W, Law C, Godfrey K, Cooper C, Inskip H, Southampton Women's Survey Study Group. Dietary patterns in infancy: the importance of maternal and family influences on feeding practice. *Brit J Nutr* 2007; 98:1029-37

3.4 Robinson SM, Marriott LD, Crozier SR, Harvey NC, Gale CR, Inskip HM, Baird J, Law CM, Godfrey KM, Cooper C, Southampton Women's Survey Study Group. Variations in infant feeding practice are associated with body composition in childhood: a prospective cohort study. *J Clin Endocrin Metab* 2009; 94:2799-805

3.5 Crozier SR, Inskip HM, Godfrey KM, Cooper C, Harvey NC, Cole ZA, Robinson SM. Weight gain in pregnancy and childhood body composition: findings from the Southampton Women's Survey. *Am.J Clin Nutr* 2010; 91:1745-1751.

3.6 Godfrey KM, Sheppard A, Gluckman PD, Lillycrop KA, Burdge GC, McLean C, Rodford J, Slater-Jefferies JL, Garratt E, Crozier SR, Emerald BS, Gale CR, Inskip HM, Cooper C, Hanson MA. Epigenetic gene promoter methylation at birth is associated with child's later adiposity. *Diabetes* 2011; 60:1528-34. [136 cites] (In Faculty of 1000 top 2% of published articles in biology and medicine <http://f1000.com/13030957>)

Key grants awarded:

2010-2014. Inskip H, Robinson S, Godfrey K, Osmond C. Medical Research Council. MRC Lifecourse Epidemiology Unit, Programme 4: Nutrition, Development and Lifelong Health: Studies in European Populations. £3,800,000.

2012-17. Koletzko B, Poston L, Godfrey KM, et al. European Union (FP7): EarlyNutrition: Long-term effects of early nutrition on later health, €11.1M.

2012-2017. Jackson A, Godfrey K, Hanson M, Calder P, Cooper C, et al. National Institute for Health Research. NIHR Southampton Biomedical Research Centre. £9,677,372

2008-2013. Hanson M, Godfrey K, Cooper C, Inskip H, Deanfield J. British Heart Foundation. Maternal, infant and childhood determinants of cardiovascular structure and function. £822,000.

4. Details of the impact

HCS and SWS research findings have directly resulted in a wide range of international, national and local policy changes towards the prevention and control of non-communicable diseases, as well as training and public education programmes, leading to health benefits for millions of people.

Public policy: Following review by the National Institute for Health and Care Excellence (NICE), SWS research findings fed directly into the formation of new public health guidance on nutrition for pregnant and breastfeeding mothers and children in low-income households (published in 2008, [5.1]) and on weight management before, after and during pregnancy (published 2010, [5.2]). NICE guidelines are used in the education and training of health professionals and by pregnant

and breastfeeding mothers to make informed decisions. Government figures show that there were over 3.9 million children living in low-income households in 2008/2009; 25-30% of those children were in the first few years of childhood.

The Scientific Advisory Committee on Nutrition's (SACN's) policy on early influences on chronic diseases in later life, published in 2011, similarly draws heavily on Southampton research. The SACN final report specifically cites SWS data and findings on the association between longer duration of breastfeeding and lower fat mass at 4 years, on low maternal vitamin D status and fetal bone development, and on low income diet and nutrition. The impact of this research becomes clear in the report's 'Public health recommendations' which include life-long nutritional interventions linked to reproductive health and chronic disease prevention, and SACN's specific recommendation of mandatory fortification of flour with folic acid in the UK as a measure to prevent pregnancies affected by neural tube defects. This measure was being considered by health ministers in July 2013 [5.3].

In 2008, Southampton research on the developmental origins of health and disease informed the World Health Organisation Action Plan for the prevention of non-communicable diseases [5.4].

In 2009, Hanson met Andrew Lansley, Secretary of State for Health, to discuss implementation of this plan. Subsequent to that meeting, Lansley attended a UN General Assembly Summit on NCDs to discuss their rising incidence, social and economic impact and risk factors (10-12 November 2009). In the public press conference following the summit, Lansley pointed to the clear links between NCDs and maternal/child health. Poor nutrition during pregnancy, he told representatives of the international press, led to higher rates of diabetes and high blood pressure later in life [5.5].

Between 2007-2010, The Food Standards Agency funded Inskip (£434,000) to undertake SWS data collection and write a comprehensive report on nutritional influences on body composition, cognitive function development and respiratory health [5.6].

Industrial impact: Through the EpiGen Consortium (an international alliance of six private and public sector epigenetics researchers - one of which is LEU - established in 2006), SWS research linking perinatal biological samples to epigenetic measurements has been further disseminated. So far this has led to more than £10 million in research collaborations, with Southampton research in metabolic programming directly leading to three patents for the formulation of nutritional products for mothers and infants filed in 2007, 2008 and 2009.

Professional practice: Launched in 2010, the Southampton Initiative for Health (SIH) is a training intervention with Sure Start Children's Centre (SSCC) staff designed to improve the diets and physical activity levels of women of childbearing age. Developed with the primary care trust and based on SWS findings, researchers have trained over 150 SSCC staff in holding 'healthy conversations' with their clients. More than 500 women have enrolled in the study so far with potential benefits for their diet and activity levels [5.7]. Sure Start trainees reported feeling empowered by the training; one said "Very good course... it has given me a lot to think about when planning my own training and support in health behaviour change."

Public benefit: In 2008, SWS researchers launched *LifeLab* - an innovative educational intervention designed to enable 11-16 year-olds to learn how diet and lifestyle lay the foundations for a healthier life, and how their own health is linked to the health of their future children. So far, more than 1,500 students in Southampton have taken part in the programme. Feedback indicates that six months after visiting, students had a greater understanding of the impact of health behaviours in early life on future health compared with peers. *LifeLab* students were significantly more likely to consider pursuing science and healthcare subjects after their GCSEs. One student said "...there's only so much you can learn in school... if you actually go there and do it for yourself it's much better." OFSTED said *LifeLab* "is making an important contribution to students' understanding of the need to adopt healthy lifestyles." *LifeLab* is now a key part of Southampton City's public health strategy [5.8].

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Public awareness and understanding of the research findings were raised through a BBC2 *Horizon* special "The Nine Months That Made You" [5.9] based on Barker's research, and BBC News coverage (13/2/2009).

5. Sources to corroborate the impact

5.1 National Institute for Health and Clinical Excellence. Maternal and child nutrition. NICE public health guidance 11. NICE 2008 <http://www.nice.org.uk/nicemedia/live/11943/40097/40097.pdf>

5.2 National Institute for Health and Clinical Excellence. Weight management, before, during and after pregnancy. NICE public health guidance 27. NICE 2010 <http://www.nice.org.uk/nicemedia/live/13056/49926/49926.pdf>

5.3 Scientific Advisory Committee on Nutrition. The influence of maternal, fetal and child nutrition on the development of chronic disease in later life. Scientific Advisory Committee on Nutrition 2011. http://www.sacn.gov.uk/pdfs/sacn_early_nutrition_final_report_20_6_11.pdf

**n.b* SWS research and findings are specifically mentioned in Sections 404-407 with associated public health recommendations appearing in Section 8.1, R1-6. See Appendix 2 for details*

5.4 World Health Organization, 2008. 2008–2013 Action Plan for the Global Strategy for the Prevention and Control of Noncommunicable Diseases. World Health Organization.

<http://www.who.int/nmh/publications/9789241597418/en/>

5.5 United Nations Political declaration of the High-level Meeting of the General Assembly on the Prevention and Control of Non-communicable Diseases (September 2011)

<http://www.un.org/en/ga/ncdmeeting2011/documents.shtml>

<http://www.un.org/News/Press/docs/2011/ga11146.doc.htm>

5.6 Inskip H, Godfrey K, Robinson S, Warner J, Calder P, Roberts G, Lucas J, Jackson A, Cooper C. FSA-N05071. *Maternal, infant and childhood diet: influence on respiratory health and asthma in childhood*. Contractor's final report to the Food Standards Agency 2010 (Confidential report held by Hazel Inskip and Barbara Thomas)

5.7 Barker M, Lawrence W, Baird J, Jarman M, Black C, Barnard K, Craddock S, Davies J, Margetts B, Inskip H, Cooper C. The Southampton Initiative for Health: a complex intervention to improve the diets and increase the physical activity levels of women and children from disadvantaged communities. *Health Psychol.* 2011;16:178-91.

5.8 NHS Southampton City. Health in Southampton 2012. Report from the Director of Public Health <http://www.southamptonhealth.nhs.uk/EasysiteWeb/getresource.axd?AssetID=140605&type=full&servicetype=Attachment>

Page 17 refers to LifeLab

5.9 BBC Horizon, August 2011 'The Nine Months That Made You'

<http://www.bbc.co.uk/programmes/b013yww4>