Institution: University of Cambridge

Unit of Assessment: UoA2

a. Overview Almost all Category A staff returned in UoA2 are based in the Department of Public Health and Primary Care (head: Danesh) and in the MRC Epidemiology Unit (director: Wareham), with the latter having transferred into the University in 2013 to cement a key partnership. Both groups are in the Cambridge Institute of Public Health (director: Brayne), which was established in the School of Clinical Medicine in 1992 to promote interdisciplinary research and training though collaboration of the University, MRC Units, and applied research groups of Public Health England. The Institute also includes:

- the MRC Biostatistics Unit (director: Richardson, who holds a University professorship)
- the MRC Human Nutrition Research Unit (director: Prentice)
- applied research groups of Public Health England
- the Public Health Genomics Foundation, a not-for-profit policy centre.

Since 2008, our significant achievements have included:
- 4-fold expansion in research output compared with the RAE 2008
- major expansion in applied health research
- establishment of nine interdisciplinary cross-departmental research centres
- greater recognition through the status of a "strategic University-wide network" in public health.

We first describe our overarching strategy and then the content of the major themes that cut across our disciplinary research groups of epidemiology, public health, and primary care.

b. Research strategy The overall objective of population health research in Cambridge is to generate evidence to inform: the prevention of premature death and disability, the promotion of health and well-being throughout the lifespan, reduction of health inequalities, and the formulation of evidence-based health policy. Our distinctive approach is the deep integration of quantitative, clinical, social, and life sciences in specific areas to help address major public health problems.

The large bulk of our research activity is long-term in nature. As an important example, the European Prospective Investigation into Cancer (EPIC, a pan-European study of 520,000 people which Cambridge scientists helped establish in the 1990s) has become even more valuable to our research as large numbers of new-onset cases of particular chronic disease outcomes have been accruing in recent years. At the other extreme of timeframes, we produce rapid-response reviews to advise the UK government, for example regarding policies on alcohol and tobacco control.

Priorities Since 2008, our research priorities have been responsive to **major national and international public health needs**, leading us to focus on the study of common chronic conditions, such as cardiovascular disease, neurodegenerative diseases, diabetes, obesity, cancer, and other ageing-related diseases as well as their major modifiable determinants, including smoking, alcohol consumption, diet, and physical activity. We contribute to the **strategic vision** of many bodies by playing an active role on numerous funding committees and advisory boards (see section e). The several-fold growth in research income achieved over the REF period in the population health sciences in Cambridge reflects the quality and relevance of our research.

Scope of output Our research ranges from underpinning methods, to basic epidemiology to discover the causes and associations of major diseases, to development and evaluation of interventions to prevent or manage illness, to interventions delivered at population level designed to promote the health of populations. Since 2008, our research output has been characterised by:

- cutting-edge **methodological strength** that underpins our applied work, eg, major contributions to methods for analysing and interpreting complex epidemiological and public health data
- the **discovery of knowledge** to lay the foundations for new disease prevention efforts, eg, identification of interleukin-6 (IL-6) signalling as a causal risk factor for coronary disease, with implications for tocilizumab and other agents that inhibit IL-6
- the **development of new tools to predict disease**, eg, the BOADICEA risk model for familial breast and ovarian cancer risk, which has been incorporated into NICE and other guidelines

● the **development of new interventions to prevent disease**, eg, demonstration that ultrasound screening in men for abdominal aortic aneurysm reduces mortality and is cost-effective, culminating in a new national screening programme by the Department of Health in England
● **policy relevant work** to promote health and well-being that has a direct impact on policy and practice, eg, our work contributing to national UK guidelines for physical activity and to nine international cardiovascular guidelines.

Elements of strategy Since 2008, our strategy has involved six inter-related elements:

i. Building of scientific capacity The first element of our strategy is to enhance scientific capacity, both through internal development of staff and students and through external recruitment. Since 2008, we have substantially enhanced scientific capacity (see section c). A crucial part of our strategy has been to foster an environment that attracts talented young researchers and integrates training with high-quality research. As a consequence of this approach, about one-half of the staff returned in UoA2 are **Early Career Researchers**.

ii. Enhancement of strategic coordination A second element of our strategy is to enhance the coordination of the rapidly-expanding population health research activities throughout Cambridge. The rationale is to maximise synergy and opportunities for interdisciplinary research. We have realised a key aim stated in RAE2008, which is to achieve greater coordination through building **cross-linkages** within the Cambridge Institute of Public Health through joint appointments and shared research programmes between groups (see below in this section), shared teaching programmes (section c), shared infrastructure (section d), and a frequent flow of staff between groups. Each constituent group in the Cambridge Institute of Public Health is represented in the Institute's executive committee, which meets regularly to discuss strategic issues.

During the next REF period, we will expand on this approach by bringing new perspectives and expertise into population health from additional disciplines. To help achieve this goal, we have created University-wide initiatives, including a **Centre for Science and Policy** with cross-cutting themes of well-being and behaviour, risk, and evidence-based policy, and in 2012, a **Strategic Research Network** (www.publichealth.cam.ac.uk) to stimulate interdisciplinary collaboration in public health across all six Schools of the University. Award of "strategic network" status to public health is a rare recognition, as there are only five other such networks across the University of Cambridge.

iii. Expansion of applied health research A third element of our strategy is the expansion of applied health research, typically organised as **cross-departmental centres** that are "mission-oriented" and interdisciplinary. The rationale is that such efforts should enable our research to have a direct impact on public health policy and practice in the UK and internationally. In the RAE2008, we anticipated that this research area would become an increasingly important part of our portfolio. This goal has been realised, with the following as examples of new research centres.

In 2008, £5 million from the UK Clinical Research Collaboration (a consortium of several major funding agencies) established the **Centre for Diet and Activity Research** (director: Wareham), one of five Centres of Excellence in Public Health Research in the UK, a collaboration of MRC Units and universities which focuses on changing diet and physical activity at a population level. In 2013, this Centre received a £4 million renewal. Also in 2008, £10 million of NIHR funding established the **Collaborative Leadership in Applied Health and Care** (director: P Jones returned in UoA4; public health theme leader: Brayne), which involves a collaboration of University departments of Psychiatry, Public Health and Primary Care, Engineering, and the Judge Business School as well as relevant NHS healthcare trusts to improve mental health services. In 2013, this initiative was expanded to the East of England with a further £12 million of funding.

These efforts encouraged us to form further research centres. In 2010, £5 million of funding from the Department of Health in England established the **Behaviour and Health Research Unit** in Cambridge (director: Marteau) to contribute evidence that will lead to sustained behaviour change that improves health outcomes and reduce health inequalities. This initiative involves MRC Units,

the University of East Anglia, and RAND-Europe, a not-for-profit policy research institute. Also in 2010, funding from the University and RAND-Europe established the **Cambridge Centre for Health Services Research** (director: Roland) to develop methods to measure and improve quality of care and to advance health policy. In 2013, this Centre was judged to be one of the two top health policy think tanks worldwide, according to an independent report from the University of Pennsylvania. In 2013, RAND-Europe cemented this strategic relationship with the establishment in Cambridge of the RAND chair in health services research.

During the next REF period, we plan to extend this approach to address public health problems in low- and middle-income countries. In 2009, funding from the US National Institutes of Health and the Wellcome Trust established a **Centre for Vascular Disease Studies in South Asia** (Danesh, Saleheen, Chowdhury, Di Angelantonio) to study risk factors (eg, arsenic exposure) distinctive to South Asian populations. In 2013, the MRC and Wellcome Trust supported the **African Partnership for Chronic Disease Research** (Sandhu) to assess the burden and causes of non-communicable in sub-Saharan Africa and to improve the evidence base underpinning potential responses to these diseases. In 2013, the Wellcome Trust named Cambridge as the site of one of its five **Centres for Global Health Research** (director: Dunne returned in UoA1, with Danesh, Roland, Wareham as co-PIs), focusing on support for public health researchers in Africa.

iv. Integration with quantitative sciences A fourth element of our strategy is to promote the development and application of innovative statistical methods and deepen their integration into our population studies. The rationale is to ensure robust scientific progress by making sound inferences in the presence of uncertainty, and to maximise new insights from our data rich studies.

We collaborate extensively with the MRC Biostatistics Unit, which conducts methodological research in four areas, each of which underpins, arises from, and is embedded in applied research done in UoA2: a) statistical genomics b) design and analysis of randomised trials (including the £2 million **MRC Hub for Trial Methodology Research** established in 2009) c) evidence synthesis for health and d) methods for complex observational and longitudinal data. To encourage research at the intersection of methodological and applied statistical research, we have created joint appointments between the MRC Biostatistics Unit and the University, including those involving the MRC Cognitive Function and Ageing Study and the Centre for Diet and Activity Research.

There is a critical mass of additional biostatistical research in the Cambridge Institute of Public Health which is cross-linked with the MRC Biostatistics Unit through joint seminars and projects. Examples include researchers in risk communication (Spiegelhalter returned in UoA10), public health modelling (S Thompson, director of the MRC Biostatistics Unit until 2011), prognostic models (Wood), case-cohort methods (Sharp), and causal inference (Burgess). To enhance campus-wide leadership, a **Professorship of Statistics in Biomedicine** was established in 2013, to be a joint appointment between the University and the MRC Biostatistics Unit.

During the next REF period, we plan to develop further linkages with other world-leading quantitative institutes in Cambridge, most notably the University Statistical Laboratory (returned in UoA10), the Sanger Institute, and the European Bioinformatics Institute. This objective has been facilitated by the establishment in 2012 of a 4-year **Wellcome Trust PhD Programme in Mathematical Genomics and Medicine**, which involves collaboration among quantitative scientists in the University, MRC Biostatistics Unit, and the Hinxton Genome Campus.

v. Integration with clinical and life sciences A fifth element of our strategy is to integrate aetiological epidemiology deeply with clinical and life sciences. The rationale is to accelerate the translation of findings about disease risk factors into new methods of treatment and prevention. Recent campus-wide initiatives have catalysed such integration.

In 2009, Cambridge University Health Partners was designated an **Academic Health Science Centre** by the Department of Health, facilitating establishment of the **Cambridge Clinical Trials Unit** which supports trials led by scientists in UoA2. In 2012, the NIHR **Cambridge Biomedical Research Centre**, a partnership between the University and Cambridge University Hospitals,

received an uplifted award of £110 million, partly to create themes that integrate population science with experimental medicine. For example, it is enabling us to embed mechanistic studies into the nationwide 50,000-person INTERVAL study (Danesh), a major component of the **NIHR Bioresource** that will help identify new disease mechanisms by providing a large-scale "recall by genotype" cohort and generating high-quality adult stem cells to discover how genomic variation impacts on cellular phenotype, capitalising on the Cambridge-led £13 million MRC / Wellcome Trust **Human Induced Pluripotent Stem Cells Initiative**.

The greater integration of epidemiology with clinical science is also proceeding along disease-specific lines. In 2012, the NIHR **Cambridge Dementia Biomedical Research Unit** was established with a £5 million award, including a component to create a registry of dementia patients (Brayne). In 2013, the MRC and Wellcome Trust awarded £24 million to the Institute of Metabolic Science (co-Directors O'Rahilly/Wareham) for a **Cambridge Metabolism Initiative**, including a component to deepen links between population and basic research. In 2013, the British Heart Foundation made a £3 million award to establish a **Cardiovascular Research Centre of Excellence** that will focus on the integration of population, clinical and biological approaches (Danesh, S Thompson). Also in 2013, the MRC and British Heart Foundation made a £3.5 million award under the **Experimental Medicine Challenge Grant** scheme to establish a UK-wide network to study the aetiology of pulmonary artery hypertension, including an epidemiology component (Danesh).

To accelerate and deepen such integration, we help lead interdisciplinary 4-year PhD programmes that involve co-supervision by population scientists and clinical scientists, such as the **British Heart Foundation Interdisciplinary PhD programme** (co-director: Danesh), renewed in 2013, and the **Wellcome Trust PhD Programme in Metabolic and Cardiovascular Disease**.

As anticipated in the RAE2008, we have been strengthening the linkages between aetiological epidemiology and thematic research institutes and departments. For example we have co-located the MRC Epidemiology Unit within the Cambridge Institute of Metabolic Science and have co-located elements of genetic epidemiology in UoA2 within the Sanger Institute (where Danesh and Sandhu hold joint appointments). During the next REF period, we plan to continue this approach by co-locating elements of the Cardiovascular Epidemiology Unit in the new **Heart and Lung Research Institute**, to be completed in 2017.

vi. Partnerships with external organisations A sixth element of our strategy is to expand engagement with key external (including international) partners in academia, the NHS, industry, the not-for-profit sector, and the general public. The rationale is to benefit from complementary perspectives and expertise of partners capable of accelerating the impact and dissemination of our research findings.

The eight-university **NIHR School for Public Health Research** was established in 2012 to increase the evidence base for effective public health action, with Cambridge scientists helping to lead ageing-related research (theme leader: Brayne). Delivering against the RAE2008's aim of 'further expanding our international linkages,' we established a strategic partnership with the University of the North Carolina **Gillings School of Global Public Health** in 2012, for which the two Universities have seed-funded collaborative research in dementia, obesity, big data, and food purchasing behaviour. Other international partnerships have included those with the **Public Health Foundation of India-UK** and **THRiVE** (Training Health Researchers into Vocational Excellence in East Africa), both being Wellcome Trust-funded capacity-building initiatives.

The **Cambridge-Pfizer Centre in Cardiovascular Genomics** (director: Danesh) was established in 2011 with funding from Pfizer and the NIHR to accelerate medicines development by using genetic epidemiology to validate risk factors proposed as new therapeutic targets. It was featured in the 2012 "Strategy for UK Life Sciences" report of the government's Department of Business, Innovation and Skills. In 2013, we expanded this approach in the **Cambridge / Merck / Pfizer / Penn Medicines Development Initiative** (Danesh, Butterworth, Saleheen). In 2012, €25 million of funding from European Commission Innovative Medicines Initiative established the **European**

Medical Information Framework for translational studies of metabolic and other diseases, with a component led by the MRC Epidemiology Unit (Wareham).

An example of a new partnership with the UK health service is the **Centre for Population Donor Health** (directors: Danesh & Di Angelantonio), established in 2012 with £6 million of funding from the NHS Blood and Transplant to inform policy to secure the nation's blood supply and protect the health and well-being of blood donors. Our partnerships with the not-for-profit sector include those mentioned above with **RAND-Europe** and the **Public Health Genomics Foundation**. To catalyse and deepen partnerships with external organisations, we have established several joint appointments since 2008, including those with RAND-Europe (Roland), NHS Blood and Transplant (Di Angelantonio), Pfizer (Howson), the Sanger Institute (Danesh, Sandhu), the University of Pennsylvania (Saleheen), and the University of Peking (Gao from January 2014).

During the next REF period, we plan to seize further opportunities for external partnerships. In 2013, the Cambridge-led East of England Academic Health Science Forum (hub leader: Roland) was designated an **Academic Health Science Network** by NHS England, a vehicle by which the NHS and universities will work with industry in research, service innovation, and wealth creation. Also in 2013, **AstraZeneca** announced that it will build a £330 million global research hub on the Cambridge Biomedical Campus by 2016, with UoA2 scientists already building new collaborations with the company based on quantitative methods and genetic epidemiology.

We are intensifying **engagement with our local communities**, such as through: studies of our campus workforce; involvement of patient representatives in all stages of our studies; "Citizen Science" projects, such as the use of crowdsourcing to classify tumour data in collaboration with Cancer Research UK (Pharoah); contribution to the curriculum of the **University Technical College Cambridge**, to open in 2014 on the Cambridge Biomedical Campus for training scientific technicians capable of working across academia and industry.

Research themes We describe below key themes of our work that cut across organisational and disciplinary groups:

i. Aetiology The goal is to lay foundations for new preventive efforts by identifying and evaluating causal risk factors for selected major diseases, including vascular diseases, cancers, neurodegenerative diseases, diabetes, and other age-related conditions.

Achievements We have led the discovery of >350 genetic loci in a range of common diseases (eg, breast, prostate, and ovarian cancers; coronary disease; type 2 diabetes) and risk factors (eg, lipids; insulin resistance) that have been reported in >30 publications in *Nature* and *Nature Genetics* since 2008. These findings have opened new avenues of biology and mechanistic understanding and helped develop new risk prediction tools in widespread use (see **iii** in this section). Using the principle of "Mendelian randomisation", we have identified risk factors likely to have causal roles (eg, triglyceride pathways and IL-6 signalling in coronary disease [Lancet 2011; Lancet 2012]; natriuretic peptides in type 2 diabetes [PLoS Medicine 2011]), and others that appear non-causal (eg, C-reactive protein [BMJ 2012, Lancet 2011]). These studies have yielded implications for industry, eg: Novartis (triglycerides results), Roche (IL-6 results), and ISIS pharmaceuticals (C-reactive protein results). We have quantified the impact of risk factors amenable to therapeutic modification, such as subclinical hypothyroidism in coronary disease (JAMA 2010) and dysglycaemia in relation to vascular and non-vascular conditions (NEJM 2011). We are testing the latter hypothesis in an HTA-funded trial of metformin (see **iv** in this section). We have shown that different subtypes of breast cancer defined by biological markers show important differences in prognosis (PLoS Medicine 2010), suggesting implications for targeting adjuvant chemotherapy.

Future plans We are integrating "multi-omics" (eg, genomics, epigenomics, metabolomics) in participants linked to multiple NHS e-health records in 100,000 well-phenotyped individuals. We are establishing an e-health study involving 2 million blood donors in England. We are extending studies of 90,000 participants in non-European populations in which certain risk factor levels are

unusually high (eg, toxic metals in Bangladesh; consanguinity in Pakistan; hepatitis C infection in Africa) and in which cardiometabolic risk is also high. We are extending major genetic sequencing efforts in Africans (eg, the African Genome Variation Project) to >20,000 South Asians.

ii. Behaviour and health The goal is to elucidate determinants of health behaviours, estimate the impact of these behaviours on chronic disease outcomes, and develop and evaluate individual- and population-level interventions that modify behaviours to promote health and prevent disease.

Achievements To define the wider determinants of risk behaviours, we study datasets throughout the lifecourse, drawing on health psychology, neuroscience, and behavioural economics to understand the basis for behaviour cued by environments and social patterning, with implications for our intervention studies. Our cohort studies have suggested that a combination of four health behaviours in adults (not smoking, moderate intake of alcohol, physical activity, consumption of ≥5 servings of fruit and vegetables daily) is associated with a 14 year greater life expectancy (PLoS Medicine 2008). Our meta-analysis has shown that higher levels of physical activity in adults attenuate the influence of FTO, the strongest known genetic susceptibility factor for obesity (PLoS Medicine 2011). Our meta-analysis has shown that physical activity promotion in primary care to sedentary adults resulted in sustained increases in physical activity levels (BMJ 2012). However, our randomised trial in sedentary individuals at familial risk of diabetes showed that a theory-based behaviour intervention was no more effective than an advice leaflet for promotion of physical activity (Lancet 2008). Our trials have shown that tailored smoking cessation messages delivered by post increase the number of smokers who try to quit, and that for web based information, tailoring did not appear to increase the effectiveness of messages encouraging patients to quit.

Future plans We are identifying which interventions at the population-level (eg, taxation, legislation, 'nudging', environmental changes) are most likely to influence behaviour. We are developing and evaluating tailored interventions for smoking cessation, physical activity and medication adherence focusing on very brief interventions delivered by health care practitioners and computer-based approaches (eg, self-monitoring, mobile phone texting, smartphone apps). We have established a portfolio of planned interventions (eg, the Baby Milk Study to evaluate a complex behavioural intervention to avoid excessive formula-milk intake during infancy) and natural experiments (eg, a cohort study to assess the impact of the introduction of the Cambridgeshire Guided Busway on travel and physical activity).

iii. Diagnosis and screening The goal is to develop and evaluate approaches that can cost-effectively enhance the diagnosis, early detection, and prediction of chronic disease outcomes.

Achievements We have shown that there are marked differences in GP referral patterns across cancer types according to socio-demographic groups, suggesting the need to prioritise younger people and ethnic minorities for early diagnosis initiatives (Lancet Oncology 2012). Our trial of approaches to diagnosing suspicious moles reinforced the importance and effectiveness of a seven point checklist for GPs (BMJ 2012), for which Walter was awarded the RCGP cancer research paper of the year. We have established the cost-effectiveness of screening men for abdominal aortic aneurysm (BMJ 2009, NEJM 2010), and defined appropriate surveillance intervals (JAMA 2013). Our trial of offering antenatal screening for sickle cell disease and thalassaemia as part of consultation for pregnancy confirmation in primary care showed an increase in the proportion of women screened before 10 weeks' gestation (BMJ 2010). We have integrated our gene-disease discoveries into widely used risk prediction algorithms for breast and ovarian cancer (BOADICEA) and cancer prognosis (PREDICT), and laid foundations for stratified approaches to breast cancer screening (NEJM 2008). We have quantified the benefits and harms of screening for type 2 diabetes (BMJ 2009, Lancet 2012) for which the ADDITION trial team (lead: Griffin) won the BMJ's paper of the year and the RCGP diabetes research paper of the year. We have demonstrated the predictive utility of routine GP data and how incorporating it in a stepwise approach to screening for cardiovascular disease would be more cost-effective than the current UK strategy (BMJ 2010). Another of our modelling studies has suggested that screening middle-aged men with symptoms of gastroesophageal reflux disease using a Cytosponge, a device developed in Cambridge, would reduce mortality in a cost-effective manner (Gastroenterology 2012). We have

influenced international cardiovascular guidelines through evaluation of the incremental value of assessing established and emerging risk factors for risk assessment, including inflammation biomarkers (NEJM 2012), lipids and lipoproteins (JAMA 2012, Lancet 2010), adiposity measures (Lancet 2011), and carotid ultrasound (Lancet 2012).

Future plans We are studying the early diagnosis of lung, pancreatic and colorectal cancers. We are developing stepwise approaches to combined risk assessment in primary care for cognate conditions (eg, diabetes, cardiovascular disease, renal disease), in contrast with fragmented single disease approaches. We are evaluating the impact on attitudes, behaviours, risk factors, and, ultimately, mortality of different approaches to disease risk prediction (eg, lifestyle-enriched risk scores that promote behaviour change vs highly accurate biomarker-enriched scores).

iv. Control of chronic disease The goal is to develop and evaluate approaches that can cost-effectively improve the control and management of chronic conditions in primary care.

Achievements Our trial concluded that intervention to promote early intensive management of type 2 diabetes was not harmful and could yield moderate benefits (Lancet 2011). Our trial in people with poorly controlled hypertension showed that a strategy of patient self-management of hypertension in combination with telemonitoring of blood pressure was superior in decreasing blood pressure than usual care (Lancet 2010). Our meta-analysis has suggested that ambulatory monitoring of blood pressure before the start of lifelong drug treatment leads to more appropriate targeting of treatment than relying on clinic or home measurement of blood pressure (BMJ 2011). Our comparative cohort study of older patients with atrial fibrillation showed that current risk stratification schemes have only limited ability to predict stroke, suggesting classification of all such patients over 75 years as “high risk” to avoid systematic under-treatment (BMJ 2011). Our cross-sectional study of primary care records showed that older people were disproportionately low users of statin medications, suggesting implications for clearer guidelines for people aged over 75 years (BMJ 2012). Our long-term cohort study indicated that the estimated median survival for incident dementia is 4.5 years (BMJ 2008), suggesting implications for prognosis and planning for patients, carers, and health services.

Future plans We are conducting trials to evaluate “polypill” interventions in cardiovascular disease prevention and ways to improve outcome following stroke. We have commenced the feasibility phase for a trial of metformin for the prevention of cardiovascular disease in people at high risk of type 2 diabetes, with the full trial of 12,000 people expected to start in 2015.

v. Health services The goal is to develop methods of measuring quality of care and burden of disease, and evaluating interventions designed to improve healthcare.

Achievements Our work has had substantial impact on measurement of quality in the NHS, in particular developing measures of patient experience in primary care and interpreting measures of patient experience in cancer. Our studies in primary care have yielded new insights about the impact of pay-for-performance programmes in the NHS (NEJM 2009) on exception reporting in primary care (NEJM 2008), and how financial incentives have diverted attention from aspects of care that were not incentivised (BMJ 2011). We have also shown the impact of hospital pay for performance schemes on reducing in-hospital mortality (NEJM 2012). Other work has informed NHS policy on areas including targets for hospital readmission rates, the impact of initiatives designed to better integrate care, and the contribution of leadership training to improving hospital quality. Our two-decade cohort study of dementia in England has informed health service provision by producing reliable prevalence estimates, adding to our understanding of neuropathology (NEJM 2009), and showing that a cohort effect exists in dementia prevalence, with later-born populations having a lower risk of prevalent dementia than those born earlier in the past century (Lancet 2013).

Future plans We will expand work on quality measurement in the NHS, showing how valid data on patient experience can be used to improve care, working in primary care, in acute hospitals, and with patients who have cancer. Our work will demonstrate how care can be better integrated and we will continue with long-term studies to improve the care of people with dementia. To inform the

blood service in England, we will complete a trial of 50,000 blood donors to determine the optimum safe interval between blood donations, as well as conduct further trials to assess how best to screen for iron deficiency and to prevent anaemia through personally-tailored dietary advice.

c. People, including: The development of staff and students is at the core of our activities.

i. Staffing strategy and staff development Since 2008, there has been more than a doubling of the number of Professors in UoA2. Seven of the 8 new professors have been recruited externally; Pharoah was promoted. We have achieved the aim stated in RAE2008 of enhancing strength and expertise in disciplines related to applied health research. Leadership in primary care has been substantially strengthened with professorial appointments (Griffin, Mant, Marteau, Roland). We have enhanced strengths in biostatistics through professorial appointments (Richardson, S Thompson), and opened new lines in risk prediction through a new Readership (Antoniou, 2013) and a new Lectureship (Di Angelantonio, 2010), with both appointees having been Cambridge-trained early career researchers. The appointment of Deaton to the Florence Nightingale Foundation Professorship of Clinical Nursing (November 2013) will open a new line as well as link with existing strengths in cardiovascular disease. We have enhanced strengths in genetic epidemiology, again, through appointment of Cambridge-trained early career researchers to Lectureships (Butterworth, 2011, Saleheen, 2012). New tenured appointments have helped maintain a balanced portfolio of staff that includes young investigators to ensure appropriate staff turnover and opportunity for new appointments. One-third of the professors in UoA2 are female.

Early career researchers We develop young academics through fellowships to full independence by providing access to scientific resources and mentorship. We mentor young clinical and non-clinical scientists through a number of research fellowship schemes or grant-supported post-doctoral posts, advancing careers locally by preparing staff for personal fellowships. Since 2008, young scientists in UoA2 have held: NIHR Clinician Scientist Fellowships (eg, Walter), CRUK Senior Non-Clinical Fellowships (eg, Antoniou), BHF Intermediate Fellowships (eg, Wijndaele), Sir Henry Wellcome Fellowships (eg, Burgess), MRC Career Development Fellowships (eg, Lakshman), Marie Curie Fellowships (eg, Keage), Future Leaders in Aging Research (eg, Stephen), MRC Biostatistics Fellowships (eg, Barrett), NIHR Post-doctoral Fellowships (eg, Lyratzopoulos). Designated senior academics in UoA2 (Mant, Forouhi) are responsible for coordination, including transferable skills training and career opportunities awareness, also linking with the University-wide Director of Post-doctoral Affairs (Abell). This latter newly created role will coordinate and develop strategy for the entire postdoctoral community, spearhead fund-raising for post-doctoral specific facilities (see North-West Cambridge project below), and act as an advocate for postdocs in the governance machinery of the University. Since 2008, NIHR funding has enabled 10 academic clinical fellows and 4 academic clinical lecturers to train in these areas. We work within a competitive personal promotion culture, and, as noted above, we have a strong track record of nurturing our early career researchers in UoA2 into permanent academic positions.

Training future leaders We have contributed substantially to national and international capacity-building, as many trainees from Cambridge have assumed leadership positions elsewhere, with some of the more striking career successes of our fellows since 2008 including: K Ray (Professor, St Georges, London), P Myint (Professor, University of Aberdeen), O Franco (Professor, Erasmus University), R Loos (Professor, Mount Sinai Hospital, New York), U Ekelund (Professor, Norwegian School of Sports Sciences), N Sarwar (Global Department Head, Pfizer), A Thompson (Senior Epidemiologist, Roche), L Ishihara (Senior Epidemiologist, GlaxoSmithKline). We promote a culture of research by holding seminar series that cut across disciplines, such as the weekly Bradford-Hill lectures, regular master-class series, and public health grand rounds, complemented by thematic seminar series related to cardiovascular disease, genetic epidemiology, primary care, metabolism, and biostatistics, plus associated journal club meetings.

University support for staff development To provide affordable accommodation for staff and post-graduate students, the £1 billion **Northwest Cambridge Development** was launched in 2013, the largest single capital development project in the University's 800-year history (it will also create 100,000m^2 of collaborative research space to accelerate the "Cambridge Phenomenon", Europe's largest cluster of technology companies). In 2012, the University of Cambridge was the

top-ranked university in the UK in relation to staff development by the Employers Network for Equality and Inclusion. The University values youth, equality and diversity, and works within a culture that embraces the Concordat to Support Career Development of Researchers (for which the University received the EC's Human Resources Excellence in Research Badge in 2011) and Athena SWAN (for which the School of Clinical Medicine received a Silver award in 2013). Heads of departments undergo Equality and Diversity education and pass an assessment before being able to make new appointments. University policies are family-friendly (eg, flexible working; generous maternity/paternity/adoption leave; a Returning Carers Scheme). All staff have inductions and regular career management reviews. We provide support for staff at key career transition points including promotion and sabbatical leave. The University provides a comprehensive range of compulsory and voluntary training schemes for young and mid-career staff, covering research, teaching, administration, and leadership.

ii. Research students The University Graduate School of Life Sciences provides support and oversight for training graduate students, ensuring induction, pastoral care, regular supervision, transferable skills training, and career development. As all our PhD students now engage in 1-year Masters courses followed by a 3-year project-based doctoral programme, we have achieved our aim stated in RAE2008 to complete a transition to 4-year PhD courses. We run three distinct and inter-connected Masters courses (in Epidemiology, Public Health, Primary Care), which, since 2008, have graduated a total of 171 students. We also contribute heavily to the MPhil course in Clinical Research Methods, established in 2009 as part of a £5 million Wellcome Trust / GSK award to the Translational Medicine and Therapeutics programme (director: Brown returned in UoA1). Since 2008, 53 PhD students registered in the University Department of Public Health and Primary Care have graduated (with 90% completing within 3-4 years) and a further 49 PhD students registered with the three MRC Units in UoA2 have also graduated during this period (though we have not counted them in our official total due to HEFCE reporting conventions).

Student recruitment and support As we aim to recruit the most able people from the UK and worldwide, a large proportion of our students are supported by competitive awards, including MRC studentships, Gates Trust, NIH-Cambridge, Cambridge Trust (eg, Commonwealth, Nehru, Yousef Jameel Foundation), Wellcome Trust, Cancer Research UK, British Heart Foundation, NIHR, and overseas governments. Our MPhil courses provide excellent feeders for our doctoral programmes, as well as PhD courses elsewhere. Since 2008, MRC-funded studentships awarded to these MPhil courses have increased 4-fold, including 16 awards for 2012-2015. Students receive the support of a PhD supervisor or supervisory team, senior PhD coordinators in UoA2 (Pharoah, Ong), and personal mentoring from College graduate tutors. Progress is monitored regularly, both through written presentations (eg, a first year report, which is required for registration for the PhD degree upon satisfactory performance) and seminar presentations (eg, students are required to give open seminars at the end of their first and final years, which are well-attended by students and faculty). PhD students are deeply embedded in their host research teams. Access to our rich and varied seminar series is augmented by teaching on entrepreneurism, informatics, computing, and transferable skills by the Graduate School of Life Sciences. Students receive access to excellent IT, library, recreational facilities, and other amenities (eg, subsidised bus routes).

Funding for PhD programmes Since 2008, seven **MRC CASE** industrial "1+3" PhD studentships have been awarded to UoA2: four related to epidemiology for therapeutics in conjunction with GSK and Pfizer (Danesh, Butterworth, Di Angelantonio), two to the epidemiology of physical activity and the genetics of insulin secretion (Wareham, Brage, Langenberg) with Unilever, and one to smoking cessation in collaboration with Unilever (Sutton). Since 2008, there has been a major expansion in 4-year interdisciplinary PhD programmes underpinned by long-term external funding, including those in: cardiovascular science (British Heart Foundation), metabolism (Wellcome Trust), mathematical genomics (Wellcome Trust), as well as those in the area of public health research allied to the Centre for Diet and Activity Research (UK Clinical Research Collaboration), Collaborative Leadership in Applied Health and Care (NIHR), and Public Health Foundation of India-UK initiative (Wellcome Trust). There has also been substantial expansion of MRC Doctoral Training for the MRC Units in Biostatistics and in Epidemiology.

d. Income, infrastructure and facilities Since 2008, a total of £131 million in external research funds has been awarded to groups returned in UoA2, about half of which has been awarded through the University. The MRC provides core support to the MRC Epidemiology Unit (£30M, 2010-2015), MRC Biostatistics Unit (£13M, 2013-2018), and MRC Human Nutrition Research Unit (£22M, 2009-2014). Since 2008, our grant income has become more diversified, exemplified by current programme grant support from: the MRC, Wellcome Trust, NIHR, European Commission, European Research Council, Cancer Research UK, British Heart Foundation, Stroke Association, US NIH, and industry (GlaxoSmithKline, Merck, Novartis, Pfizer). Of the University funds, 20% derive from Research Councils, 41% Research Charities, 19% from NIHR and UK Departments of Health (including NHS R&D and other government departments), 7% from industry, and 13% from EU, NIH or other competitively won international sources.

Population resources Cambridge is the coordinating hub of many important national and international studies which comprise a crucial element of our infrastructure by serving as multi-purpose platforms for epidemiology, public health, and policy research. The portfolio of such resources in Cambridge is unusually broad and deep, encompassing different study designs, geographical locations, risk factors, and disease outcomes. One example of an international Cambridge-led consortium is **the Emerging Risk Factors Collaboration**, which has harmonised individual-participant data on 2.5 million participants in 130 cohort studies, bringing together 250 investigators from 25 countries. This consortium, which evaluates the clinical and population relevance of established and emerging risk factors for vascular disease, has reported >15 papers in NEJM, Lancet, and JAMA since 2008 and influenced nine international cardiovascular guidelines. Other examples include the **Breast Cancer Association Consortium** (300,000 participants), **Consortium of Investigators of Modifiers of BRCA 1/2**, the analysis centre for the **Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome**, and the nascent **Global BMI and Mortality Consortium** (10 million participants).

We have also helped establish and lead multi-purpose prospective studies. One example is the 520,000-participant **EPIC** cohort, in which Cambridge leads studies of type 2 diabetes (**InterAct**), coronary disease (**EPIC-Heart**), and stroke (**EPIC-CVD**). An efficient case-cohort design in EPIC is involving measurement of >1 million genetic variants and hundreds of soluble biomarkers in a random sub-cohort of 15,000 “common controls” who serve as referents for 40,000 incident cases of type 2 diabetes, coronary disease, and stroke. This resource is enabling research programmes on gene-lifestyle interaction, Mendelian randomisation analysis, and disease risk assessment.

Further examples include: **EPIC-Norfolk** (25,000 participants in East Anglia to study healthy ageing), the **Cognitive Function and Ageing Studies** (25,000 participants in the UK with serial detailed cognitive assessments, including a brain bank), and **Fenland** (12,000 participants with serial detailed metabolic assessments). More recently, we have established studies in low- and middle-income countries, eg: **PROMIS** (case-control studies of acute vascular outcomes and diabetes in Pakistan involving >50,000 participants), the **Golestan Cohort Study** (follow-up study of 50,000 people in northern Iran to identify risk factors for oesophageal cancer), and **BRAVE** (case-control study of acute myocardial infarction in Bangladesh, involving 10,000 participants).

We are also closely involved in developing and harvesting the open-access 500,000-participant **UK Biobank** study, eg: Danesh is a member of the UK Biobank Steering Committee and chair of the Outcomes Working Group; Danesh and Wareham are PIs in the UK Cardiometabolic Consortium, which has helped to fund the assay of a genetic array in all participants in UK Biobank. Brayne is a PI in the UK Dementia Platform, which involves UK Biobank.

Facilities and accommodation Scientists in UoA2 can access state-of-the-art laboratory and computing facilities relevant to maintaining and harvesting our large and detailed studies.

i. Laboratory facilities In 2011, the **MRC / NIHR BioRepository** was established to support the storage and rapid retrieval of samples in population studies, and to develop high-throughput multiplex assay capabilities. In 2010, £2 million of funding from the MRC to the MRC Human Nutrition Research Unit established the **Cambridge Lipidomics Initiative**, which is enabling

lipidomics and metabolomics measurements in samples of >50,000 participants. In 2013, our 'omics assays were substantially expanded by the award of £2.5 million to the MRC Epidemiology Unit under the **MRC High-throughput Science call**. To ensure that we can conduct measurements in the time-sensitive manner required in genetic epidemiology, we have access to considerable parallel capacity for genotyping and sequencing (eg, at the Centre for Genetic Epidemiology, Cambridge Genomics Services, Sanger Institute).

ii. Computing facilities Although by conventional standards we have state-of-the-art in-house computing facilities, the computing demands of genomic epidemiology (eg, multi-omics, e-health) are unconventional and massive. Hence, we have established an excellent service-level relationship with the **Cambridge High Performance Computing Cluster**, the largest and fastest academic supercomputer in the UK. As one example, we are accessing this supercomputer to process and analyse data in the 100K Exome+ Consortium, in which very dense genotypic and phenotypic data are being generated in 100,000 people. In 2013 the University commenced a £20 million building programme to accommodate an upgraded version of this supercomputer.

iii. Buildings Since 2008, our expansion has been enabled by the provision of about 500m^2 re-furbished space. We plan to continue embedding elements of epidemiology within thematic institutes to deepen links with clinical sciences, but we also wish to realise other synergies through greater co-location of departments in UoA2. Hence, there are plans to rebuild the former Laboratory of Molecular Biology by 2018 to co-locate most groups in UoA2 in a single state-of-the-art building at the heart of the Cambridge Biomedical Campus (currently, our groups are located in three principal buildings <10 minutes walk from one another, with the exception of the MRC Human Nutrition Research Unit which is located on a science park 3km away). During the next REF period, we plan to achieve greater integration with the MRC Human Nutrition Research Unit, which plans to re-locate to the Cambridge Biomedical Campus by 2016.

e. Collaboration or contribution to the discipline or research base As described above, the activities of interdisciplinary collaboration, partnership with external organisations, and engagement with policy makers are deeply woven into our research strategy.

Interdisciplinarity Our work is closely linked with thematically cognate research returned in other UoAs in the Clinical School, such as in cancer (eg, Ponder in UoA1), cardiovascular disease (eg, Morrell in UoA1), metabolic disease (eg, O'Rahilly in UoA1), and neuropsychiatry (eg, P Jones in UoA4). We have encouraged cross-departmental collaboration by creating joint appointments, eg: Easton and Pharoah have appointments in the departments of Public Health and Primary Care and of Oncology. There are major joint research programmes with non-University MRC Units in Biostatistics (eg, MRC Cognitive Function and Ageing Study) and in Human Nutrition (eg, lipidomics). There are strong collaborations in genetic epidemiology with the Hinxton Genome Campus, again, underpinned by joint appointments (eg, Barroso, Soranzo [both returned in UoA1], Danesh, Sandhu) and collaboration in major research programmes (eg, the UK10K sequencing study). The Public Health Genomics Foundation provides campus-wide input into issues relevant to the evaluation and implementation of evidence-based technologies in healthcare.

We also collaborate with many departments of the University, eg: **Anthropology** (eg, Cohn returned in UoA24, whose appointment is in UoA2) and **Sociology** (eg, Burchell returned in UoA23), both in relation to the health of blood donors; **Philosophy** on causal inference (eg, John returned in UoA32b); **Engineering** on healthcare design (eg, Clarkson returned in UoA15); the **Judge School of Business** on health management (eg, Scholtes returned in UoA19); **Mathematics** on risk communication (eg, Spiegelhalter); and **Chemistry** on sensors to detect atmospheric pollutants (eg, R Jones returned in UoA8).

Multi-institutional collaborations We lead many international scientific collaborations, including complex multi-institutional collaborations. One example is the EU Framework 7 **EPIC-CVD** initiative, which aims to provide policy makers throughout Europe with a menu of evidence-based options for targeted and cost-effective cardiovascular risk assessment approaches tailored to the needs of Europe's diverse populations. There are 30 institutions involved in EPIC-CVD (including universities, not-for-profit research institutes, and small biotechnology companies), an initiative that

involves population, laboratory, translational, and implementation scientists. Another example is the **100K Exome+ Consortium**, which aims to advance discovery and medicines development through genetic epidemiology. This initiative involves several universities worldwide and several industry partners (Merck, Novartis, Pfizer), which have agreed to collaborate in a pre-competitive manner under our leadership. Other examples of multi-institutional international initiatives we lead include: **InterAct** (FP6), the **Collaborative Oncological Gene-Environment Study** (FP7), and the **European Medical Information Network**. This experience should enhance our ability to respond to future calls requiring this expertise, such as EC's Horizon 2020.

Engagement with policy makers As a consequence of increasingly applied research themes, our engagement with policy makers has intensified since 2008. Marteau is scientific adviser to the Cabinet Office Behavioural Insights Team, and, as Director of a DH-funded Policy Research Unit, she provides advice to various policy teams in DH. Mant has chaired development groups for three NICE guidelines (chronic heart failure; acute heart failure; type 2 diabetes), and is adviser to the QOF Indicator Programme. Roland advises the DH on quality indicators to provide publicly available information on the performance of the NHS. S Thompson was member of a DH/CRUK-appointed special committee to advise the government on mammographic screening for breast cancer. Wareham chaired the NICE Public Health Programme Development Group on prevention of diabetes. The Public Health Genomics Foundation provided input into the House of Lord's White Paper on Genomic Medicine in 2009. Danesh has advised the UK Biomedicine Forum on electronic health records. Brayne served on the organising committee of the G8 dementia research summit. Khaw advises the World Economic Forum Global Agenda on Ageing. Wareham was a member of the WHO expert committee on the use of HbA1c in the diagnosis of diabetes. Spiegelhalter advises the European Society of Cardiology on risk communication. Danesh serves on international advisory boards of pharma (Merck, Novartis, Pfizer) and small companies (eg, BioScale). Roland is special adviser to RAND-Europe.

Contributions to the research base Since 2008, we have contributed to the review process both for grant applications and submitted manuscripts through service on:

● **boards of major UK funding agencies**, eg: Chair NIHR Clinician Scientist Panel (Roland), Chair Wellcome Trust Expert Review Group on Society and Health (Marteau), Chair MRC Steering Committees for several cohorts (Khaw), Deputy Chair Wellcome Trust Expert Review Group on Populations/Genetics (Danesh), Deputy Chair NIHR Public Health Research Funding Board (Wareham), MRC Population and Systems Medicine Board (Danesh, Wareham), Wellcome Trust Population Board (Brayne), NIHR Programme Grants Panel (Mant); NIHR In-Practice Fellowship Panel (Mant), CRUK Science Committee (Easton), Breast Cancer Campaign (Pharoah, Antoniou), BHF Trustee (Khaw), BHF Chairs and Programme Grants Committee (Wareham), BHF Projects Grant Committee (Danesh), Diabetes UK Research (Forouhi, Wareham), Alzheimer's research charities (Brayne), MRC Biomarkers and High-throughput Science Panels (Danesh)

● **boards of major international funding agencies**, eg: Genome Canada (Danesh, Easton), French National Cancer Institute (Marteau), Swiss National Science Foundation, Academy of Finland, Netherland Genomics Initiative, Canadian Partnership against Cancer (Khaw)

● **editorial boards of journals**, eg: PLoS Medicine (Danesh), Eur J Epidemiol (Brayne, Danesh), Human Genomics (Danesh), Diabetologia (Wareham), Diabetes (Wareham – Associate Editor), Familial Cancer (Easton), Eur J Cardiovasc Prev Rehab (Khaw), Statist Medicine (S Thompson).

We have contributed substantially to the research base in terms of **scientific leadership**, both for the UK and internationally. Our submission contains 5 Fellows of the Academy of Medical Sciences (S Thompson elected in 2011), Foreign Associate Member of the Institute of Medicine (Roland 2012), and 7 NIHR Senior Investigators (Brayne, Danesh and Wareham since 2008). Examples of other indicators of esteem include: Guy Medal of the Royal Statistical Society in Silver (Richardson 2009), European Research Council Advanced Investigator Award, BHF Personal Chair (Danesh 2011, 2012), Chair of International Society of CVD Epidemiology and Prevention (Khaw 2008-2011). Our scientists are among the highest cited in the world in their disciplines, eg: in 2012, an independent study reported that S Thompson's paper on heterogeneity in meta-analysis was the most cited biostatistics paper of the past decade.