Institution: Ulster University

Unit of Assessment: Allied Health Professions, Dentistry, Nursing and Pharmacy (3)

Title of case study: ICS-1 Folic acid: informing evidence-based policy and practice for health and food sectors

Period when the underpinning research was undertaken: 2000-2020

Details of staff conducting the underpinning research from the submitting unit:

Names:	Current Role(s)	Period(s) employed by submitting HEI:
Professor Helene McNulty	Professor of Nutritional Sciences	1992-present
Professor Kristina Pentieva	Professor of Human Nutrition	1998-present
Professor Mary Ward	Professor of Nutrition and Dietetics	1998-present
Dr Leane Hoey	Lecturer in Food and Nutrition	2002-present
Dr Maeve Kerr	Lecturer in Food Regulatory Affairs	2006-present
Professor JJ Strain	Professor of Human Nutrition	1981-present

Period when the claimed impact occurred: 2014-2020

Is this case study continued from a case study submitted in 2014? N

1. Summary of the impact

Relevant context: Conclusive evidence has existed for nearly 30 years that folic acid supplementation before and in early pregnancy prevents neural tube defects (NTD) in the developing foetus, leading to clear recommendations for women of reproductive age worldwide. Policy in this area is however problematic because, despite a proven benefit in NTD, there are concerns that folic acid could be harmful at high levels of exposure. Research by Ulster on folic acid (aka folate, a B vitamin) has:
I1: directly impacted international **health policy for women of reproductive age** aimed at preventing major birth defects in their babies.
I2: provided the necessary scientific opinion to **set new dietary recommendations** across age- and sex-groups to benefit populations worldwide.
I3: informed the **risk-benefit assessment underpinning food policy for folic acid-fortification** in the UK, Ireland and New Zealand.
I4: contributed to **translating the scientific evidence** into practice for policy makers and health professionals globally, ultimately to benefit patients and consumers.

2. Underpinning research

Supported by significant external funding (> **GBP5M;** 2000-2020) from the Food Standards Agency, the European Commission, UKRI and industry, we have a built a dedicated, and internationally recognised, research programme focussed on folate in health and disease.

Our landmark findings showed important stability and bioavailability differences between naturally-occurring food sources of folate and the synthetic vitamin form, folic acid (**R3**). We showed that, compared with folic acid (present only in fortified foods and supplements), the naturally-occurring (polyglutamylated) forms of folate in food have poor stability under normal conditions of cooking and limited bioavailability once ingested by the body (**R3**). These findings, in turn, greatly limit a person's ability to achieve optimal nutritional status of folate from natural food sources alone (**R5**). We showed that the addition of a low-dose folic acid supplement to the diet can greatly enhance folate status in the blood, and in turn substantially lower homocysteine (**R4)**, a metabolite linked with adverse health outcomes throughout life from pregnancy to older age. Furthermore, we demonstrated that regular consumers of folic acid-fortified foods had significantly higher blood concentrations of folate, and lower homocysteine, compared with non-consumers (**R5).**

A policy of folic acid fortification of staple foods on a mandatory basis would ensure that the population as a whole benefited (and not just those choosing to consume fortified foods as shown in **R5**), but this is controversial. Our papers highlighted the beneficial effect of folic acid intervention, at doses within the dietary range, in achieving a blood folate concentration associated with the lowest risk of NTD in women of reproductive age (**R1, R2, R5**). We also showed that these benefits are not confined to preventing NTD, but also relevant in maintaining better health throughout the lifecycle including an effect of folic acid in lowering blood homocysteine, widely considered to be a risk factor in cardiovascular and other diseases (**R4, R5, R6).** Notably, we conducted a randomised dose-finding trial of the effect of long-term folic acid intervention in older adults, including cardiovascular disease patients, and provided novel findings showing that the dose of folic acid required for beneficial effects was much lower than previously believed, and that exposing populations to higher levels was unnecessary (**R4**); this paper triggered an accompanying editorial at the time of publication in the leading nutrition journal, the *American Journal of Clinical Nutrition,* highlighting the importance of the research. More recently, we addressed an important scientific concern related to the potential for folic acid to exert adverse biological effects in a randomised trial in pregnant women, and demonstrated that folic acid supplements taken at recommended levels throughout pregnancy does not lead to increased circulating unmetabolized folic acid in mothers or their babies (**R2**).

We have also identified important roles and interactions of the closely related B vitamins in maintaining normal folate metabolism and function throughout the lifecycle. Our papers showed that optimal folate metabolism and related health benefits require adequate nutritional status of not only folate, but also vitamin B12, vitamin B6 and riboflavin **(R5, R6).** Our earlier findings showed for the first time that, once folate status is optimised, a much greater dependency on vitamin B12 emerges in order to prevent the accumulation of homocysteine (**R6**). Preventing elevated homocysteine in middle and older age is important as higher concentrations are linked with an increased risk of adverse health outcomes including cardiovascular disease and dementia. Our research also identified the influence of genetic variations and new gene-nutrient interactions in folate metabolism on disease risk, in turn leading to the discovery by Ulster of a highly novel role for riboflavin in lowering blood pressure in people with impaired folate metabolism owing to a common gene variant (**R3**). Our research has also informed the evidence base by identifying new roles for maternal folate nutrition in influencing offspring health beyond NTD. Recently, we provided the first evidence from a randomised trial of a beneficial effect of continued folic acid supplementation through trimesters 2 and 3 of pregnancy on cognitive performance in the child up to 7 years, with impacts for revising current folic acid recommendations in pregnancy (**R1).**

3. References to the research Outputs can be provided by Ulster University on request.

Quality: With the exception of **R3** (a state-of-art review providing significant addition to the conceptual framework of the field), the following outputs report results of randomised trials or observational studies in adults at different lifecycle stages, including pregnancy, providing significant addition to knowledge and applicable for international policy in food and health sectors.

R1 = **H. McNulty**, M. Rollins, T Cassidy, A. Caffrey, B. Marshall, J. Dornan, M. McLaughlin, B.A. McNulty, **M. Ward**, **J.J. Strain**, A.M. Molloy, D.J. Lees-Murdock, C.P. Walsh, **K. Pentieva**. 'Effect of continued folic acid supplementation beyond the first trimester of pregnancy on cognitive performance in the child: a follow-up study from a randomized controlled trial (FASSTT Offspring Trial)'. *BMC Medicine, 17, 196* (2019)

R2 = **K. Pentieva**, J. Selhub, L. Paul, A.M. Molloy, B.A. McNulty, **M. Ward**, B. Marshall, J. Dornan, R. Reilly, A. Parle-McDermott, M. Ozaki, J.M. Scott, **H. McNulty**. 'Evidence from a randomized trial that exposure to supplemental folic acid at recommended levels during pregnancy does not lead to increased unmetabolized folic acid concentrations in maternal or cord blood'. *Journal of Nutrition, 146, 494-500* (2016)

R3 = L.B. Bailey, P.J. Stover, **H. McNulty**, M.F. Fenech, J.F. Gregory, J.L. Mills, C.M. Pfeiffer, Z. Fazili, M. Zhang, P.M. Ueland, A.M. Molloy, M.A. Caudill, B. Shane, R.J. Berry, L.R. Bailey, D. Hausman, R. Raghavan and D.J. Raiten 'Biomarkers of Nutrition for Development—Folate Review' *Journal of Nutrition, 145, 1636S-1680S* (2015)

R4 = P. Tighe, **M. Ward**, **H. McNulty**, O. Finnegan, A. Dunne, **J.J. Strain**, A.M. Molloy, M. Duffy, **K. Pentieva** and J.M. Scott 'A dose-finding trial of the effect of long-term folic acid intervention: implications for food fortification policy' *American Journal of Clinical Nutrition, 93, 11-18* (2011)

R5 = L. Hoey, **H. McNulty**, N. Askin, A. Dunne, **M. Ward**, **K. Pentieva**, **J.J. Strain**, A.M. Molloy, C. Flynn, J.M. Scott 'Effect of a voluntary food fortification policy on folate, related B-vitamin status and homocysteine in healthy adults' *American Journal of Clinical Nutrition, 86, 1405-13* (2007)

R6 = E.P. Quinlivan, J. McPartlin, **H. McNulty**, **M. Ward**, **J.J. Strain**, D.G. Weir and J.M. Scott 'Importance of both folic acid and vitamin B12 in reduction of risk of vascular disease' *Lancet, 359, 227-228* (2002)

Key research grants (active 2000-2020):

Research grants worth a total of **GBP5,179, 784** were awarded to Ulster for this research area, a selection of which is listed below:

- H McNulty (PI), C Walsh, M Ward, K Pentieva (with partners in Canada and Spain). *EpiBrain, Epigenetic Effects of B-Vitamins on Brain Health Throughout Life: Scientific Substantiation and Translation of Evidence for Health-Improvement Strategies*. Sponsor: UKRI BBSRC (JPI-ERA-HDHLscheme). (2019-2022): **GBP266,880**
- M Ward (PI), H McNulty, M Kerr. *Impact of fortified breakfast cereals on nutritional status of British children and adults – findings from the NDNS survey*. Sponsor: CPW Cereal Partners Worldwide. (2017-2018): **GBP98,292**
- H McNulty (PI). JJ Strain, M Ward, J Wallace. *Irish Universities Nutrition Alliance project*. Sponsor: Northern Ireland Department of Employment and Learning (DEL) (Strengthening the all-Island Research Base initiative). (2009-2011): **GBP1,242,392**
- H McNulty (PI), K Pentieva, MBE Livingstone, JJ Strain. *EURRECA, Harmonizing micronutrient recommendations across Europe with special focus on vulnerable groups and consumer understanding.* Sponsor: C.E.C. (FP 6), Food Quality & Safety NoE. (2008-2012): **GBP320,469**
- H McNulty (PI), K Pentieva, M Ward, L Hoey, JJ Strain. *Influence of gender, age and genotype on the known suboptimal status of folate, vitamin B-12, vitamin B-6 and riboflavin.* Sponsor: UK Food Standards Agency. (2003-2007): **GBP471,101**
- H McNulty (PI), JJ Strain. *Bioavailability of folic acid and natural folates: Studies using the functional marker plasma homocysteine*. Sponsor: UK Food Standards Agency. (1998-2002): **GBP681,444**

4. Details of the impact

Research by Ulster in folate/folic acid in 2000-2020 has been instrumental in informing policy in the health and food sectors, tackling policy implementation issues and translating the evidence into practice for health professionals and policy makers, most notably concerning the prevention of spina bifida and related NTD. These birth defects occur when there is a failure of the neural tube to close properly in very early pregnancy, with devastating and lifelong implications for sufferers, their families and society. Preventing NTD is therefore an urgent priority globally, especially in Ireland where NTD rates are among the highest in the world. The impacts are thus greatest in the Island of Ireland, but have global reach and significance. Our research has underpinned impacts in 4 areas:

Impact 1: Our research findings, showing that folic acid (in supplements and fortified food) are beneficial in achieving optimal nutritional status of folate (**R4, R5**), have had significant impacts in informing health policy for women of reproductive age aimed at preventing NTD occurring during the 3rd to 4th week of foetal life. Notably, Ulster author Professor H McNulty was invited as one of a panel of international experts in the field to participate in the BOND project convened by the US National Institutes for Health to review folate as a priority nutrient. The outcome of the panel's research (in 2014-2015) was an extensive report (**R3**), widely considered a state-of-the-art review of all aspects of folate biology and biomarkers, and which has proven to be highly applicable for international health policy and significant to policy makers. This, and our other research outputs, have directly impacted public health policy to prevent NTDs in countries worldwide: Ireland in 2016 (**C1: R3**), the UK in 2017 (**C2: R2**), New Zealand in 2018 (**C3: R2, R3**).

Impact 2: Our underpinning research has also informed the evidence base to support other roles for folate throughout the lifecycle from pregnancy through to older age, and thus contributed to generating dietary recommendations for folate intake within populations worldwide. Our reports of beneficial effects of folate and related B vitamins (B12, B6 and riboflavin) in reducing homocysteine concentrations (**R4, R5, R6**), highlighted the potential for these vitamins to protect against diseases of ageing, such as stroke, heart disease and cognitive decline. This research has provided valuable scientific evidence required to set new dietary folate recommendations across age and sex groups for population health, directly impacting policy in this area in European countries by providing the European Food Safety Authority (EFSA) with the necessary scientific opinion on dietary reference values for folate in 2014 (**C4: R4**).

Impact 3: Research at Ulster has informed the risk-benefit assessment underpinning food policy for folic acid-fortification under discussion in the UK and Ireland. Mandatory folic acid-fortification of staple foods, aimed at reducing pregnancies affected by NTD, is now in place in over 85 countries worldwide (including North America and Australia), but this policy has not yet been implemented in the UK, Ireland or elsewhere in Europe. Our papers, reporting on benefits **(R1, R4, R5, R6**) and potential risks **(R2, R4)** of this population-based intervention**,** have provided greater understanding of the risks and the benefits, pivotal to bringing policy discussions to a successful conclusion. Our paper reporting on a dose-finding trial, showing that the dose of folic acid required for beneficial effects was much lower than previously believed (**R4**), was selected for inclusion in the American Society of Nutrition's *Best of Nutrition* compilation of papers, selected by experts for "*their impact in addressing evidence-based issues of our day in food, diet and health*". Our recent randomised trial evidence (**R2**) addressed a major health concern for policy makers, by showing that exposure to supplemental folic acid at recommended levels during pregnancy had no adverse metabolic effects in mothers or their babies. In this way our research outputs have informed international health and food regulatory authorities in relation to folic acid fortification policy: Ireland in 2016 (**C1: R3**), the UK in 2017 (**C2: R2**) and New Zealand in 2018 (**C3: R2, R3**).

Impact 4: Our research was pivotal in disseminating the scientific evidence by showing how optimal folate status can be achieved in practice in patients and consumers (**R2**, **R4, R5**), so that the necessary public health policy could be effectively implemented (**C1, C2, C3**) in order to ensure that women and their families (main beneficiaries) could benefit. Notably, Professor H McNulty chaired the Folic Acid Review Committee at the Food Safety Authority of Ireland (2014-2016), the outcome of which was an extensive policy document *Folic Acid and the Prevention of Birth Defects in Ireland* **(C1).** We have also contributed to translating evidence into practice guidelines for health professionals internationally in order to ensure that the patients they care for can benefit: Position Statement from the Canadian Paediatric Society in 2016 **(C5)**; Professional Factsheet from the National institutes for Health USA in 2019 (**C6**). Finally, as a pathway to impact to reach relevant users of the research and stakeholders beyond academia**,** Ulster contributed invited speaker (H McNulty) presentations to translate the science for health professionals and government bodies at numerous international conferences and workshops (2014-2020), in North America, Australia and Europe, as well as in Ireland and the UK; the latter

included a presentation delivered in the House of Commons in 2017, at the All-Party Parliamentary Group on Health.

5. Sources to corroborate the impact

C1 = Food Safety Authority of Ireland, FSAI (2016) Update report on folic acid and the prevention of birth defects in Ireland.

C2 = Scientific Advisory Committee on Nutrition (SACN, UK) Folate and Disease Prevention Report; SACN Update on folic acid (2017).

C3 = Office of the Prime Minister's Chief Science Advisor (New Zealand) and the Royal Society *Te Apārangi* (2018) The health benefits and risks of folic acid fortification of food.

C4 = European Food Safety Authority (2014) Scientific opinion on dietary reference values for folate.

C5 = Canadian Paediatric Society (2016) Position Statement. Folate and neural tube defects: The role of supplements and food fortification.

C6 = Office of Dietary Supplements, National Institutes of Health USA (2019) Folate – Health professional fact sheet.