Cardiovascular magnetic resonance imaging in the UK Biobank: A major international health research resource

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Abstract

The UK Biobank (UKB) is a health research resource of major international importance, incorporating comprehensive characterisation of over 500,000 men and women recruited between 2006-2010 from across the UK. There is prospective tracking of health outcomes for all participants through linkages with national cohorts (death registers, cancer registers, electronic hospital records, primary care records). The dataset has been enhanced with the UKB imaging study, which aims to scan a subset of 100,000 participants. The imaging protocol includes magnetic resonance imaging of the brain, heart, and abdomen, carotid ultrasound, and whole-body dual x-ray absorptiometry (DXA). Since its launch in 2015, over 48,000 participants have completed the imaging study with scheduled completion in 2023. Repeat imaging of 10,000 participants has been approved and commenced in 2019. The cardiovascular magnetic resonance (CMR) scan provides detailed assessment of cardiac structure and function comprising bright blood anatomic assessment (sagittal, coronal, axial), left and right ventricular cine images (long and short axis), myocardial tagging, native T1 mapping, aortic flow, and imaging of the thoracic aorta. The UKB is an open access resource available to health researchers across all scientific disciplines from both academia and industry with no preferential access or exclusivity. In this paper, we consider how we may best utilise the UKB CMR data to advance cardiovascular research and review notable achievements to date.

Keywords: UK Biobank; cardiovascular magnetic resonance; epidemiology; population health; big data

Introduction to the UK Biobank

The UK Biobank (UKB) comprises a cohort of over 500,000 men and women aged 40-69 years at recruitment (2006-2010). Baseline assessment included a comprehensive series of questionnaires, face-to-face interviews, physical measures, and blood sampling. The full protocol is publicly available[1] and summary data may be viewed on the UKB website: www.ukbiobank.ac.uk. Blood biomarker (haematology, biochemistry) and whole genome sequencing are available for all participants (released 2019). The UKB imaging study was launched in 2015, with the aim of scanning 20% of the original cohort, that is, 100,000 participants[2]. The imaging protocol includes magnetic resonance imaging of the brain, heart, and abdomen, carotid ultrasound, and whole-body dual x-ray absorptiometry (DXA). To date (September 2020), over 48,000 participants have completed the imaging study with scheduled completion by the end of 2023. Repeat imaging of 10,000 participants commenced in 2019 and is also due for completion in 2023. Selected components of the baseline assessment were repeated for a subset of 20,000 participants between 2012-2013 (calibration visit) and at both imaging visits, permitting adjustment for random measurement error and estimation of longitudinal variations.

Health outcomes for all UKB participants are prospectively tracked through linkages with electronic hospital records, cancer registers, death registers, and primary care records. The UKB has also produced algorithmically defined outcomes for incidence of key illnesses, such as myocardial infarction, through cross-checking over multiple data sources[3]. The scale of the UKB and the indefinite follow up of participants means that there should be sufficient numbers of a wide range of incident illnesses for adequately powered nested case-control studies (Table 1)[1], and indeed for prospective cohort analyses for more common outcomes. The documentation of incident outcomes some years after assessment of exposures reduces (although does not remove completely) the chance of reverse causation explaining observed associations. In addition, whilst there is, as is usual with such cohorts, evidence of healthy selection; there is, for the majority of variables, a substantial range

of risk factor levels and disease rates within the UKB population, with sufficient variation to allow adequately powered analyses, which may be generalisable across a range of demographics[4,5].

The UKB is an open access resource available to health researchers across all scientific disciplines from both academia and industry with no preferential access or exclusivity. New researchers can find details on formal access procedures (including the modest access charges based on a cost recovery model) on the UKB website: www.ukbiobank.ac.uk.

Thus, the UKB comprises a very large sample phenotyped in great detail at multiple time-points using a variety of methods and linked to prospectively verified health outcomes (Figure 1), available at minimal cost to all bona fide researchers globally. The unique combination of this level of breadth, depth, and scale in a single dataset makes for a powerful research resource. In this paper, we consider how we may best utilise the cardiovascular magnetic resonance (CMR) data in conjunction with all the other information in the UKB to advance cardiovascular research and review notable achievements to date.

The UK Biobank CMR protocol

The UKB imaging study is conducted across four UK sites (Reading, Stockport, Newcastle, Bristol) using uniform equipment, staff training, and acquisition protocols. The purpose-designed CMR protocol consists of a 20-minute scan performed using a 1.5 Tesla scanner (MAGNETOM Aera, Syngo Platform VD13A, Siemens Healthcare, Erlangen, Germany). The practical and ethical considerations posed by the large scale and observational nature of the UKB preclude the use of contrast or stress agents. The rationale, challenges, and details of the CMR protocol are described in dedicated publications[6,7]. The protocol includes bright blood anatomic assessment (sagittal, coronal, axial), left and right ventricular cine images (long and short axis), myocardial tagging (three short axis slices), native T1 mapping, aortic flow, and imaging of the thoracic aorta (Table 2).

Conventional right and left ventricular (RV, LV) indices such as chamber volumes, ejection fraction, and LV mass may be derived from the short axis cine stack. LV end-diastolic volume is an important indicator of adverse cardiac remodelling[8]. Ejection fraction[9] and LV mass[10] are established prognostic markers. Tagging sequences allow measurement of strain, which reflects myocardial contractile function at a more granular level compared to conventional indices, such as, ejection fraction[11]. As such, alterations in myocardial strain may be appreciated at earlier or subclinical disease stages[12,13]. Feature tracking techniques using long and short axis cine images are an alternative method of deriving measures of myocardial strain. They use block-matching algorithms to estimate myocardial motion by marking regions of interest along the myocardial boundaries. Feature tracking does not directly label tissue in the same way as tagging, however, post-processing is considerably faster, and estimates are adequately reliable for appreciation of associations[14]. The long axis cine images may also be used to obtain measures of atrial size and function, such as left atrial ejection fraction, which are reliable predictors of atrial fibrillation in the general population[15]. This is important, as atrial fibrillation is the most common cardiac arrhythmia, particularly in older populations, with significant clinical consequences, such as the need for anticoagulation and increased risk of stroke[16]. Native T1 mapping allows for myocardial tissue characterisation without the need for contrast administration, specifically, identification of areas of fibrosis and/or infarction[17]. Myocardial fibrosis has been linked to a number of cardiac diseases and is a marker of adverse cardiovascular outcomes such as ventricular arrhythmias and death[18]. Infarction reflects underlying ischaemic cardiomyopathy and is also linked to increased cardiovascular risk[19]. Aortic flow sequences permit assessment of aortic valve anatomy and function, in particular valvular stenosis. Aortic stenosis is the most common valvular pathology in older individuals, with adverse prognostic consequences and potential for alteration of its natural history with timely intervention[20]. Aortic distensibility, a measure of vascular compliance, may be derived from transverse cine images of the thoracic aorta through consideration of the relative cross-sectional area change of the aorta (aortic strain) per unit pressure[21]. Aortic distensibility reflects aortic bioelastic function with lower distensibility indicating a less compliant aorta and poorer vascular health[22]. There is an inverse association between aortic distensibility and cardiovascular risk,

specifically, ischaemic heart disease and stroke[23]. Thus, aortic distensibility provides a continuous measure of ischaemic cardiovascular risk across the population.

In summary, the UKB CMR protocol provides a comprehensive assessment of cardiovascular health, providing measures of cardiac structure, function, and tissue characterisation alongside multiple prognostic indices, biomarkers of subclinical disease, and indicators of important conditions such as atrial fibrillation and aortic stenosis. The CMR imaging phenotypes allow objective assessment and quantification of exposure effects on cardiovascular health and permit finer delineation of disease trajectories with potential for disease-specific assertions.

Manual analysis of the first 5,000 CMR scans

Manual segmentation of all four cardiac chambers has been completed for the first 5,000 UKB CMR scans. Analysis was across two core laboratories (London, Oxford) according to a pre-defined protocol in line with international guidance[24]. The analysis protocol is available in a separate publication[25]. Readers across both sites received dedicated training and standardised quality control procedures were implemented. In this way, a 5,000 subject manual analysis ground truth database was created. This dataset has been utilised to derive age- and sex-specific CMR normal reference ranges for the LV, RV, and atria in the largest reported cohort of validated healthy adults[25]. The UKB CMR dataset has also resulted in a number of significant achievements providing novel insights into classical and non-classical cardiovascular risk factors, and enabling development and evaluation of novel CMR biomarkers and automated image analysis pipelines (Supplementary Table 1)[26].

Novel insights into classical cardiovascular risk factors

A number of researchers have used the UKB CMR dataset to provide new insights into classical cardiovascular risk factors. For instance, Petersen et al.[27] define and quantify alterations in cardiac structure and function associated with known modifiable cardiovascular risk factors in individuals without pre-existing cardiovascular disease, reporting greatest effects with systolic blood pressure and body mass index. Building on these observations, Jensen et al.[28] present novel insights into diabetic

cardiomyopathy, demonstrating subclinical remodelling of all four cardiac chambers in diabetics without known cardiovascular disease. In a study assessing the causality of previously established associations between increased systolic blood pressure and adverse LV remodelling, Hendriks et al.[29] use the genetic data in UKB to demonstrate a novel line of evidence supporting a causal relationship between elevated systolic blood pressure and higher LV mass. Linkage with the genetic data has also enabled discovery of 14 genetic loci corresponding to prognostically important LV phenotypes including end-diastolic and end-systolic volumes, mass, and ejection fraction, enhancing understanding of the genetic architecture of cardiac phenotypes and providing insights into potential novel therapeutic targets[30].

Investigating non-classical cardiovascular risk factors

The scale of UKB and detailed characterisation of participants has enabled assessment of the effects of non-classical cardiovascular risk factors on CMR phenotypes, providing insights into novel determinants of cardiovascular disease. In a study of 1,406 individuals without cardio-respiratory disease, Thomson et al.[31] report association of poorer respiratory function by spirometry with adverse ventricular remodelling. Somewhat linked to these observations, Aung et al.[32] report association of adverse cardiac phenotypes with past exposure to poorer air quality in 3,920 individuals without clinical cardiovascular disease. Khanji et al.[33] present the first study of cardiac phenotypes associated with recreational cannabis use, demonstrating larger LV volumes and impaired circumferential strain in regular cannabis users compared with never/rare users. Van Hout et al.[34] consider the abdominal magnetic resonance images in UKB alongside the CMR data to investigate the relationship of body fat distribution with cardiac structure and function, demonstrating the importance of visceral obesity (vs. subcutaneous adiposity) and its association with smaller LV end-diastolic volumes and lower systolic cardiac function. In a study incorporating biochemistry, imaging, and clinical outcome data, Raisi-Estabragh et al.[35] demonstrate association of poorer bone health with worse arterial health and adverse ischaemic cardiovascular outcomes and explore potential mediating mechanisms of these relationships. The UKB data has also been used to explore the association of cardiac health to other

non-classical cardiovascular risk factors such as menopausal hormone therapy, spontaneous pregnancy loss, and resting heart rate[36–38].

Development of novel imaging biomarkers

Several researchers have used the UKB CMR platform to investigate novel imaging biomarkers. Cardiac morphometric atlases are derived from existing CMR data and provide statistical shape models of the heart with highly detailed morphometric information[39]. LV cardiac atlas morphometrics have been associated with a number of important cardiovascular risk factors[40]. In the first study to compare cardiac atlases derived using different methodologies, Gilbert et al.[41] use the UKB dataset to demonstrate robust associations between cardiac atlas shape measures and cardiovascular risk factors irrespective of methodology. Further, they demonstrate superior performance of cardiac atlas morphometric scores for detection of differences in LV shape associated with cardiovascular risk factors compared to conventional CMR shape indices. Building on this work, Mauger et al.[42] used the UKB dataset to quantify reference RV morphometry and demonstrate complex relationships between biventricular shape and cardiovascular risk factors (Figure 2).

CMR radiomics is another novel image analysis technique whereby voxel-level information is used to derive multiple quantifiers of shape and texture (Figure 3)[43]. There is no requirement for dedicated acquisitions or post-processing and radiomics analysis may be retrospectively applied to existing CMR images. Machine learning techniques are often used to incorporate the many extracted radiomics features (usually 100s) as covariates into clinical prediction models. CMR radiomics models have demonstrated incremental diagnostic and predictive value in comparison to conventional methods for a number of important cardiovascular conditions[43]. Cetin et al.[44] have used data from the UKB to demonstrate the superior performance of CMR radiomics models, compared to conventional CMR indices, in discriminating individuals with hypertension from healthy comparators.

Artificial intelligence technologies for automated image analysis

The large volume of data in the UKB image bank necessitates the development of automated image analysis pipelines that are scalable, require minimal manual interaction, and have standardised quality control measures. The 5,000 reference cohort and their corresponding contours have enabled development and evaluation of machine learning methods for cardiac chamber segmentation with some promising results[45]. In particular, Attar et al.[46] present a fully automatic pipeline performing end-to-end analytics from cine images to anatomic and functional quantification (LV, RV) on 20,000 UKB CMR scans validated against the ground truth cohort of manual segmentations. A fully automated image analysis tool for measurement of aortic distensibility has also been developed and validated on a large subset of UKB studies (*n*=5,100); the analysis pipeline can detect and locate aortic areas and has in-built quality control mechanisms[47].

In addition to these purpose-built pipelines, fully automated LV quantification is performed as part of UKB image acquisitions using the Siemens syngo InlineVF software (Siemens Healthcare, Erlangen, Germany, version D13A). The InlineVF analysis algorithm determines the LV endocardial contours on the short axis slices, defines the LV base (mitral valve) and apex on long axis slices, and outputs standard LV indices (volumes, ejection fraction, stroke volume). Whilst raw results from this analysis are provided by the UKB, the InlineVF software is intended for use in clinical settings with expert assessment of contour quality. Therefore, it is advisable to apply quality control measures to the fully automated outputs of UKB. After formal evaluation of the InlineVF outputs, we recommend that these be used with implementation of visual assessment for quality control and linear bias correction[48].

Potential for future work

In order to best utilise the UKB, we must consider the resource in its entirety and appreciate the complementary value of its different components. The scale and extensive participant phenotyping in UKB permits consideration of a large number of exposures and their potential interactions with many disease conditions. These research opportunities will increase as incident disease outcomes accrue and the imaging study is completed. The breadth, depth, and scale of phenotypic information in UKB also

yields unique opportunities to investigate relationships of risk factors acting across organ systems. There is increasing interest in exploration of cross-system interactions with notable work exploring the heart-brain[49] and heart-gut[50] axes. Already, researchers have demonstrated links between cognition and structural brain MRI features and cardiac health in the UKB[51]. As disease outcomes accrue within the UKB cohort, there will be greater opportunity to explore these important cross-system interactions.

The large standardised UKB imaging datset provides an ideal platform for development and evaluation of automated image analysis pipelines. Artificial intelligence technologies for high volume image phenotype extraction could translate readily to clinical settings, improving time and resource efficiency. Substantial progress has been made with automated extraction of conventional ventricular indices and aortic distensibility in the UKB. Similar work is underway to develop scalable automated processes for analysis of tagging, native T1 mapping, tissue tracking, and aortic flow sequences. These areas have not yet been published on and are ripe for exploration. The dataset is also the ideal setting for development of novel CMR biomarkers. In addition to providing a platform for technical development, linkage to participant characteristics and outcomes uniquely enables assessment of clinical utility within the same sample.

Conclusions

The UKB presents the opportunity to examine prospectively, in a single, robustly powered and characterised cohort, a wide range of exposure-outcome relationships and the potential interactions between them. As incident health outcomes accrue, and the imaging study is completed, UKB will offer huge opportunities to undertake highly powered studies to comprehensively investigate the determinants of cardiovascular disease. It is now up to the imagination and expertise of researchers to translate this unique resource into real benefits for our patients and thus reduce the burden of cardiovascular disease worldwide.

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Table 1. Estimated number of years from baseline to accrue cases of selected conditions in UK Biobank*

	Time to achieve				
	1,000 cases	2,500 cases	5,000 cases	10,000 cases	20,000 cases
MI and coronary death	2 years	4 years	5 years	8 years	13 years
Stroke	5 years	8 years	12 years	18 years	28 years
Diabetes mellitus	2 years	3 years	4 years	6 years	10 years
COPD	4 years	6 years	8 years	13 years	23 years
Colorectal cancer	5 years	9 years	14 years	22 years	42 years
Hip fracture	7 years	11 years	15 years	21 years	31 years
Alzheimer's disease	7 years	10 years	13 years	18 years	23 years
Parkinson's disease	6 years	10 years	15 years	23 years	37 years

Table 1 caption: COPD: chronic obstructive pulmonary disease; MI: myocardial infarction.

*Estimated years from start of recruitment in 2006 with allowance for healthy cohort effect, overseas migration and comprehensive withdrawal of 1 in 500 participants. Adapted from: UK Biobank: Protocol for a large-scale prospective epidemiological resource (2007)[1].

Table 2. Summary of UK Biobank cardiac magnetic resonance imaging protocol

	Sequence	Imaging planes	Related CMR indices	Clinical utility
Anatomic assessment	Bright blood, bSSFP	Sagittal, coronal, and transverse slices covering the chest and abdomen	Modified anatomic measures e.g. aortic dimensions, lung diameters	Markers of aortic/pulmonary disease
Cardiac function	bSSFP cine	HLA, VLA, LVOT (sagittal, coronal), short axis stack covering the right and left ventricles	RV/LV: volumes, ejection fraction, stroke volume; LV mass	Conventional markers of cardiac remodelling and function with established prognostic significance.
			Atrial size and function	Predictors of AF in the general population
			LV strain (tissue tracking)	Early marker of myocardial dysfunction
Tagging	Strain CMR (GRE)	Three short axis slices (base, mid, apex)	LV strain (tissue tagging)	Early marker of myocardial dysfunction
Thoracic aorta	bSSFP cine	Transverse cut at the level of the pulmonary trunk and right pulmonary artery	Aortic distensibility at the ascending and descending aorta	Markers of cardiovascular risk, in particular ischaemic disease
Aortic flow	Phase contrast flow (GRE), VENC set at 2m/s with upward adjustment as needed	Cut plane placed at or just above the sinotubular junction at end-diastole in LVOT views (sagittal, coronal)	Aortic flow	Aortic valve anatomy and assessment of aortic stenosis
Native T1 mapping	ShMOLLI (WIP780B)	Mid-ventricular short axis	Native T1 values	Indicator of myocardial fibrosis/infarction-markers of cardiovascular disease and risk.

Table 2 footnote: AF: atrial fibrillation; bSSFP: balanced steady state free precession; GRE: gradient echo; HLA: horizontal long axis; LV: left ventricle; LVOT: left ventricular outflow tract; m/s: meters/second; RV: right ventricle; ShMOLLI: Shortened Modified Look-Locker Inversion recovery; VENC: velocity encoding; VLA: vertical long axis.

Figure legends

Figure 1: No legend required.

Figure 2: Adapted from Mauger et al. 2019[42]. Panel A: hypertension; Panel B: no hypertension; models in end-diastole (left) and end-systole (right); the colours denote displacements from the mean in mm. Blue - inwards 3mm; red -outwards 3mm.

Figure 3: Radiomics features may be extracted from a defined region of interest. In this example, the left (orange) and right (green) ventricular endocardial and left ventricular epicardial (blue) contours are drawn in end-systole on the short axis stack cine images. Thus, defining three regions of interest: left ventricular blood pool, right ventricular blood pool, and left ventricular myocardium. Radiomics shape features are extracted from a 3D image mask constructed from these contours. Histogram based first-order features and more complex texture features are derived from analysis of the distribution and pattern of voxel signal intensities in the defined regions of interest. Figure courtesy of: Dr. Polyxeni Gkontra and Prof. Karim Lekadir, University of Barcelona.

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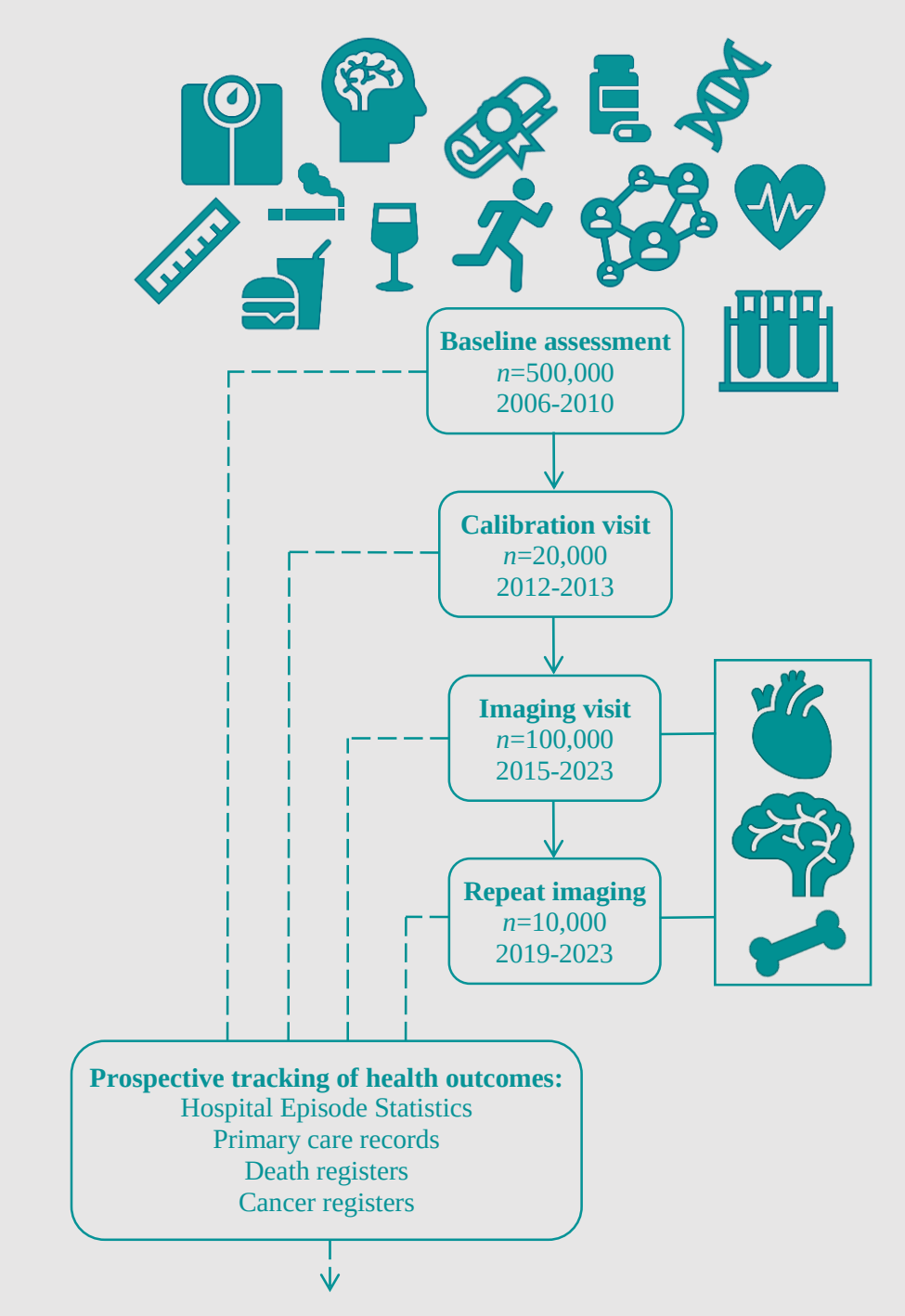
Figure

Figure 1. Approach to participant phenotyping in the UK Biobank



Figure

Figure 2. Cardiac atlas models demonstrating morphometric differences in UK Biobank participants with and without hypertension*

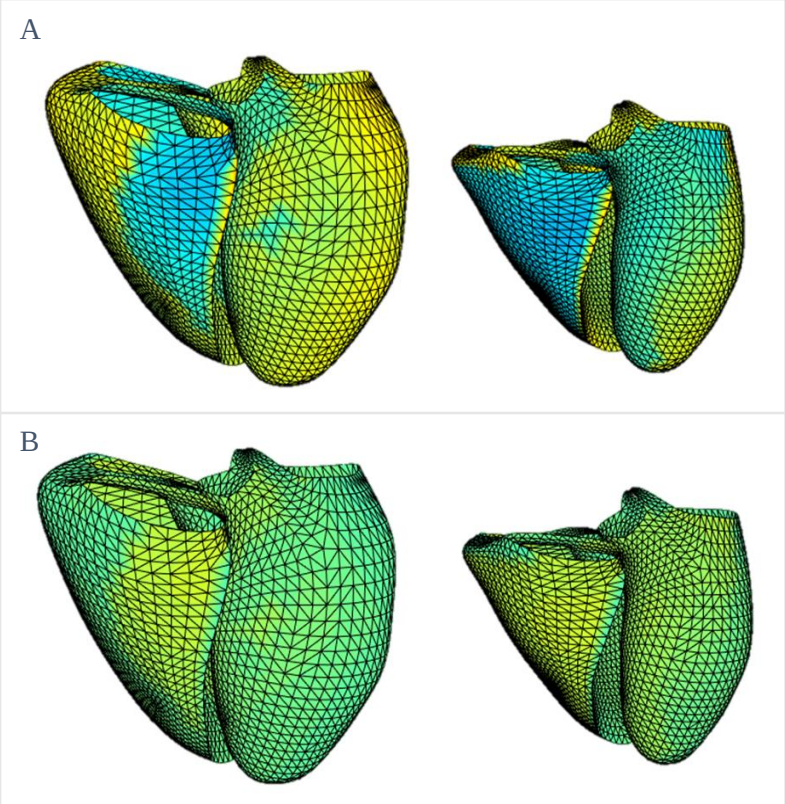


*Figure 2 caption: Adapted from Mauger et al. 2019[39]. Panel A: hypertension; Panel B: no hypertension; models in end-diastole (left) and end-systole (right); the colours denote displacements from the mean in mm. Blue - inwards 3mm; red -outwards 3mm.

Figure

Figure 3*. Summary of typical cardiovascular magnetic resonance radiomics feature extraction workflow

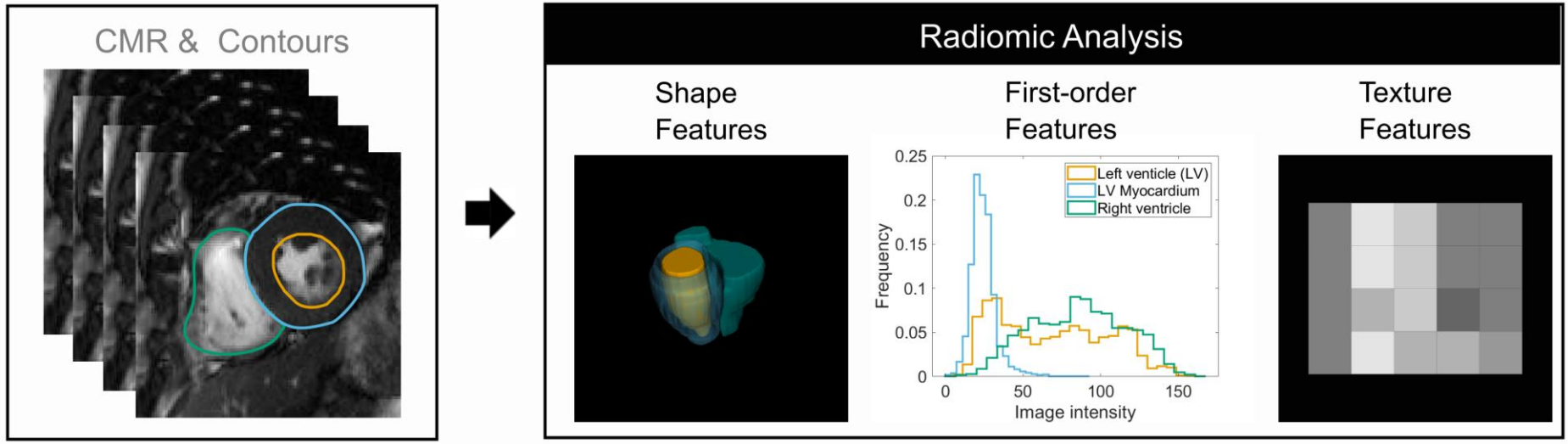


*Figure 3 caption: Radiomics features may be extracted from a defined region of interest. In this example, the left (orange) and right (green) ventricular endocardial and left ventricular epicardial (blue) contours are drawn in end-systole on the short axis stack cine images. Thus, defining three regions of interest: left ventricular blood pool, right ventricular blood pool, and left ventricular myocardium. Radiomics shape features are extracted from a 3D image mask constructed from these contours. Histogram based first-order features and more complex texture features are derived from analysis of the distribution and pattern of voxel signal intensities in the defined regions of interest. Figure courtesy of: Dr. Polyxeni Gkontra and Prof. Karim Lekadir, University of Barcelona.

Supplementary Table 1. Summary of selected studies using UK Biobank CMR data

Author, year of publication	Research question/aim	Methods	Summary of findings
Raisi-Estabragh et al. 2020	What is the association of speed of sound from quantitative heel ultrasound with measures of arterial stiffness (AoD, ASI) and with ischaemic cardiovascular outcomes and what are the mediating factors?	Mutivariable linear regression models of the association between speed of sound and ASI/AoD. Cox/competing risk regression models to test association of speed of sound with incident myocardial infarction and ischaemic heart disease death. Subanalysis by sex and menopause status. Multiple mediation analysis to examine mediating effect of a range of biochemical variables.	Findings support a positive association between bone and vascular health with consistent patterns of association in men and women. The underlying mechanisms are complex and appear to vary by sex.
Hout et al. 2020	What is the association of body fat distribution with cardiovascular structure and function?	Multivariable regression models were used to test the association of subcutaneous adiposity, visceral adiposity and body fat percentage with CMR cardiovascular phenotypes in 4,590 UKB participants.	Visceral obesity was associated with a smaller LV EDV and subclinical lower LV systolic function in men, suggesting that visceral obesity might play a more important role compared to general obesity in LV remodelling.

Biasiolli et al. 2019	To develop and validate a fully automated method to detect and localise the ascending and descending aorta for AoD measure with a quality control mechanism.	The automated AA and PDA detection-localization algorithm followed these steps: 1) foreground segmentation; 2) detection of candidate ROIs by Circular Hough Transform; 3) spatial, histogram and shape feature extraction for candidate ROIs; 4) AA and PDA detection using Random Forest (RF); 5) quality control based on RF detection probability. The algorithm was tested on 3,900 UKB CMR scans.	The proposed method for automated AA and PDA localization was extremely accurate and the automatically derived detection probabilities provided a robust mechanism to detect low quality scans for further human review.
Attar et al. 2019	To develop and evaluate a fully automated CMR image analysis pipeline.	The authors present and evaluate a fully automatic scalable CMR image analysis pipeline with inbuilt quality control using 20,000 cases from the UKB for LV/RV quantification. The pipeline is validated on 4,620 manually annotated UKB cases.	The presented pipeline performs end-to-end image analytics from multi-view cine CMR to LV/RV quantification without need for manual user interactions, with quality control of image input and outputted segmentations.
Jensen et al. 2019	What are the early alterations in cardiac structure and function associated with DM?	Multivariable regression models were built to ascertain the association of DM status with CMR phenotypes in a subpopulation without pre-existing cardiovascular disease and LVEF $\geq$ 50% (n=3984)	In a low-risk general population without known cardiovascular disease and with preserved LV ejection fraction, DM was associated with early changes in all 4 cardiac chambers.

Hendriks et al. 2019	What are the effects of lifelong exposure to high SBP on LV structure and function?	A genetic risk score to estimate genetically predicted SBP (gSBP) was constructed based on 107 previously established genetic variants. Manual CMR image analysis was performed for 300 individuals at the extremes of gSBP. Multivariable linear regression analyses of imaging biomarkers were performed using gSBP as continuous independent variable.	This study provides a novel line of evidence for a causal relationship between SBP and increased LV mass and with increased LV global radial strain.
Aung et al. 2019	What is the genetic basis of LV image-derived phenotypes?	Genome wide association study of LVEDV, LVESV, LVEF, and LVM, using 16,923 CMR cases from the UK Biobank and genotyping data at baseline.	14 novel genetic loci were identified for LV CMR phenotypes.
Khanji et al. 2019	What is the association of cannabis use with cardiovascular structure and function on CMR?	Multivariate regression models were used to test effect of regular, never/rare, or previous cannabis use on CMR cardiovascular indices in a sample of 3,407 UKB participants.	Regular cannabis use was associated with larger LVEDV, LVESV, and impaired global circumferential strain compared with rare/no cannabis use.
Elmahi et al. 2019	What is the association between history of pregnancy loss and imaging	Multivariable linear regression models were used to test association between self-reported pregnancy loss and CMR measures of cardiac structure and function and	In this analysis, women who self-report pregnancy loss did not have significant differences in cardiac

	measures of cardiovascular function?	carotid ultrasound measures of arterial health in 2660 women from UKB.	structure, cardiac function, or carotid structure in later life.
Gilbert et al. 2019	What are the associations of cardiac atlas morphometric measures with cardiovascular risk factors and do these vary by type of atlas?	Two independent LV atlases were constructed from 4,547 UKB CMR scans. The strength of associations between atlas principal components and cardiovascular risk factors (smoking, DM , high blood pressure, high cholesterol and angina) were quantified with logistic regression models. Comparison was made between different atlases.	Morphometric variations associated with each risk factor could be quantified and visualized and were similar between atlases. UK Biobank LV shape atlases are robust to construction method and show stronger relationships with cardiovascular risk factors than mass and volume.
Mauger et al. 2019	What are the associations between cardiovascular disease risk factors and the biventricular cardiac atlas morphometrics?	A biventricular shape atlas was automatically constructed using contours and landmarks from 4,329 UKB CMR studies. A reference sub-cohort was identified consisting of 630 participants with no cardiovascular risk factors. Morphometric scores were computed using linear regression to quantify shape variations associated with high cholesterol, high blood pressure, obesity, smoking, DM, previous myocardial infarction and angina.	Morphometric relationships between biventricular shape and cardiovascular risk factors in a large cohort show complex interactions between RV and LV morphology. These can be quantified by z-scores, which can be used to study the morphological correlates of disease.

Bai et al. 2018	To develop automated methods for CMR cardiac chamber segmentation?	Aa fully convolutional network was trained and evaluated on a 4,875 CMR studies from the UK Biobank to develop a fully an automated analysis method for segmentation of LV, RV, LA, and RA.	The presented automated method achieves a performance on par with human experts in analysing CMR images and deriving clinically relevant measures.
Sanghvi et al. 2018	What is the effect of menopausal hormonal therapy on CMR cardiovascular phenotypes?	Multivariable linear regression was performed to examine the relationship between CMR cardiac parameters and menopausal hormonal therapy use ≥ 3 years in 1,604 postmenopausal women from UKB.	Menopausal hormonal therapy use was not associated with adverse, subclinical changes in cardiac structure and function
Aung et al. 2018	What is the effect of exposure to ambient air pollution on CMR cardiovascular phenotypes?	Multivariable linear models were built to test association of previous exposure to ambient air pollution on CMR indices of cardiac structure and function in 3,920 UKB participants without pre-existing cardiovascular disease.	Higher past exposure to particulate matter with an aerodynamic diameter <2.5 μm and nitrogen dioxide was associated with cardiac ventricular dilatation, a marker of adverse remodelling.
Thomson et al. 2018	What is the relationship between lung function and CMR cardiovascular phenotypes in individuals without respiratory disease?	Multivariable linear models were built to test association of spirometry measures of lung function (obtained at baseline UKB visit) with CMR indices of cardiac structure and function in individuals without respiratory disease (n=1,406)	This study shows that reduced FEV1 and FVC are associated with smaller ventricular vol- umes and reduced ventricular mass. The changes seen per standard deviation change in FEV1 and FVC are comparable to one decade of ageing.

Petersen et al. 2017	What is the impact of classical cardiovascular risk factors on cardiac CMR phenotypes?	Multivariable regression models were built to ascertain the association of risk factors (Age, sex, ethnicity, SBP, DBP, smoking status, exercise, BMI, high cholesterol, DM, alcohol intake) on LV, RV, LA and RA CMR parameters in 4,651 UKB participants.	Modifiable risk factors are associated with subclinical alterations in structure and function in all four cardiac chambers. BMI and SBP were the most important factors affecting CMR parameters known to be linked to adverse outcomes.

Supplementary Table 1 caption: AA: ascending aorta; AoD: aortic distensibility; ASI: arterial stiffness index; BMI: body mass index; CMR: cardiovascular magnetic resonance; DM: diabetes mellitus; EDV: end-diastolic volume; FEV1: forced expiratory volume 1; FVC: forced vital capacity; LA: left atrium; LV: left ventricle; LVEF: left ventricular ejection fraction; LVM: left ventricular mass; PDA: proximal descending aorta; RA: right atrium; ROI: region of interest; RV: right ventricle; SBP: systolic blood pressure; UKB: UK Biobank