

**Institution:** University of Southampton

**Unit of Assessment:** 01 Clinical Medicine

**Title of case study:** 01-03 The Role of Vitamin D in Reducing Osteoporotic Fractures

### 1. Summary of the impact

Building on work which has contributed, via NICE guidance, to £1 billion in annual savings to the NHS in its healthcare provision for osteoporotic fractures in older adults, research at the £14.4 million MRC Lifecourse Epidemiology Unit (LEU), University of Southampton, has inspired the world's first randomised controlled trial of vitamin D supplementation versus placebo in pregnancy. This work was designed to provide a definitive answer to the question of whether supplementing pregnant women with vitamin D leads to increased bone mineral accrual in the offspring. This work has also shaped national and international guidance on vitamin D supplementation both during pregnancy and in older age; Southampton's programme of osteoporosis research has attracted £10 million in research funding from health organisations and the EU.

### 2. Underpinning research

Osteoporosis constitutes a major public health problem through its association with age-related fractures, estimated to cost the UK National Health Service up to £2.1bn a year. Led by Cyrus Cooper, Professor of Rheumatology, and Nicholas Harvey, Senior Lecturer in Rheumatology, research at the University of Southampton has sought to quantify the human and economic costs of the disease and explore whether vitamin D supplementation across the lifecourse can reduce fracture incidence.

In the early to mid-2000s opinion was moving towards recommending universal vitamin D supplementation in the elderly to reduce the risk of osteoporotic fractures. However, following two trials conducted by Southampton, one published in *The Lancet* in 2005 and one in *Rheumatology* in 2009, and a systematic review in the *British Medical Journal* in 2010, our group concluded that recommended levels of vitamin D supplementation had no discernible effect on fracture incidence, findings which informed national (NICE TA160 and 161 [5.3]) and international (WHO [5.2]) guidance on fracture prevention.

Switching the focus to younger life, over the past decade we have carried out research that has demonstrated that the risk of osteoporotic fracture in older age is modified by environmental influences during intrauterine and early postnatal life. Epidemiological evidence for this developmental origin of osteoporotic fracture has emerged from two groups of studies:

- (a) retrospective cohort studies among adults, whose detailed birth and child records have been preserved, have shown that growth in utero and during infancy is associated with adult bone mass, geometry, strength, and with fracture risk [3.1, 3.2]; and
- (b) prospective mother-offspring studies have shown that maternal body build, smoking, nutrition and physical activity influence bone mass and geometry of offspring during childhood [3.3].

In 2006, in *The Lancet*, we directly linked maternal vitamin D insufficiency with poor offspring bone mineral accrual during childhood, a situation likely to lead to an increased risk of fracture in late adulthood. In a cohort of 198 mothers, 31% had insufficient levels of circulating 25(OH)-vitamin D during late pregnancy [3.4]. When the children were assessed at nine years old using DXA to measure bone size and density, both of these indices of bone strength were reduced in children born to mothers who had insufficient levels of vitamin D during pregnancy.

In the Southampton Women's Survey (SWS), an ongoing prospective mother-offspring cohort, low maternal vitamin D concentrations during pregnancy were associated with reduced bone mass in the babies at birth [3.5]. In SWS, and confirmed in a second cohort, fetuses of mothers with low levels of circulating 25(OH)-vitamin D were found to have altered femoral morphology, consistent with an early effect of vitamin D on bone development in utero [3.6].

All of this work suggests that maternal vitamin D insufficiency is likely to influence offspring skeletal development from an early stage of gestation and have a long-term impact on postnatal bone growth, thus rendering the child at increased risk of osteoporosis in later adult life. As such it has informed national and international guidance on maternal diet, and vitamin D status in particular,

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during pregnancy in relation to offspring health [5.7-5.10].

**Key researchers:** Professor Cyrus Cooper (Director MRC Lifecourse Epidemiology Unit (LEU), Professor of Rheumatology, 1992-current); Dr Nicholas C Harvey (Senior Lecturer in Rheumatology, MRC LEU, 2003-current), Professor Elaine M Dennison (Professor of Musculoskeletal Epidemiology, MRC LEU, 1999-current), Professor Avan Aihie Sayer (Professor of Geriatric Medicine, MRC LEU, 2000-current), Professor Hazel M Inskip (Deputy Director MRC LEU, Professor of Statistical Epidemiology, 1992-current); Professor Sian M Robinson (Professor of Nutritional Epidemiology, MRC LEU, 1992-current), Professor Richard OC Oreffo (Professor of Musculoskeletal Science and Associate Dean International and Enterprise, Faculty of Medicine, 1999-current); Professor Keith M Godfrey (Professor of Epidemiology & Human Development, Director of Operations, NIHR Southampton Biomedical Research Centre, 1992-current)

### 3. References to the research

**3.1** Baird J, Kurshid MA, Kim M, Harvey N, Dennison E, Cooper C. Does birthweight predict bone mass in adulthood? A systematic review and meta-analysis. *Osteoporos Int* 2011;22:1323-34.

**3.2** Javaid MK, Eriksson JG, Kajantie E, Forsen T, Osmond C, Barker DJ, Cooper C. Growth in childhood predicts hip fracture risk in later life. *Osteoporos Int* 2011;22:69-73.

**3.3** Godfrey K, Walker-Bone K, Robinson S, Taylor P, Shore S, Wheeler T, Cooper C. Neonatal bone mass: influence of parental birthweight, maternal smoking, body composition, and activity during pregnancy. *J Bone Miner Res* 2001;16:1694-1703.

**3.4** Javaid MK, Crozier SR, Harvey NC, Gale CR, Dennison EM, Boucher BJ, Arden NK, Godfrey KM, Cooper C. Maternal vitamin D status during pregnancy and childhood bone mass at age 9 years: a longitudinal study. *Lancet* 2006;367:36-43.

**3.5** Harvey NC, Javaid MK, Poole JR, Taylor P, Robinson SM, Inskip HM, Godfrey KM, Cooper C, Dennison EM. Paternal skeletal size predicts intrauterine bone mineral accrual. *J Clin Endocrinol Metab* 2008;93:1676-1681.

**3.6** Ioannou C, Javaid MK, Mahon P, Yaqub MK, Harvey NC, Godfrey KM, Noble JA, Cooper C, Papageorgiou AT. The Effect of Maternal Vitamin D Concentration on Fetal Bone. *J Clin Endocrinol Metab* 2012;97:E2070-7

### Grants

MRC Lifecourse Epidemiology Unit (Cyrus Cooper). **Medical Research Council, 1 April 2010 – 31 March 2015: £14.4m.**

A randomised, double-blind, placebo controlled trial of vitamin D supplements for pregnant women with low levels of vitamin D in early pregnancy (MAVIDOS) (with Profs N Bishop, S Kennedy, A Prentice, Dr E Dennison, Dr N Arden, Dr N Harvey, Prof K Godfrey, Prof H Inskip). **Arthritis Research Campaign, 01 March 2008 – 30 December 2013: £650,732.**

NIHR Biomedical Research Unit: Musculoskeletal Disease (with A Carr, P Dieppe, A Price, D Murray, R Gill, N Arden, J Rees). **National Institute for Health Research, 2008 – 2012: £4m.**

NIHR Biomedical Research Unit: Nutrition, Diet and Lifestyle (with A Jackson, K Godfrey, M Hanson, C Byrne, P Calder, M Elia, M Stroud). **National Institute for Health Research, 2008 – 2012: £4m.**

A pragmatic randomised controlled trial of the effectiveness and cost-effectiveness of screening for osteoporosis in older women for the prevention of fractures (SCOOP). (With Dr L Shepstone, Dr R Fordham, Dr N Gittoes, Prof I Harvey, Dr R Holland, Prof A Howe, Prof J Kanis, Dr T Marshall, Dr E McCloskey, Dr T O'Neill, Prof T Peters, Dr A Shaw, Prof D Torgerson). **Medical Research Council, 01 February 2007 – 01 May 2014: £3,424,229.**

How do early environment, diet and physical activity interact to determine bone development in young children? ARC Clinical Research Fellowship: Dr Zoe Cole **Arthritis Research Campaign, 01 October 2006 – 30 September 2009: £164,135.**

A life course approach to healthy ageing: capitalising on the value of UK life course cohorts (with Prof D Kuh, Prof Y Ben-Shlomo, Dr A Aihie Sayer, Dr R Hardy, Prof I Deary, Dr M Richards, Dr C Gale, Dr B Jane Elliott, Prof T von Zglinicki, Prof I Day, Dr P Shiels, Dr H Southall, Dr A Stephen,

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Prof J Starr, Prof C Power, Dr J Gallacher, Dr E Breeze, Dr R Martin, Prof L Whalley). **ESRC, 01 September 2008 – 31 August 2012: £1.8m.**

The role of vitamin D supplementation in maternal and neonatal bone metabolism (with Dr Nicholas Harvey, Dr Elaine Dennison). **Bupa Foundation 2009-2012, £142,686.**

Vitamin D supplementation in pregnancy: A systematic review (with Dr N Harvey, Dr MK Javaid, Dr J Baird, Dr M Kim, Dr Z Cole, Dr T Tinati, Prof K Godfrey, Prof E Dennison) **NIHR Health Technology Assessment 01 September 2011 to 31 August 2012, £54,534.**

Understanding the early life and environmental determinants of bone strength and structure using participants from the Hertfordshire cohort study. Arthritis Research UK Clinical PhD Studentship: Dr Mark Edwards **Arthritis Research UK, 03 August 2011 to 02 August 2014.**

EU FP 7 programme: Long-term effects of early nutritional on later health. (with Prof Keith Godfrey, Prof Mark Hanson, Dr Karen Lillycrop, Dr Graham Burdge, Prof Hazel Inskip, Dr Nicholas Harvey, Dr Sian Robinson, Dr Mary Barker, Dr Janis Baird). **EU, 01 January 2012 to 31 December 2016 £1,041,082**

We have successfully competed for 5 Academic Clinical Fellowship and 2 Clinical Lecturer posts in the national NIHR Walport competition, with additional supervision of 5 Academic Foundation Trainees.

### 4. Details of the impact

Our research into the epidemiology of osteoporosis-related fractures has shaped national and international policy designed to reduce the burden of osteoporosis and is contributing to an estimated 20% decrease in fracture incidence. A decline of this magnitude has been documented in a recent systematic review of the secular trends in osteoporosis-related fracture **[5.1]**.

Additionally, this research played a key role in the establishment of the MRC Lifecourse Epidemiology Unit at the University of Southampton, and contributed to recent successful bids for grant awards from Bupa Foundation, NIHR Health Technology Assessment, and EU FP7 schemes.

Our work has informed the World Health Organisation's international assessment of osteoporosis treatment in primary care settings, which built on previous guidelines – also based on Southampton's underpinning research, and still guiding practice during the REF period – by the Royal College of Physicians. The WHO assessment **[5.2]**, was first published in 2007 and has guided practice such that its main impact has been made during the REF period: it led directly to the development of the FRAX tool in 2008, a 10-year absolute risk calculator for osteoporosis-related fracture risk, for which Southampton provided epidemiological data **[5.2]**. Now used in over 170 countries, FRAX is established as the international standard risk assessment tool. Its website has more than two million hits worldwide annually, and about one third of UK GP computers possess FRAX software.

Our findings have also informed two NICE technology appraisals, resulting in cost savings for the NHS estimated at £1bn per year (Department of Health figures for 2011). TA160 and TA161 **[5.3]**, published in 2011, set out guidelines for both the primary and secondary prevention of osteoporosis through differing drug treatments for postmenopausal women. We used epidemiological data to model the specific drug types best suited to particular patients, minimising the risks of costly and ineffective treatments. Our research has demonstrated that widespread vitamin D supplementation in the elderly is not cost-effective but that this intervention should be targeted to those at greatest need. Research also informed RCP guidance on postmenopausal and steroid-induced osteoporosis **[5.4]**, published in 2002 and still the standard of care today, together with recent National Osteoporosis Society guidance on vitamin D in clinical practice **[5.5]**.

Professor Cooper was a member of the RCP Guidance Panel, NICE Guideline Development Group and WHO Expert Committee which effected these impacts.

Our observation that maternal vitamin D status during pregnancy is linked to childhood bone mass has led directly to a series of government recommendations that encourage vitamin D supplementation during pregnancy to optimise skeletal development in offspring and reduce the risk of osteoporosis in later life. Based on our findings, a recommendation of 400 IU (10 micrograms) of vitamin D daily during pregnancy has been made nationally. The Department of

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Health emphasises this recommendation during pregnancy and breastfeeding throughout its 2009 edition of the *Pregnancy Book*, which is distributed free to every expectant mother and parent in the UK [5.6]. The same recommendation was made by the Food Standards Agency in its report *Eat Well, Be Well* [5.7] and by the National Institute for Health and Care Excellence (NICE) in its CG62 guideline for health professionals (GPs and midwives) on antenatal care [5.8]. Additionally, it features on the NHS Choices website, accessed by up to 400,000 visitors each day.

The research underpinning these new recommendations has led us to institute the definitive investigation of whether maternal supplementation with vitamin D in pregnancy will improve offspring bone development. The charity Arthritis Research UK has awarded us £650k for a randomised controlled trial of maternal vitamin D supplementation versus placebo, the first such study in the world able to address this issue directly. MAVIDOS – Maternal Vitamin D Osteoporosis Study – is ongoing at Southampton and will report its findings in 2014. By randomising women to either placebo, 500 IU or 1,000 IU from 14 weeks pregnancy until delivery of the baby, the study will determine whether the current dose of vitamin D recommended in pregnancy delivers optimum benefit or whether it should in fact be much higher. The MAVIDOS study has been featured several times in local and national media, for example Professor Cooper interviewed on ITV's "Daybreak" in 2011; indeed the work of the unit as a whole has formed the basis for a recent documentary series on BBC Radio 4, "The First 1000 days" [5.9].

### 5. Sources to corroborate the impact

**5.1** Cooper C, Cole ZA, Holroyd CR, Earl SC, Harvey NC, Dennison EM, Melton LJ, Cummings SR, Kanis JA; The IOF CSA Working Group on Fracture Epidemiology. Secular trends in the incidence of hip and other osteoporotic fractures. *Osteoporos Int.* 2011 May;22(5):1277-88

**5.2** Assessment of osteoporosis at the primary health care level; WHO technical report, WHO 2007 <http://www.who.int/chp/topics/Osteoporosis.pdf>

First report of FRAX was by Kanis JA et al in *Osteoporos Int.* 2008 April; 19(4): 385-97 – "FRAX™ and the assessment of fracture probability in men and women from the UK"

*CC was a member of the groups which developed UK RCP and WHO guidance and FRAX, contributing to the methodology and underlying data.*

**5.3** Osteoporosis-primary prevention. NICE Health Technology Assessment TAG160 <http://www.nice.org.uk/guidance/TA160>

Osteoporosis-secondary prevention. NICE Health Technology Assessment TAG161 <http://www.nice.org.uk/guidance/TA161>

**5.4** Glucocorticoid-induced osteoporosis: Guidelines for prevention and treatment. RCP, London Dec-2002. Prepared by a working group in collaboration with The Royal College of Physicians, The Bone and Tooth Society of Great Britain and The National Osteoporosis Society

*CC was a member of panels/ committees contributing to the above guidelines; our work has directly informed guideline development.*

**5.5** Vitamin D and Bone Health: A Practical Clinical Guideline for Patient Management. National Osteoporosis Society 2013: <http://www.nos.org.uk/document.doc?id=1352>

**5.6** Department of Health Pregnancy Book: [http://webarchive.nationalarchives.gov.uk/+www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyandGuidance/DH\\_107302](http://webarchive.nationalarchives.gov.uk/+www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyandGuidance/DH_107302)

**5.7** Food Standards Agency: <http://www.eatwellscotland.org/agesandstages/pregnancy/whenyrepregnant/index.html#cat226062>

**5.8** NICE CG62: <http://www.nice.org.uk/nicemedia/live/11947/40115/40115.pdf>

**5.9** Media: The First 1000 Days (BBC Radio 4, August 2011): <http://www.bbc.co.uk/programmes/b0137z06>

ITV Daybreak (August 2011) [no ITV archive exists]: [http://www.southampton.ac.uk/mediacentre/news/in\\_the\\_news/archive/in\\_the\\_news\\_august2011.shtml](http://www.southampton.ac.uk/mediacentre/news/in_the_news/archive/in_the_news_august2011.shtml)