Institution: University of Southampton		
Unit of Assessment: 01 Clinical Medicine		
Title of case study: 01-03 Preventing transmission of NCD risk across generations: impact on clinical practice, health policy and the health literacy of young people		
Period when the underpinning research was undertaken: 2000 - 2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Mark Hanson	BHF Professor of Cardiovascular science	January 2000 – present
Keith Godfrey	Professor of Epidemiology and Human Development	February 1990 – present
Cyrus Cooper	Professor of Rheumatology	April 1992 – present
Period when the claimed impact occurred: August 2013 - December 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

The Developmental Origins of Health and Disease (DOHaD) Centre at the University of Southampton has made key discoveries demonstrating that the diet and lifestyle of pregnant mothers can have a critical impact on the long-term health of their children. The research has shown that epigenetic processes underlie the mechanism of transmission of disease risk, which can be mitigated by changes in lifestyle, and has transformed inter-governmental, government and non-government organisation health policies in the UK and internationally. It has led to wide uptake of new guidelines for clinical practice, including e-learning platforms for healthcare professionals used by 89,000 people around the world. Southampton researchers pioneered the hospital-based science education programme *LifeLab*, engaging 11,500 teenagers and 334 teachers from 72 schools and motivating them, as evidenced by clinical trial data, to improve their own health and that of future generations.

2. Underpinning research

The conditions within the womb have a lasting effect on a child's life. Known as the Developmental Origins of Health and Disease (DOHaD) concept, research has shown that exposure to certain environment influences at critical periods of development and growth will have significant consequences for the individual's short and longer-term health. Two pioneering Southampton longitudinal cohort studies have been fundamental in the establishment of the DOHaD concept: the Hertfordshire Cohort Study (active since 1989) was a retrospective study of adults and includes continuing long-term follow up and the Southampton Women's Survey (active since 1998) was the first large scale prospective study of women and their children starting before conception. Together these have provided a unique view of how early life exposures establish disease risk, particularly of non-communicable diseases (NCDs), across the life-course and across generations.

Research at Southampton since 2000 has seen the DOHaD field take significant strides forward and its impact has been felt on clinical practice and health policy around the world. In 2003, the International DOHaD Society was established by Professors Mark Hanson, Keith Godfrey and Cyrus Cooper, with an opening address by HRH The Princess Royal; it now has 1,000 members from 50 countries and a dedicated academic journal. Southampton research utilised human cohorts and animal models to identify modifiable early life risk factors, especially before they demonstrated the role of epigenetic processes in the underlying mechanisms of transmission of such risk. Southampton studies caused a major revision of the concept that NCDs are predominantly a combination of inherited fixed genetic risk and unhealthy adult lifestyle, with the realisation that a substantial proportion of NCD risk is not explained by these factors at the population level. Their discovery of epigenetic mechanisms opened new avenues for early prediction and intervention to reduce risk of later NCDs. They demonstrated the important contribution of early life epigenetic changes, related to aspects of maternal diet, lifestyle or adiposity in relation to a range of childhood risk factors for later NCDs in the next generation. These include: childhood adiposity [**3.1**]; a measure of arterial stiffness which relates to cardiovascular function [**3.2**]; and bone density which relates to peak bone mass attained in young adulthood [**3.3**] – all risk factors for later NCDs. The epigenetic marks (particularly DNA methylation) are mechanistically important; the Southampton team has

shown functionality in the DOHaD lab, taking their ongoing epidemiological cohort studies beyond correlation to causality. The work has highlighted the transmission of risk from parents to offspring by non-genetic biological and social factors, with particular focus on the preconception and pregnancy phases of the life-course. Animal studies demonstrated for the first time that epigenetic processes induced in early development by unbalanced maternal diet can be prevented [**3.4**]. The team subsequently showed in animals that risk can be transmitted by both maternal and paternal lines and can be induced even in the early embryo, creating awareness of the importance of the preconception environment [**3.5**].

Studies demonstrating mechanisms underlying potential reversibility of NCD risk for the next generation supported the Southampton approach of taking continued epidemiological cohort studies beyond correlation to causality and to pioneering interventions through new randomised controlled trials (RCTs). MAVIDOS is the first major RCT of vitamin D supplementation in pregnancy, following the finding in the Southampton Women's Survey that 35% of women in the city are vitamin D insufficient [**3.6**]. Based on this basic and clinical research, the DOHaD Centre has conducted qualitative research to explore how these new concepts can inform health policy, particularly in the prevention of childhood obesity and the application of life-course concepts underlying DOHaD. Hanson and Cooper served or chaired World Health Organisation (WHO) technical and policy meetings to develop the application and measurement of the life-course concept in health policy for member states.

3. References to the research

3.1 Godfrey KM, Sheppard A, Gluckman PD, Lillycrop KA, Burdge GC, McLean C, Rodford J, Slater-Jefferies JL, Garratt E, Crozier SR, Emerald BS, Hanson MA. Epigenetic gene promoter methylation at birth is associated with child's later adiposity. Diabetes. 2011 May 1 ;60(5):1528-34. https://doi.org/10.2337/db10-0979

3.2 Murray R, Bryant J, Titcombe P, Barton SJ, Inskip H, Harvey NC, Cooper C, Lillycrop K, Hanson M, Godfrey KM. DNA methylation at birth within the promoter of ANRIL predicts markers of cardiovascular risk at 9 years. Clinical epigenetics. 2016 Dec;8(1):90. https://doi.org/10.1186/s13148-016-0259-5

3.3 Curtis EM, Murray R, Titcombe P, Cook E, Clarke-Harris R, Costello P, Garratt E, Holbrook JD, Barton S, Inskip H, Godfrey KM. Perinatal DNA methylation at CDKN2A is associated with offspring bone mass: findings from the Southampton Women's Survey. Journal of Bone and Mineral Research. 2017 Oct;32(10):2030-40. https://doi.org/10.1002/jbmr.3153

3.4 Lillycrop KA, Phillips ES, Jackson AA, Hanson MA, Burdge GC. Dietary protein restriction of pregnant rats induces and folic acid supplementation prevents epigenetic modification of hepatic gene expression in the offspring. The Journal of nutrition. 2005 Jun 1;135(6):1382-6. https://doi.org/10.1093/jn/135.6.1382

3.5 Fleming TP, Watkins AJ, Velazquez MA, Mathers JC, Prentice AM, Stephenson J, Barker M, Saffery R, Yajnik CS, Eckert JJ, Hanson MA, Forrester T, Gluckman PD, Godfrey KM. Origins of lifetime health around the time of conception: causes and consequences. Lancet. 2018 May 5;391(10132):1842-1852. https://doi.org/10.1016/s0140-6736(18)30312-x

3.6 Cooper C, Harvey NC, Bishop NJ, Kennedy S, Papageorghiou AT, Schoenmakers I, Fraser R, Gandhi SV, Carr A, D'Angelo S, Crozier SR. Maternal gestational vitamin D supplementation and offspring bone health (MAVIDOS): a multicentre, double-blind, randomised placebo-controlled trial. The Lancet Diabetes & Endocrinology. 2016 May 1;4(5):393-402. https://doi.org/10.1016/s2213-8587(16)00044-9

4. Details of the impact

University of Southampton research has shown that the environment experienced in the womb, and at conception, can have profound consequences on the long-term health of a person including the risk of obesity and NCDs. This has had a direct impact on intergovernmental, government and NGO health policy, clinical practice and health literacy in the UK and around the world.

Impact on intergovernmental, government and NGO health policy

According to WHO [**5.1**], the research of Hanson, Godfrey, Cooper and colleagues '*has led to recommendations by WHO in relation to the prevention of childhood obesity, through the ECHO (End ChildHood Obesity) Commission and also the Nurturing Care Framework, both of which have been adopted by the World Health Assembly and are now having an effect on government nutritional policy in many countries*'. Specifically, this policy impact at WHO and UN level involved:

- Influencing the WHO Guideline on Improving Early Child Development (March 2020) [**5.1**].
- Informing the UN's Global Strategy for Women's, Children's and Adolescents' Health 2016-2030 (published 2015); DOHaD research by Hanson and Cooper cited on page 103 [**5.1**].
- 'Catalysing' the WHO-coordinated, 10-year, multi-country Healthy Life Trajectories Initiative, which is examining the effect of preconception health on markers of metabolic health. [**5.1**].
- Co-chairing (Hanson), of the Working Group on Science and Evidence for WHO's ECHO Commission. The resulting implementation plan was adopted at the World Health Assembly in 2017, which mandated 194 member states to adopt the plan [**5.1**].
- Introducing the concept of 'nurturing care' to promote healthy development across the first 1000 days of life through a co-authored (Hanson) paper in The Lancet (2017). The paper underpinned WHO's Nurturing Care Framework, which was adopted at the World Health Assembly in 2018, again mandating 194 member states to adopt the framework [**5.2**].
- Authoring (Cooper and Hanson) the WHO Health Evidence Network report (2019): *What quantitative and qualitative methods have been developed to measure the implementation of a life-course approach in public health policies at the national level?* [**5.3**]
- Chairing (Hanson) international expert meetings at WHO on the effects of environmental toxicants on development in June 2016 and Nov 2017, which led to the new initiative *Don't Pollute My Future! The impact of the environment on children's health* [**5.4**].
- Informing the WHO-UNICEF-The Lancet Commission *A Future for the World's Children* March 2020 (paper by Cooper and Hanson cited on page 651) [**5.5**].

DOHaD research also influenced policy development and debates in the UK. Due to Southampton's ground-breaking findings on the effect of maternal diet and lifestyle on offspring health, Hanson was invited by the UK's Chief Medical Officer to author a chapter on preconception health for her 2014 Annual Report [**5.6**]. For the first time, this report focused on the importance of the preconception environment, making recommendations for greater continuity of health care to reduce transmission of NCD risk across generations and focussing on the most vulnerable sections of the population. In 2018, Hanson made a significant contribution to the Parliamentary Office of Science and Technology POSTnote *The Ageing Process and Health* (No. 571, Feb. 2018), which emphasises DOHaD (papers by Hanson and Godfrey both cited) [**5.7**]. Godfrey's work on preconception health was cited in a House of Lords debate in April 2018 that was called in order to challenge the Government on the steps it was taking to address childhood obesity [**5.8**].

Their research and involvement in policy formulation at an international level led Hanson and Godfrey, in 2019, to establish the first Preconception Partnership, a group of leading epidemiologists, scientists and clinical academics. It proposed an annual 'report card' to measure progress in improving a set of preconception health markers. The report card uses metrics from data sources such as the Maternity Services Dataset and the Sexual and Reproductive Health Activity Dataset, and is designed to hold governments to account. As a result, Public Health England (PHE) updated their policies on preconception care to identify opportunities for intervention, and issued resources to primary and secondary care trusts detailing the available interventions [**5.9**]. PHE also made an unprecedented move to release national maternity and newborn data to Southampton researchers to assess against the report card.

Impact on clinical awareness and practice

University of Southampton research demonstrating the importance of nutrition before conception and during the first 1000 days of life led Godfrey and colleagues to initiate eLearning platforms to educate the healthcare workforce, in both low-middle and high income settings. The aim was to impact real-world healthcare practice in early nutrition at scale. The eLearning programmes in Early Life Nutrition have been developed and distributed to healthcare professionals and young couples in areas such as Africa, Europe, the Middle East and South East Asia. Collectively the platforms have more than 89,000 registered users. [**5.10**]

With DFID funding, the team developed an eLearning programme for management of malnutrition. Their evaluation in Ghana, Guatemala and El Salvador for 2015-2017 showed it cut mortality rates from severe acute malnutrition from 5.8% to 1.9% (difference -4.0% (95% CI -6.7 to -1.8), p<0.001). The malnutrition eLearning course improved knowledge, understanding and skills of health professionals in the diagnosis and management of children with severe acute malnutrition, and changes in clinical practice and confidence were reported following the completion of the course [**5.10**]. Based on WHO guidelines, the course has been taken by 17,000 health professionals, trainees and educators in 120 countries [**5.10**]. It has improved clinical practices in hospitals and community settings in Ghana which has seen an improvement in mortality rate as demonstrated by a director of the district health directorate, who said: "rehabilitation rate has increased from about 80% to about 95%. And the mortality rate … has decreased to about 50% of what we used to see before the training." [**5.11**]

Southampton research on nutrition in the adolescent, preconception and maternal periods and on transgenerational passage of NCD risk led directly to mutliple guidelines [**5.12**] developed by the International Federation of Gynecology and Obstetrics (FIGO), which represents national professional organisations in 130 countries. The *Think Nutrition First* guideline was chaired by Hanson and launched in 2016 at FIGO World Congress in Vancouver, attended by 5,000 delegates. The FIGO Global Declaration on Hyperglycemia in Pregnancy, co-chaired by Hanson, was launched at the Congress in Rio de Janiero in 2018, attended by 11,500 delegates. The guidelines were disseminated to 132 Obs and Gynae professional societies globally and translated into several languages. In 2020, Hanson led the development of the Pregnancy Obesity and Nutrition Initiative under the Pregnancy and NCDs Committee at FIGO, which published guidelines on obesity management before, during and after pregnancy. This led to a clinical nutrition checklist being developed for healthcare professionals to assess pregnant women's diets and identify any nutritional risk in early pregnancy. Early analysis of its use in Hong Kong showed that among the 156 women who used the checklist, 95% had nutritional issues identified. [**5.12**]

Increasing health literacy and inspiring positive lifestyle changes among teenagers

The research on nutrition in adolescence and the importance of the preconception environment to the transmission of NCD risk to the next generation led Hanson, Godfrey and colleagues to develop a purpose-built teaching laboratory, *LifeLab*, at Southampton General Hospital to educate school students about how their current health and life choices affect the health of their future children. LifeLab is a structured education programme over a two-week period. It comprises: a professional development day for science teachers; pre-visit lessons at school; an immersive, hands-on visit to the LifeLab facility; follow-up lessons at school; and a celebration event for all LifeLab students, parents, local health professionals and public officials.

The facility was formally launched in 2014. Since then, 11,591school pupils and 342 teachers from 66 schools have participated in the programme [**5.13**]. Schools embed the programme into their science curriculum for Years 8 and 9; it is designed to be linked into several work strands and referred back to over the year. Southampton's RCT of LifeLab [**5.14**] demonstrated that, prior to participation, 50% of teenagers had an above average score, whereas 12 months after participation the proportion increased to 61% (adjusted difference between groups = 0.27 SDs (95%CI=0.12, 0.42)). Students also judged their own lifestyles more critically, with fewer reporting their behaviours as healthy (53.4%) compared to the control group (59.5%) (adjusted PRR=0.94 [0.87, 1.01]). Additionally, they had greater understanding than control students of the influences of health behaviours on their long-term health and that of their children; for example, they knew that our nutrition starts to affect our future health before we are born (p <0.001) and the food a father eats before having a baby will affect the health of his children (p<0.001).

Qualitative data [**5.15**] also demonstrated the profound impact that LifeLab has had on the health literacy of students. Representative feedback included: "*If we change our lifestyle, we can more than halve our chance of getting an illness later on in life"*; *"Eating unhealthy is not only bad for your health but your child's also"*; *"How unhealthy my lifestyle actually is and the small changes that need to be made just to make sure I'm at less of a risk"*; *"I've eaten less fatty foods and seen how it could actually affect it [my health], before I thought I could just change it and it would all be better, but it can actually affect it long-term as well*". There is evidence of the programme inspiring students to consider future careers relating to science and health, and changing perceptions of science as an academic discipline. Representative feedback included: "*I found them (the scientists) really*

inspirational and am now considering going into nursing or medical care"; *"They (the scientists) made me change my mind about what I went to be when I am older"*.

According to the CEO of University Hospital Southampton NHS Foundation Trust, LifeLab has contributed directly to meeting this aspect of the Trust's vision: '*We will play our part in the fight to improve population health working with the University of Southampton on their world-renowned research demonstrating how lifestyle and behaviour not only impacts on an individual's health but that of future generations* [**5.16**].' LifeLab resources form part of the Royal Society for Public Health (RSPH)-accredited Level 2 Young Health Champions qualification. LifeLab was awarded RSPH centre status in 2017 and in 2019 won the RSPH national *Centre for Excellence* Hygeia Award [**5.17**]. It was a key part of BBC Horizon episode *Why are we getting so fat?* (2016) [**5.18**] which was watched by 1.82m people and was the 11th highest-rated BBC2 programme that week.

5. Sources to corroborate the impact

5.1 Letter from Department of Maternal, Newborn, Child and Adolescent Health and Ageing, WHO.
5.2 Nurturing Care Framework: Britto et al. 2017 https://doi.org/10.1016/s0140-6736(16)31390-3 Framework launched at 71st World Health Assembly, 2018: https://nurturing-care.org
5.3 https://www.euro.who.int/en/publications/abstracts/what-quantitative-and-qualitative-methods-have-been-developed-to-measure-the-implementation-of-a-life-course-approach-in-public-health-policies-at-the-national-level-2019
5.4 Poore, Hanson, Faustman, Neira. 2017 https://doi.org/10.1016/s2542-5196(17)30048-7 led to new WHO initiative *Don't Pollute My Future! The impact of the environment on children's health* https://www.who.int/ceh/publications/don-t-pollute-my-future/en
5.5 A future for the world's children? A WHO-UNICEF-Lancet Commission (2020). https://doi.org/10.1016/S0140-6736(19)32540-1. Hanson, Cooper et al. 2016 cited as ref. 9, p.651.
5.6 Hanson led and Godfrey co-authored Chapter 5 of Chief Medical Officer's Annual Report 2014: https://www.gov.uk/government/publications/chief-medical-officer-annual-report-2014-womens-health
5.7 https://researchbriefings.files.parliament.uk/documents/POST-PN-0571/POST-PN-0571.pdf
5.8 Children and Young People: Obesity, Volume 790: debated in House of Lords on 17 April 2018 https://hansard.parliament.uk/lords/2018-04-17/debates/39772C88-BA33-49ED-B4D5-C015DFA37511/ChildrenAndYoungPeopleObesity
5.9 https://www.gov.uk/government/publications/preconception-care-making-the-case
5.10 eLearning platforms: https://www.enea-sea.eu/en/home https://www.med.soton.ac.uk/nutrition
5.11 Peer-reviewed evaluations of eLearning programmes:
a) Choi et al. Effectiveness of the Malnutrition eLearning Course for Global Capacity Building in the Management of Malnutrition: Cross-Country Interrupted Time-Series Study. J Med Internet Res. 2018 Oct 3;20(10):e10396. https://doi.org/10.2196/10396
b) Choi S, et al Improved care and survival in severe malnutrition through eLearning. Archives of Disease in Childhood 2020;105:32-39. https://doi.org/10.1136/archdischild-2018-316539
c) Annan RA et al. Implementing effective e-Learning for scaling up global capacity building: findings from the malnutrition elearning course evaluation in Ghana. Glob Health Action. 2020 Dec 31;13(1):1831794. https://doi.org/10.1080/16549716.2020.
5.12 FIGO guidelines and initiatives underpinning by Southampton research:
a) Think Nutrition First https://doi.org/10.1016/s0020-7292(15)30034-5
b) Global Declaration on Hyperglycemia in Pregnancy: https://www.figo.org/GlobalDeclaration-HIP
c) Pregnancy Obesity and Nutrition Initiative: https://www.figo.org/news/pregnancy-obesity-and-nutrition-initiative-poni-figo-releases-new-supplement
d) Evaluation of FIGO Nutrition Checklist https://doi.org/10.1002/ijgo.13324
5.13 LifeLab annual report 2019/20 showing total figures since opening.
5.14 Woods-Townsend et al. 2018 https://doi.org/10.1017/S2040174418000429 Woods-Townsend et al. 2015 https://doi.org/10.1186/s13063-015-0890-z. Third paper under review – PDF supplied.
5.15 A selection of impact outcomes for LifeLab.
5.16 Letter from CEO of University Hospital Southampton NHS Foundation Trust.
5.17 Corroborating statement from RSPH.
5.18 *Why are we getting so fat?* (2016) https://www.bbc.co.uk/programmes/p03xkszk