Institution: University of Southampton		
Unit of Assessment: 01 Clinical Medicine		
Title of case study: 01-02 A lifecourse approach to reducing the burden of osteoporotic fractures		
Period when the underpinning research was undertaken: 2001 – 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:**
Cyrus Cooper	Director, MRC Lifecourse Epidemiology Unit; Professor of Rheumatology	April 1992 – present
Nicholas Harvey	Professor of Rheumatology and Clinical Epidemiology	October 2003 – present
Elaine Dennison	Professor of Musculoskeletal Epidemiology	August 1995 – present
Kate Ward	Professor of Global Musculoskeletal Health	January 2016 – present
Hazel Inskip	Professor of Statistical Epidemiology	December 1991 – present
Richard Oreffo	Professor of Musculoskeletal Science	February 1999 – present
Keith Godfrey	Professor of Epidemiology & Human Development	February 1990 – 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

Research at the MRC Lifecourse Epidemiology Unit, University of Southampton, has influenced government policy and clinical guidelines in the UK and internationally to improve bone density in younger people and to reduce osteoporosis and fracture rates in older age.

Southampton researchers' demonstrations of the efficacy and cost-effectiveness of Fracture Liaison Services (FLS) have directly informed UK policy and global recommendations. This has led to more than 400 services being established worldwide, 73 being set up in the UK between January 2016 and December 2019, and an increase in rates of osteoporosis medication prescription from 25% to 65% in the UK over the same time period.

The group's description of UK fracture epidemiology and demonstration that systematic screening for fracture risk prevents hip fractures using the FRAX® online fracture risk calculator has informed UK and European guidelines on osteoporosis management. The UK guidelines were incorporated into NICE quality standards and underpin 22 national guidelines globally.

Findings from the MAVIDOS maternal pregnancy vitamin D trial and preceding research informed recommendations from the World Health Organization (2015 Declaration of Minsk), the UK Royal College of Obstetrics and Gynaecology (2014), the UK Scientific Advisory Committee on Nutrition (2016), and subsequent advice from Public Health England, which recommended consideration of vitamin D supplements during the winter months.

2. Underpinning research

Osteoporosis constitutes a major public health problem through its association with age-related fractures, estimated to cost the NHS up to £4bn a year. Led by Professor Cyrus Cooper and Professor Nicholas Harvey, research at the MRC Lifecourse Epidemiology Unit (LEU) developed a unique lifecourse methodology to quantify the human and economic costs of the disease and explore whether interventions across the lifecourse to maximise peak bone mass in early adulthood and minimise fracture risk in older age can reduce fracture incidence. Studies demonstrated a clear treatment gap in primary and secondary prevention of osteoporotic fractures. The work addressed both these urgent healthcare priorities and the longer-term need to incorporate bone health into population-level strategies.

Fracture Liaison Services (FLS) identify older patients presenting, typically to A&E, with a fracture, and ensure that they receive appropriate assessment and treatment for osteoporosis, to minimise the risk of sustaining a further fracture event. MRC LEU research informed optimal approaches to implementation of FLS and subsequently evaluated the clinical effectiveness of FLS models in a population-based longitudinal study from 2003 to 2013 at 11 acute hospitals in South-Central

England. This clearly established the beneficial effect of these models of post fracture care on subsequent mortality (27% reduction at 30 days and 19% at 1 year) and a trend towards reduction in second hip fracture [**3.1**]. Interventions were clearly cost-effective, irrespective of stratification by age, sex and Charlson comorbidity score [**3.2**]. Using linked primary and secondary care data taken from 1999 to 2003 in the Clinical Practice Research Datalink, the study demonstrated that the introduction of national secondary fracture prevention guidance by NICE was associated with an immediate increase in osteoporosis medication prescriptions post fracture, and with a reduction in the incidence of subsequent major osteoporotic and hip fractures [**3.3**].

The group conducted the first study worldwide (SCOOP trial, 2008 – 2014, alongside the Universities of Sheffield and of East Anglia) to assess, in a multi-centre randomised controlled trial, screening for fracture risk using age-dependent treatment thresholds based on 10-year fracture probabilities derived from the global standard FRAX® online fracture risk calculator [**3.4**]. More than 12,000 women (70-85 years) were recruited to the SCOOP trial and were randomised to either usual NHS care or hip fracture risk assessment using the FRAX® tool +/- dual-energy X-ray absorptiometry (DXA), with medication recommended for those at high risk of hip fracture. The study showed that systematic primary care screening for fracture risk in older women results in a 28% reduction in risk of future hip fracture [**3.4**]. Over the five year follow-up, screening led to greater use of osteoporosis medications compared with the usual care arm, particularly in those screened participants found to be at high risk of fracture (73% vs 2% using osteoporosis medications). Relative adherence to treatment was 70% greater in these participants after five years [**3.5**]. This is the first study worldwide to demonstrate the feasibility, effectiveness and cost-utility of primary fracture prevention.

MRC LEU research focusing earlier in the lifecourse, building on our established demonstration of the Barker hypothesis in musculoskeletal disease, documented links between maternal pregnancy vitamin D status and offspring bone development [**3.6**] and led to a unique randomised, double-blind, placebo-controlled trial of gestational vitamin D supplementation (MAVIDOS), which began in 2008. The trial recruited more than 1100 pregnant women at 11 weeks' gestation, who were randomised to either 1000 IU vitamin D or matched placebo daily from 14 weeks' gestation until delivery of the baby. The study demonstrated that the intervention led to a marked improvement (0.5SD) in offspring bone mass at birth for those pregnancies delivering in the winter months (when background 25(OH)-vitamin D concentrations are lowest) [**3.7**]. Critically, offspring bone mass at four years was also greater (0.2SD) in children of supplemented vs unsupplemented mothers, unstratified by birth season, suggesting that the skeletal benefit is maintained into childhood. The study demonstrated the underpinning genetic and epigenetic mechanisms whereby maternal vitamin D supplementation leads to sustained benefits in offspring bone health.

3. References to the research

3.1 Hawley S, Javaid MK, Prieto-Alhambra D, Lippett J, Sheard S, Arden NK, Cooper C, Judge A (2016) Clinical effectiveness of orthogeriatric and fracture liaison service models of care for hip fracture patients: population-based longitudinal study. Age Ageing 45:236-242 https://doi.org/10.1093/ageing/afv204

3.2 Leal J, Gray AM, Hawley S, Prieto-Alhambra D, Delmestri A, Arden NK, Cooper C, Javaid MK, Judge A (2017) Cost-Effectiveness of Orthogeriatric and Fracture Liaison Service Models of Care for Hip Fracture Patients: A Population-Based Study. J Bone Miner Res 32:203-211 https://doi.org/10.1002/jbmr.2995

3.3 Hawley S, Leal J, Delmestri A, Prieto-Alhambra D, Arden NK, Cooper C, Javaid MK, Judge A (2016) Anti-Osteoporosis Medication Prescriptions and Incidence of Subsequent Fracture Among Primary Hip Fracture Patients in England and Wales: An Interrupted Time-Series Analysis. J Bone Miner Res 31:2008-2015. https://doi.org/10.1002/jbmr.2882

3.4 Shepstone L, Lenaghan E, Cooper C, et al. (2018) Screening in the community to reduce fractures in older women (SCOOP): a randomised controlled trial. Lancet 391:741-747. https://doi.org/10.1016/S0140-6736(17)32640-5

3.5 Parsons CM, Harvey N, Shepstone L, et al. (2020) Systematic screening using FRAX® leads to increased use of, and adherence to, anti-osteoporosis medications: an analysis of the UK SCOOP trial. Osteoporos Int 31:67-75. https://doi.org/10.1007/s00198-019-05142-z

3.6 Javaid MK, Crozier SR, Harvey NC, Gale CR, Dennison EM, Boucher BJ, Arden NK, Godfrey KM, Cooper C (2006) Maternal vitamin D status during pregnancy and childhood bone mass at age 9 years: a longitudinal study. Lancet 367:36-43. https://doi.org/10.1016/s0140-6736(06)67922-1

3.7 Cooper C, Harvey NC, Bishop NJ, et al. (2016) Maternal gestational vitamin D supplementation and offspring bone health (MAVIDOS): a multicentre, double-blind, randomised placebo-controlled trial. The Lancet Diabetes & Endocrinology 4:393-402 https://doi.org/10.1016/S2213-8587(16)00044-9

Grants

G1 MRC Lifecourse Epidemiology Unit, **Medical Research Council, 1 April 2015 – 31 March 2020: £15.4m**

G2 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, 1 February 2007 – 1 May 2014: £3,424,229.**

G3 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, 1 March 2008 – 30 December 2013: £650,732.**

4. Details of the impact

Impact on global guidelines

As a combined body of work, MRC LEU research has directly informed patient care through policy and clinical guidelines globally. Studies in older age informed the WHO Report on Ageing and Health 2016 (Cooper is co-chair of the Healthy Ageing Coordinating Committee) [**5.1**]. The early life work informed the WHO Minsk Declaration through the core involvement of Cooper, who gave the keynote speech at the European Health Ministers Conference, Minsk, 2016; European Member States formally adopted the lifecourse approach as the basis for improving population health and wellbeing [**5.2**]. Together these documents demonstrated a commitment to the lifecourse approach to health which Southampton has pioneered and for which MRC LEU has delineated the key clinical assessments necessary to operationalise its evaluation and implementation worldwide.

Secondary fracture prevention

Using state of the art epidemiological techniques and study designs, Southampton work led the field in demonstrating the effectiveness and cost-effectiveness of Fracture Liaison Services (FLS). These studies have informed the global standard of care in FLS, set out by the International Osteoporosis Foundation *Capture the Fracture* initiative, which provides international quality standards for global benchmarking, key performance indicators and practical support [**5.3**]. Capture the Fracture led to the operationalisation of more than 400 registered FLS across 46 countries over the impact period, directly improving patient care by ensuring patients who experience a fragility fracture get the best assessment and treatment to minimise the risk of a subsequent fracture and associated ill health and death. The operationalisation of this strategy is estimated to have reduced hip fracture incidence by 25% in European countries [**5.4**]. The CEO of the International Osteoporosis Foundation confirmed Southampton research had underpinned its European guidelines and multiple position papers. He said the work '*has established key critical advances in fracture prevention, demonstrating the value of fracture liaison services, indeed instituting the global framework ensuring best practice worldwide (Capture the Fracture), together with the achievement of major advances in fracture risk assessment and screening.*' [**5.3**]

Capture the Fracture is cited as an example of best practice in the 2019 global Consensus Clinical Recommendations on Secondary Fracture Prevention, published by a multi-stakeholder coalition formed by the American Society for Bone and Mineral Research and including Southampton contributions through leadership positions of Cooper and Harvey at International Osteoporosis Foundation and Royal Osteoporosis Society [**5.5**]. The development of FLS across the UK was directly underpinned by MRC LEU research, through i) the National Osteoporosis Guideline Group (NOGG) recommendations [**5.6**] linked to guidance from the Royal Osteoporosis Society [**5.7**] and

ii) the Royal College of Physicians (RCP) FLS Database and associated NHS-wide audit in England and Wales, commissioned by the Healthcare Quality Improvement Partnership as part of the Falls and Fragility Fracture Audit Programme [**5.7**]. This national service development programme has led to dramatic improvements in the reach and quality of FLS provision, with FLS covering 61% of the UK population (100% in Scotland). MRC LEU research was pivotal in the establishment of 73 FLS nationwide between January 2016 and December 2019 and the 230,000 patients subsequently recorded on the RCP FLS national database. The Southampton group's work to develop Key Performance Indicators, addressing secondary fracture prevention for each acute NHS Trust in the country, was instrumental in achieving increases in risk assessment and in rates of osteoporosis medication prescription rising from 25% to 65% nationally **[5.7]**. Data from the Royal Osteoporosis Society demonstrate a nationwide saving of £800 million over five years as a result of FLS introduction [**5.7**].

Screening for fracture risk in older age

In order to further reduce the treatment gap in osteoporosis, MRC LEU has undertaken extensive work to develop optimal approaches to primary fracture prevention. Studies into the UK epidemiology of fracture, associated mortality and medication use, funded by the Royal Osteoporosis Society, together with SCOOP trial results, underpinned the assessment of disease burden and risk stratification in the NOGG recommendations (Harvey and Cooper are members of the advisory committee). Published in 2017, they have been cited in 234 publications and downloaded over 24,000 times [**5.6**], and they underpinned the 2019 ESCEO-IOF European guidance for the diagnosis and management of osteoporosis in postmenopausal women [**5.8**], which have been downloaded 17,500 times and cited in 184 articles. The NOGG recommendations have been accredited by NICE and incorporated into the NICE Quality Standards and Osteoporosis Treatment Pathway [**5.9**].

Linked to the NOGG approach and the SCOOP trial, the effectiveness of FRAX contributed to the tool being incorporated in 120 guidelines around the world, 22 of which use age-dependent fracture probability thresholds based on the NOGG methodology, to identify individuals who warrant treatment with osteoporosis medications [**5.10**]. To date, the FRAX website (linked to the NOGG website) has been used to calculate fracture risk in 27 million people worldwide [**5.11**]. In a 2017 assessment of FRAX and NOGG website activity, using Google Analytics, over a one-year period there were a total of 1.77m sessions (a user interaction with the website) on the FRAX website [**5.11**]. More than 250,000 sessions were recorded on the NOGG website, congruent with close to 350,000 visits to the FRAX website from the UK. The findings indicated that users of FRAX in other countries make use of the NOGG guidance, demonstrating impact beyond the UK, and that the vast majority of UK visits to the NOGG website were via FRAX (95.7%), with most from NHS sites (79.9% of locations which were identifiable). MRC LEU has further refined implementation by demonstrating that this FRAX-NOGG approach identifies patients at high risk of fracture and makes most efficient use of DXA scanning, optimising the use of NHS resources and minimising patient exposure to ionising radiation [**5.12**].

"The efforts of the Royal Osteoporosis Society have depended upon the evidence generated through the leadership of Professors Cooper and Harvey, informing our drive to ensure 100% fracture liaison service coverage for the whole of the UK (already achieved in Scotland), and leading the way globally in terms of quality benchmarking. Their work on the epidemiology of fracture, with a large recent project funded by ROS, has established detailed understanding of fractures, medication use and related deaths in the UK and globally; linked to their findings from the seminal SCOOP trial, work from this group has been absolutely central to UK advances in fracture risk assessment, using the FRAX-NOGG approach. Professors Cooper and Harvey have definitively advanced the field in a way that directly improves patient care and health outcomes". CEO, Royal Osteoporosis Society. [**5.13**]

Maternal vitamin D supplementation in pregnancy and offspring MSK development

The initial work on vitamin D in pregnancy [**3.6**], published in *The Lancet* and cited 901 times, underpinned part of the 2014 guidelines on pregnancy vitamin D status from the UK Royal College of Obstetricians and Gynaecologists (RCOG) [**5.14**]. The MAVIDOS trial informed the 2016 recommendations for maternal vitamin D supplementation during pregnancy from the UK Scientific Advisory Committee on Nutrition [**5.15**]. These were translated into public health guidance by Public

Health England [**5.16**]. Consistent with the winter effect of maternal gestational vitamin D supplementation on offspring bone mass as demonstrated in MAVIDOS, the PHE guidance incorporated seasonal stratification into supplementation advice. MAVIDOS also contributed to the Minsk Declaration on the lifecourse approach [**5.2**]. The 2016 MAVIDOS trial, among the first definitive validations of the Barker hypothesis, [**3.7**] received widespread global media coverage and subsequently informed other guidelines internationally, for example from the Australian Department of Health [**5.17**]. Clinical evidence of the impact of MRC LEU studies on vitamin D in pregnancy comes from the group's own observations of a 30% rise over the last decade in pregnancy 25(OH)-vitamin D concentrations from the original Princess Anne Cohort Study [**3.6**], through MAVIDOS, to the most recent SPRING trial [**5.18**].

5. Sources to corroborate the impact

5.1 WHO World Report on Ageing and Health (lifecourse research cited pages xi, 119)
http://apps.who.int/iris/bitstream/10665/186463/1/9789240694811_eng.pdf?ua=1
5.2 World Health Organization Minsk Declaration on the life-course approach
http://www.euro.who.int/__data/assets/pdf_file/0009/289962/The-Minsk-Declaration-EN-rev1.pdf
5.3 Letter from the CEO of the International Osteoporosis Foundation (IOF)
5.4 Evaluative study (2015) of the implementation of Capture the Fracture® after 12 months.
https://link.springer.com/article/10.1007%2Fs00198-015-3192-0
5.5 International Consensus Clinical Recommendations on Secondary Fracture Prevention
https://asbmr.onlinelibrary.wiley.com/doi/full/10.1002/jbmr.3877
5.6 National Osteoporosis Guideline Group 2017 Clinical guideline for the prevention and treatment of osteoporosis (Southampton research cited as reference 131).
https://www.sheffield.ac.uk/NOGG/NOGG%20Guideline%202017.pdf
5.7 Royal Osteoporosis Society FLS Guidance and Royal College of Physicians FLS Database (FLS-DB) Audit report: https://theros.org.uk/media/1eubz33w/ros-clinical-standards-for-fracture-liaison-services-august-2019.pdf
FLS-DB Analysis plan (cited as reference 1):
https://www.rcplondon.ac.uk/projects/outputs/fracture-liaison-service-database-fls-db-methodology
5.8 European guidelines on assessment and treatment of osteoporosis
https://doi.org/10.1007/s00198-018-4704-5
5.9 NICE Osteoporosis quality standard (QS149) and Care pathway
https://www.nice.org.uk/guidance/qs149; https://pathways.nice.org.uk/pathways/osteoporosis
5.10 Systematic review of FRAX in fracture risk assessment guidelines globally
https://link.springer.com/content/pdf/10.1007%2Fs11657-016-0278-z.pdf
5.11 FRAX website usage and NOGG guidance usage
https://link.springer.com/content/pdf/10.1007%2Fs00198-016-3696-2.pdf
5.12 Demonstration of utility and efficiency of NOGG approach in targeting DXA and treatment
https://link.springer.com/article/10.1007%2Fs00198-015-3176-0
https://link.springer.com/article/10.1007%2Fs00223-015-0092-4
5.13 Letter from the CEO of the Royal Osteoporosis Society, UK
5.14 Vitamin D in RCOG pregnancy guidelines (Southampton research cited as ref 40).
https://www.rcog.org.uk/globalassets/documents/guidelines/scientific-impact-papers/vitamin_d_sip43_june14.pdf
5.15 UK Scientific Advisory Committee on Nutrition Vitamin D Recommendations
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/537616/SACN_Vitamin_D_and_Health_report.pdf
5.16 Public Health England (NHS) guidance on vitamin D in pregnancy; and National Institute for Health and Care Excellence pregnancy guidance
https://www.nhs.uk/conditions/vitamins-and-minerals/vitamin-d/
5.17 Australian Department of Health guidance on vitamin D in pregnancy (**3.7** cited in references)
https://www.health.gov.au/resources/pregnancy-care-guidelines/part-g-targeted-maternal-health-tests/vitamin-d-status
5.18 25(OH)-vitamin D concentrations in pregnancy
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(06)67922-1/fulltext
https://www.thelancet.com/action/showPdf?pii=S2213-8587%2816%2900044-9