Cardiovascular Research

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Corresponding Author:	Steffen Erhard Petersen, MSc MPH MD DPHIL Queen Mary University of London London, UNITED KINGDOM
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	Queen Mary University of London
Corresponding Author's Secondary Institution:	
First Author:	Steffen Erhard Petersen, MSc MPH MD DPHIL
First Author Secondary Information:	
Order of Authors:	Steffen Erhard Petersen, MSc MPH MD DPHIL
	Zahra Raisi-Estabragh, MBBS
Order of Authors Secondary Information:	

Cardiovascular research highlights from the UK Biobank: Opportunities and Challenges

Zahra Raisi-Estabragh[1,2], Steffen E. Petersen[1,2]

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1. William Harvey Research Institute, NIHR Barts Biomedical Research Centre, Queen Mary University of London, Charterhouse Square, London, EC1M 6BQ, UK

2. Barts Heart Centre, St Bartholomew's Hospital, Barts Health NHS Trust, West Smithfield, EC1A 7BE, London, UK

Biographical sketch

Zahra Raisi-Estabragh is a PhD fellow and trainee Cardiologist at Queen Mary University of London and Barts Health NHS Trust. She is supported by a British Heart Foundation clinical research training fellowship. She holds MBCHB (Hons) from the University of Liverpool and a PG cert. in Medical Education from University College London (UCL).

Steffen E. Petersen is a Professor of Cardiovascular Medicine at the William Harvey Research Institute, Queen Mary University of London and a Consultant Cardiologist and Clinical Director for Research at Barts Heart Centre, Barts Health NHS Trust. He is also the Cardiovascular Programme Director of UCL Partners Academic Medical Centre. He is Vice President of the European Society of Cardiology's (ESC) European Association of Cardiovascular Imaging (EACVI) and chair of the Cardiovascular MRI section. He is the chief specialty editor of Frontiers in Cardiovascular Medicine's Cardiovascular Imaging section. He holds an MBCHB and MDRES equivalent (Dr med.) from Johannes Gutenberg University Mainz, Germany, a DPHIL (OXON) from the Department of Cardiovascular Medicine, University of Oxford, an MPH from Harvard School of Public Health and an MSc in Health Economics, Outcomes and Management in Cardiovascular Science from the London School of Economics.

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Introduction to UK Biobank

UK (United Kingdom) Biobank (UKB) is one of the largest and most comprehensive population studies in the world, incorporating data from over half a million individuals from across the UK recruited between 2006-2010. Participants underwent detailed baseline assessment including characterisation of socio-demographics, health status, blood sampling, and a series of physical measures. Health outcomes for all participants are prospectively tracked through linkages with national cohort sources (death registries, cancer registries, hospital episode statistics, primary care records). Incidence of selected illnesses (e.g. myocardial infarction, stroke) are defined through adjudicated algorithms that incorporate data from self-report, hospital episode statistics, and death registers. Detailed baseline phenotyping of participants includes a comprehensive blood biomarker panel and full genotyping of all 500,000 participants. The dataset has been further enhanced by the UKB imaging study, which aims to image 100,000 of the original UKB participants. The imaging protocol includes magnetic resonance imaging (MRI) of the heart, brain, and abdomen. Since its launch in 2015, over 45,000 individuals have completed the imaging protocol, already making the UKB imaging study the largest imaging bank of its kind. Data from UKB is available to researchers from across the world through a formal access application process.

Opportunities for cardiovascular research

UKB provides unique opportunities for cardiovascular research. The scale and depth of UKB data heralds a new era in cardiovascular epidemiology allowing conduction of robust, high-powered studies with the potential to translate directly to improvements in public health. The large sample allows better definition of existing cardiovascular risk factors and identification of disease patterns that may be diluted or inconsistent in smaller sample sizes. Characterisation of diverse environmental factors in conjunction with genetic data allows for consideration of their combined role in disease causation and the development of generalisable risk scores to better predict and treat disease. In addition, genetic instruments may be used to infer causation between exposure-outcome variables using mendelian randomisation methodologies.

UKB also acts as a platform for scientific discovery. Novel cardiovascular risk factors with small but important impact and potential mechanistic significance can be readily identified and studied. CMR images of UKB participants provide an invaluable resource for evaluating the cardiac consequences of various exposures, but also for the development of innovative image analysis techniques and new imaging biomarkers. Furthermore, the scale of the imaging project provides a platform and motivator for the development and validation of artificial intelligence image analysis algorithms.

The power of UKB will increase with time as increasing number of participants develop disease, however, valuable findings have already emerged from the project and are shaping how we conduct research and think about cardiovascular health. We present highlights from UKB in the last 12 months and discuss upcoming challenges and opportunities.

New insights into existing cardiovascular risk factors

In a UKB mendelian randomisation study, Hendriks et al.[1] present a novel line of evidence supporting a causal relationship between elevated systolic blood pressure and higher left ventricular (LV) mass. Through analysis of biomarker and disease profiles of UKB participants, Welsh et al.[2] demonstrate the clinical utility of lipid testing, particularly, non-HDL (high density lipoprotein) cholesterol in low-risk middle-aged populations. They also observe, that in individuals with multiple vascular risk factors, apolipoprotein B may inform cardiovascular risk not captured by other cholesterol measures. Building on these findings, Ference et al.[3] use genetic risk scores to demonstrate an inverse association between cardiovascular risk and lifetime exposure to lower levels of low-density lipoprotein cholesterol and lower systolic blood pressure. Zhao et al.[4] highlight the potential sex-differential impact of cardiovascular risk factors, reporting a positive association between genetically predicted insulin levels and important cardiovascular outcomes (myocardial infarction, angina, heart failure) in men, but not in women.

Exploring novel cardiovascular risk factors

Karlsson et al.[5] identify visceral adiposity as a causal predictor of important cardiac disease and risk factors (hypertension, heart attack/angina, type 2 diabetes, hyperlipidaemia). Using data from UKB abdominal MRI scans, the authors derived novel loci for visceral adiposity volume (visceral adipose tissue, VAT) and demonstrated higher risk of all four outcomes in individuals with greater genetically predicted VAT and report a causal relationship supported by mendelian randomisation analysis. In a prospective survival analysis, Graham et al.[6] demonstrate greater hazard of first onset cardiovascular disease in individuals with major depressive disease and hypertension than those with hypertension alone, suggesting incorporation of depression into cardiovascular risk scores. Through a prospective and mendelian randomisation study design, Daghlas et al.[7] identify sleep duration as a predictor of myocardial infarction with support for a causal relationship. Jensen et al.[8] present novel insights into diabetic cardiomyopathy demonstrating subclinical remodelling of all four cardiac chambers in diabetic individuals without cardiovascular disease, suggesting a global disease process, rather than a localised condition of the LV. Cox et al.[9] consider the interaction of vascular and brain health, through demonstration of the association of vascular risk factors with adverse brain MRI indices. The presence of genetic data coupled with imaging phenotypes has enabled identification of genetic loci that determine important cardiac phenotypes, which is critical for risk stratification and for the development of novel therapeutic targets. Aung et al.[10] report 14 new genetic loci for LV CMR phenotypes and Fung et al.[11] identified novel loci for arterial stiffness index.

Novel CMR imaging biomarkers

Several groups have used CMR images of UKB participants to develop and validate novel imaging biomarkers. For instance, Cetin et al.[12] have demonstrated the feasibility of CMR radiomics in UKB and demonstrate the ability of CMR radiomics analysis to distinguish between individuals with and without hypertension. In another study, Gilbert et al.[13] explore the impact of cardiovascular risk factors on cardiac remodelling through cardiac morphometric LV atlases derived from UKB CMR scans and demonstrate the superior sensitivity of morphometric scores for detection of differences in LV shape associated with cardiovascular risk factors in comparison to conventional CMR indices.

Developing artificial intelligence CMR image analysis techniques

The UKB CMR bank has been a driver for development of artificial intelligence algorithms for automated CMR image analysis. Chen et al.[14] present a convolutional neural network based segmentation method for analysis of CMR images developed and tested using UKB CMR data. Attar et al.[15] have used UKB CMR scans to develop pipelines permitting scalable fully automated analysis of images.

Challenges and directions for future work

The unique value of UKB derives from linkage of prospectively ascertained outcome data for all participants that is accurate and sufficiently detailed to conduct robust studies and draw meaningful conclusions. The collation and harmonization of health outcome data from the variety of sources with which linkages are established in a scalable manner presents significant challenges for the organisers of UKB, as does the subsequent safeguarding and storage of such data. The scale of the UKB imaging project warrants the development of fully automated image analysis approaches including automated quality control, grading of quality, and automating batch processing of images. This is currently underway, facilitated by positive industry partnerships. The challenge for the scientific community is to adapt through training and collaborations to attain within their teams the skillsets required for handling and analysis of such large datasets. The breadth of data permits imaginative projects and collaborative approach with different disciplines is likely to produce the most novel insights.

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Disclosures

SEP acts as a paid consultant to Circle Cardiovascular Imaging Inc., Calgary, Canada.

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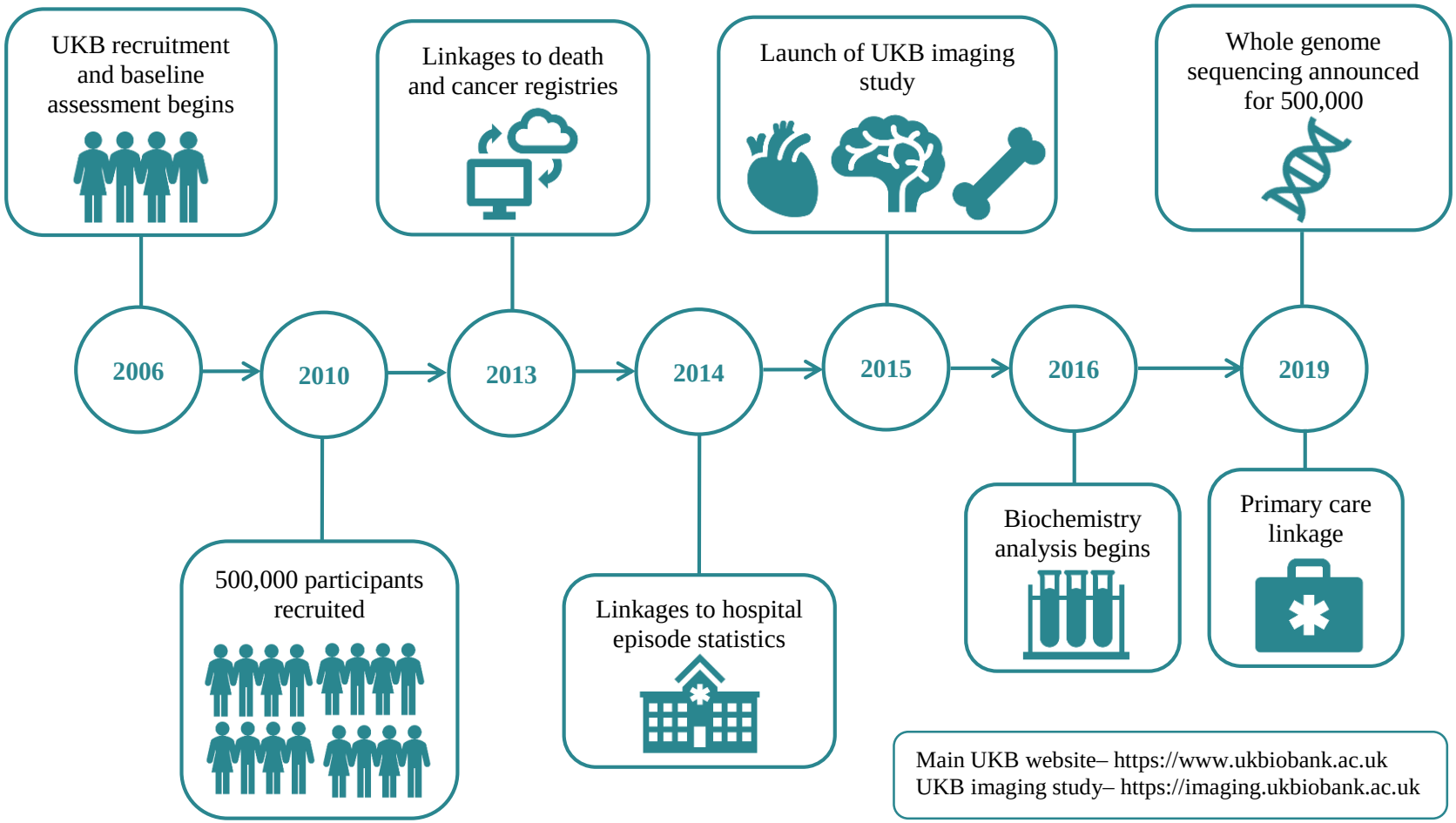
Figure(s)



Central figure. Selected events from the UK Biobank (UKB) timeline

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