ADVANCES IN POPULATION-BASED IMAGING USING CARDIAC MAGNETIC RESONANCE

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ABSTRACT

Large population-based studies have helped to identify cardiovascular risk factors and to understand the natural progression of diseases. Cardiac magnetic resonance (CMR) is the reference method for the assessment of ventricular morphology and function given the low variance between scans. In addition, advanced sequences such as MR tagging, T1 mapping, and late gadolinium enhancement allow to assess regional ventricular function and fibrotic changes. MESA was the first study to use CMR on a large scale in a sample of the general population. Subsequent studies focused on cohorts of particular ethnicities or from certain locations with the Jackson Heart Study looking at African-Americans and the Dallas Heart Study at Dallas County Residents. More recently, the German National Cohort and UK Biobank have started to perform CMRs in a significantly larger number of participants (30,000 and 100,000, respectively). The introduction of CMR into prospective cohort studies has allowed to characterize ventricular remodeling in individuals of different age, sex, and gender and has found associations with new environmental exposures. The ability to detect subclinical changes in asymptomatic individuals has also been highlighted by reports of a high number of missed myocardial infarctions (MI) using CMR. In this review, we discuss the use of CMR in the different large population-based studies and compare the various associations found with left and right ventricular structure and function. In addition, we outline automated image analysis strategies aimed at overcoming challenges posed by the large amount of data in population-based studies.

Keywords: CMR; cardiac magnetic resonance; cohort studies; population-based studies

INTRODUCTION

Chronic cardiovascular diseases such as myocardial infarction or heart failure are associated with significant morbidity and mortality. Prospective cohort studies help to identify risk factors associated with the development of those conditions and may allow to characterize high risk individuals for targeted intervention. Early cohort studies such as the Framing Heart Study characterized major cardiac risk factors including smoking[1] and different hypertension phenotypes[2]. More recent studies also include different cardiac imaging techniques including coronary artery calcium scores, echocardiography and cardiac magnetic resonance (CMR)[3,4] in addition to the standardized questionnaires and exams. These approaches have allowed to characterize early changes in cardiac phenotypes and to find novel associations with cardiac risk factors[5]. Further, they have helped to prognosticate long-term outcomes based on specific imaging biomarkers[6].

This review describes the use of CMR across large-scale prospective population studies, highlights novel associations found in the setting of the wide application of those imaging techniques, and discusses novel automated image analysis strategies to overcome challenges posed by the large amount of data obtained in population-based studies.

LARGE-SCALE PROSPECTIVE POPULATION STUDIES THAT HAVE USED CMR

Patient selection and follow up

The first prospective cohort study to use CMR to study cardiac morphology and function was the Multi-Ethnic Study of Atherosclerosis (MESA)[7]. It included a total of 6,814 asymptomatic individuals aged 45-84 who have been followed since 2000-2002[8]. The study included participants of four different ethnicities: Approximately 38% are white, 28% are African-American, 22% are Hispanic, and 12% are Asian. CMR was performed on 5,004 participants at baseline. 3,016 participants also underwent a repeat CMR after approximately 10 years, making it the only large population-based study allowing to study longitudinal changes in cardiac morphology and function. Of note, repeat CMR scans were performed with steady-state free precession (SSFP) cine sequences, while a gradient echo (GRE) cine sequence was used as baseline. The study's CMR protocol is also notable for the additional use of intra-venous (IV) contrast which allowed to better characterize myocardial fibrosis using T1 mapping and late gadolinium enhancement [9]. In addition, MR tagging was performed, a technique that is used to evaluate regional myocardial function.

While MESA included participants of different ethnicities, the Jackson Heart Study investigated cardiovascular disease (CVD) risk factors exclusively in African-Americans, a group with higher rates of CVD and cardiovascular (CV) risk factors than the general population[10]. The study consisted of 5,301 men and women enrolled between 2000 and 2004 [11]. 1,672 participants underwent CMR around 9 years after the baseline visit. Similar to MESA, contrast-enhanced MRI was performed, but only in a subset of individuals with CMR.

The discrepancies between different ethnicities were further studied in the Dallas Heart Study, a multiethnic cohort which enrolled 6,101 Dallas County Residents between 2000 and 2002 [12,13]. African-Americans were oversampled to represent 50% of the final cohort. CMR was performed on a sample of 2,971 participants aged 30-65. Of note, the study was later transformed from a cross-sectional into a longitudinal study and is still ongoing, but CMR has not been repeated.

The two epidemiological studies with the highest number of participants are the UK Biobank and the German National Cohort. Both are in their early phases. The UK Biobank recruited more than 500,000 men and women aged 40-69 between 2006 and 2010 in the UK[4]. A random subset of those participants have been invited back for comprehensive imaging visits including a CMR examination with the goal to perform 100,000 CMR scans by 2023 [14]. The German National Cohort is currently recruiting 200,000 participants of the general population aged 20-69. 30,000 randomly selected participants are undergoing whole-body MRI at the baseline visit and possibly at a follow-up visit 4-5 years later[15,16]. Neither of those studies is performing contrast-enhanced CMR. The German National Cohort is, however, the only large population-based study that will use 3 Tesla MRI machines for CMR.

Other cohort studies that performed CMR include the Study of Health in Pomerania (SHIP)[17], a study of residents in the German region Pomerania, Age, Gene/Environment Susceptibility (AGES)-Reykjavik[18], a study of Icelanders, Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS)[19], and the Framing Heart Study Offspring cohort[20]. While CMR scanning has been completed for all of these studies, clinical follow up is still ongoing. Large cohort studies that are being planned or that are in their very early stages are the Hamburg City

Health Cohort Study[21] and the Canadian Alliance of Healthy Hearts and Minds[22]. Further details are summarized in Table 1.

Table 1. Large-scale cohort studies (>1,000 participants) that have used CMR.

Study	Population	CMR participants	Time of CMR	CMR protocol	Length of follow up since CMR imaging
MESA[3,7,23]	6,814 asymptomatic men and women (ages 45-84) of 4 different ethnicities without known CVD	Baseline: 5,004 Follow up: 3,016 (completed)	At baseline visit and after ~10 years (2010-2012)	1.5T. LV / RV cine images, MR tagging, LGE, MOLLI, phase-contrast flow images of the ascending aorta, images of the carotid arteries.	Ongoing
Jackson Heart Study[11,24]	5,301 African-Americans (ages 35-84) residing in Jackson, MS	1,672, 600 with IV contrast (completed)	Between 2008-2012 (~8 years after baseline visit)	1.5T. LV / RV cines, MR tagging, contrast sequences, aortic structure and function	Visit 1 2000-2004, visit 2 2005-2008, visit 3 2009-2012
Dallas Heart Study[12]	6,101 Dallas County Residents (ages 18-65). Participants undergoing imaging were ages 30-65.	2,971 (completed)	At baseline visit in 2000-2002	1.5T. LV / RV cines, phase-contrast gradient echo sequence of aorta	Ongoing
UK Biobank[4,25]	>500,000 men and women (aged 40-69) of the general population	Goal 100,000 (ongoing)	Several years following the baseline visit	1.5T. LV / RV cines, MR tagging, aortic flow sequences, native T1, aortic distensibility	Ongoing
German National Cohort[15,16,26]	200,000 men and women (aged 20-69) of the general population	Goal 30,000 (ongoing)	Baseline	3T. LV / RV cines, native angiography, parametric T1 mapping	Ongoing
SHIP[17,27,28]	6,753 men and women (aged 20-79) of the general population of Pomerania	528 contrast-enhanced CMR	2008-2012 (at SHIP-2)	1.5T. LV / RV cines. MRA. LGE in men.	SHIP-0 1997-2001 SHIP-1 2002-2006 SHIP-2 2008-2012 SHIP-3 2014-2016
SHIP-Trend[17,27,28]	4,420 men and women (aged 20-79) of the general population of Pomerania	997 contrast-enhanced CMR	2008-2012 (at baseline visit)	1.5T. LV / RV cines. MRA. LGE in men.	SHIP-Trend 2008-2012 SHIP-Trend-1 Since 2016
Canadian Alliance of Healthy Hearts and Minds[22]	9,700 male and female Canadians aged 35-69	All 9,700 participants	Baseline	Standard CMR: LV / RV cines. Extended CMR: LV / RV cines. MR tagging. Phase-contrast cine. LGE. T1 mapping. T2 star-weighted sensitive sequence.	Ongoing

AGES-Reykjavik Study[18]	5,764 Icelanders born between 1907 and 1935	936 as part of the ICELAND MI cohort (completed)	~40 years after initial enrollment in AGES in 1967	1.5T. LV / RV cines. LGE.	Ongoing
Hamburg City Health Cohort Study[21]	45,000 inhabitants (aged 45-74) of the city of Hamburg, Germany	12,362 (planned)	Baseline	1.5T. LV / RV cines. LGE. Mapping. Aortic / mitral flow measurements. Angiography. Aortic distensibility.	Ongoing
PIVUS study[19]	1,016 residents in the municipality of Uppsala, Sweden (aged 70 and over)	259 (completed)	3-22 months after primary investigation	1.5T. LV cines. LGE. MRA.	Completed
Framingham Heart Study Offspring Cohort[20,29]	5,135 residents of Massachusetts, offspring of original FHS cohort	1,837 (completed)	~30 years following initial evaluation	1.5T. LV / RV cines.	Ongoing

CMR, cardiac magnetic resonance; CVD, cardiovascular disease; LV, left ventricle; RV, right ventricle; LGE, late gadolinium enhancement; MOLLI, modified Look-Locker inversion recovery; IV, intra-venous; T, Tesla; SHIP, Study of Health in Pomerania; AGES, Age, Gene/Environment Susceptibility; PIVUS, Prospective Investigation of the Vasculature in Uppsala Seniors

CMR imaging and power of study

There are three factors that affect the power of the study: (i) prevalence of exposure, (ii) prevalence / incidence of outcome, and (iii) number of CMR scans performed. While the number of CMR scans is readily available, the former two factors might easily be overlooked.

The closer the prevalence of the exposure and outcome is to 50%, the higher is the power of the study. This becomes important when looking at the different research questions cohort studies using CMR have tried to answer. Most studies focus on either cardiac structure and function as outcome parameters and try to determine which cardiac risk factors are associated with different cardiac phenotypes, or they try to find imaging biomarkers that are associated with the future outcome of the patient (using cardiac structure and function as assessed by CMR as exposure). Certain cardiac risk factors such as hypertension may be present in up to 40% of the population [30], making it relatively easy to find associations with CMR outcomes. Clinical outcomes such as myocardial infarction may, however, only occur in <1% of the population per year[30], requiring either a higher number of CMR scans or a longer follow up. Tables 2 and 3 show the lowest odds ratios (OR) that are detectable with a power of 80% by the prevalence of the exposure and the number of CMR scans performed as part of the study.

For Table 2, the prevalence of the outcome was assumed to be 4%, while it was assumed to be 2% for the calculations in Table 3. So far, the largest study that has been completed remains the MESA study with 5,000 CMR scans. When investigating the association between a risk factor such as diabetes mellitus, which has been found to be present in approx. 2.5% in the general population[31], and an imaging marker that is present in approximately 4% of the general population, the lowest OR the MESA study could detect would be 2.61, whereas the UK Biobank

will be able to detect an OR as low as 1.30. Even more pronounced are the differences when it comes to associations between CMR findings and long-term clinical outcomes. When investigating an association between an imaging biomarker that is present in 2.5% of participants and a cardiovascular outcome such as myocardial infarction, the lowest detectable OR of the MESA study and the UK Biobank would be 3.36 and 1.43, respectively. Those calculations assume that 2% of participants have had a myocardial infarction (MI). The power of the study can be increased through longer follow-up periods, although at a risk of selection bias due to drop out.

Table 2. Lowest detectable OR with a power of 80% assuming a baseline prevalence of the outcome of 4%.

	Prevalence of exposure			
# of CMR scans	**2.5%**	**5%**	**10%**	**20%**
1,000	5.62	3.93	3.00	2.43
2,000	3.87	2.88	2.30	1.95
5,000	2.61	2.09	1.77	1.56
10,000	2.07	1.74	1.52	1.39
30,000	1.58	1.41	1.29	1.22
100,000	1.30	1.22	1.16	1.12

OR, odds ratio; CMR, cardiac magnetic resonance.

Table 3. Lowest detectable OR with a power of 80% assuming a baseline prevalence of the outcome of 2%.

	Prevalence of exposure			
# of CMR scans	**2.5%**	**5%**	**10%**	**20%**
1,000	7.88	5.38	3.99	3.15
2,000	5.25	3.78	2.92	2.39
5,000	3.36	2.59	2.11	1.81
10,000	2.55	2.06	1.75	1.55
30,000	1.83	1.58	1.41	1.31
100,000	1.43	1.30	1.22	1.16

OR, odds ratio; CMR, cardiac magnetic resonance.

ASSOCIATIONS WITH LV STRUCTURE AND FUNCTION

The relationship of sex and age with CMR based outcomes has been widely studied across the different cohorts. Among individuals without overt cardiovascular disease, male sex has repeatedly been linked to greater left ventricular (LV) volumes and mass. LV ejection fraction (EF) has, however, consistently been found to be higher in women than in men [20,32–34]. While the results of different cohorts indicate that LV volumes decrease with age [32,34,35], striking differences are seen between cross-sectional and longitudinal changes in LV mass: In the cross-sectional analysis of the UK Biobank, no association was seen between age and LV mass [32], findings similar to those in the SHIP study [27]; a cross-sectional analysis of the baseline data of MESA found an inverse relationship between age and LV mass [36]; and a longitudinal increase in LV mass was seen between the MESA baseline and follow up visits [37].

One possible explanation is that those differences are due to selection bias given that only individuals without overt cardiovascular disease at baseline were included in the MESA study - older participants without cardiovascular disease at baseline are likely different from younger participants as they had to be able to remain healthy despite a longer exposure to cardiovascular risk factors. While a longitudinal analysis of the Framingham Heart Study also found an increase in LV mass in men using echocardiography, it also found a longitudinal increase in LV mass in women [38], further complicating the interpretation of the results and also highlighting difficulties when comparing CMR to – especially 2D – echocardiography. Physiologically, a follow-up study provided some insight into potential mediators of the effect of age on LV mass: Subramanya et al. [39] found that higher free testosterone levels and lower sex hormone binding globulin levels (i.e. more androgenic profiles) were associated with higher LV mass in both men and women.

Independently of the cause of the intriguing LV mass findings, it seems clear that LV mass to volume ratio (LVMR), a marker of adverse remodeling [40], increases over time.

MESA's unique design makes it ideal for comparisons of different ethnicities. LV mass and volumes were lower among Asian Americans compared to white Americans, African Americans, and Hispanics for both men and women [33]. In addition, Hispanics were found to have a higher prevalence of both concentric and eccentric LV remodeling and LV hypertrophy (LVH). The association with LVH remained significant for Mexican-origin and Caribbean-origin Hispanics even after adjustment for all covariates including a higher proportion of elevated blood pressures [41]. The different population-based studies have also allowed a detailed analysis of the effect of various CVD risk factors on the cardiac structure and function among the different cohorts. Using the Jackson Heart Study, Kamimura et al. [42] recently demonstrated the deleterious effect of cigarette smoking on LV mass and function among African Americans. Similar findings have been described in the UK Biobank [43] and MESA [44].

Many of the other traditional CV risk factors and their associations with CMR parameters in population cohort studies have been reviewed previously [44,45]. Notably, cohort studies using CMR were able to extend prior reports by demonstrating that various inflammatory markers are associated with worse cardiac function [46]. High-sensitivity CRP [47], homocysteine [48], and fibrinogen [49] were associated with systolic myocardial function even in asymptomatic individuals, emphasizing the role of inflammation in the pathogenesis of cardiac dysfunction. Several other inflammatory markers including IL-6, soluble thrombomodulin, Factor VIII, and vWF have been found to be associated with LV mass [46]. Of note, in this MESA study elevated

CRP and IL-6 were negatively associated with LV mass after adjustment for obesity, indicating a mediating effect.

A unique advantage of the large cohorts lies in the ability to study associations between environmental exposures and precise and reproducible CMR measurements. One UK Biobank study sought to examine the relationship between ambient air pollution and cardiac structure and function in 3,920 individuals free from pre-existing CVD [50]. Spatial variations of average annual concentrations of particulate matters of different sizes, nitrogen dioxide, and nitrogen oxides were calculated for the participant's home addresses. The adjusted analysis was notable for a significant association between higher concentration of particulate matter and larger ventricular volume (changes that have been linked to a higher risk of heart failure [51]) with the results indicating that the association was predominantly driven by finer particles. A similar association was found for nitrogen dioxide, but not for nitrogen oxide. The study highlights how CMR can be used in population-based studies to discover biological pathways and to identify high-risk populations.

More recently, population-based cohort studies have also helped to understand cardiac side effects of commonly used medications. One MESA study examined the association between H2 receptor antagonists and changes in LV morphology [52], a relationship that had previously mostly only been studied in animal models. Another MESA study looked at new statin use and cardiac remodeling [53] and a UK Biobank study evaluated the impact of menopausal hormone therapy (MHT) in post-menopausal women free of CVD [54]. Compared to non-users, H2 receptor antagonist users had fewer detrimental changes in LV parameters. They had a smaller decline in LV volumes, a smaller decline in LV stroke volume, and a smaller increase in mass/volume ratio. Similarly, new statin therapy was associated with less progression of LV mass index and

mass/volume ratio, though the effects were small in magnitude. The effect sizes increased as the statin dose increased. MHT>3 years was associated with significantly smaller ventricular volumes and stroke volumes. As described above, smaller ventricular volumes may be associated with more favorable outcomes.

CMR TAGGING AND STRAIN ANALYSIS

CMR tissue tagging allows to quantify parameters of cardiac physiology such as myocardial strain, strain rate, and torsion [55]. Strain represents either segment shortening (longitudinal or circumferential strain) or thickening (radial strain) and is typically expressed as the fractional change from the original dimension. Temporal integration of strain rate is used to calculate regional strain. Strain rate, a rate of change of deformation, is derived as a spatial derivative of velocity. Circumferential strain is often measured separately at the base, mid-segments, and the apex. Torsion describes the relative rotation of short-axis sections between diastole and systole [55]. While several population-based cohort studies are planning to include tagging, so far only MESA has been used to examine associations with risk factors, cardiac structure, and long-term outcomes [56] as described in a review by Yoneyama et al [44].

CMR tagging in MESA has provided further insight into longitudinal changes in cardiac function. As detailed above, while ventricular volumes increase in both sexes, LV mass increases longitudinally in men, but decreases longitudinally in women. In contrast, the association with LV circumferential strain is the opposite (it decreases longitudinally in men and increases in women) [57]. Torsion was found to increase with age in both sexes and could be an important compensatory mechanism to counter remodeling and maintain global systolic function.

Notably, in addition to insights into the physiology behind alterations in strain patterns, the study [57] highlights another important issue: the need for similar investigations in different population-based studies even if the individual cohorts are large and reliable techniques such as CMR are used. This is illustrated by another positive finding in the study: A V-shaped relationship between change in LV mass/volume ratio and change in torsion, a rather new and not immediately intuitive

finding. The findings are difficult to interpret because of the use of non-standard measure of torsion. Rather than twist per unit length of the ventricle which doesn't scale appropriately between hearts of different sized, the torsional shear angle or shear strain should be calculated [58]. In addition, the p-value of those results is 0.02 and therefore reaches statistical significance based on the standard 0.05 cutoff. In reality, however, it is almost entirely unclear what those results actually mean. Using a Bayesian approach, it can be shown that it all depends on the prior probability and that even if we assume that to be close to 50% in the absence of comparable cohort studies, the final probability of a true null is well above 10% (and in practice likely even higher than that) [59]. The abundance of observable associations should therefore always be viewed cautiously, especially in the absence of comparable analyses from other cohorts.

ADDITIONAL BENEFIT OF IV CONTRAST IN POPULATION-BASED STUDIES

In addition to classic applications such as angiography, IV contrast allows for the identification of myocardial fibrosis. Post-contrast T1 mapping, a relatively new technique, has been used to assess diffuse interstitial fibrosis, a marker of cardiac remodeling [60]. Post-contrast T1 mapping detects extracellular volume (ECV) expansion [61], a finding that can be associated with a variety of conditions including myocarditis, which lead to myocardial edema [61]. However, in the absence of these pathologies, it can be presumed that ECV expansion is the result of increased interstitial fibrosis [62].

While several different post-contrast T1 mapping sequences exist, the modified Look-Locker inversion recovery (MOLLI) sequence has been used most widely in population-based studies using CMR [63,64]. The findings in MESA that women tend to have higher ECV fractions and that CMR parameters suggestive of fibrosis tend to be associated with older age [64] have previously been summarized [44]. Notable additional findings include the inverse associations between extracellular expansion and ventricular volumes, mass, and reduced circumferential strain in men and women (torsion and LV EF were only negatively associated in men, whereas strain rate was only inversely associated in women) [63]. More recently, a borderline significant association was found between inflammatory markers IL-6 and CRP and diffuse fibrosis in men [65], while no association was found between the extent of LV trabeculation and markers of diffuse fibrosis [66].

Late gadolinium enhancement on the other hand can be used to detect focal myocardial fibrosis and the anatomical pattern can be used to differentiate ischemic from non-ischemic etiologies [67]. This technique has been used in the ICELAND-MI cohort to detect unrecognized myocardial

infarction [18]. More recently, Shanbhag et al. [68] extended those prior findings by also investigating the prevalence of non-ischemic myocardial fibrosis. In their study, 23.4% of participants had radiologic evidence of a prior MI, while major and minor non-ischemic patterns of fibrosis were seen in 6.0% and 26.4%, respectively. Compared to patients with prior MI, non-ischemic fibrosis was associated with a higher LV mass, but a lower coronary artery calcium score and a lower prevalence of diabetes type II. Interestingly, while the prevalence of recognized and unrecognized myocardial infarction in ICELAND-MI was very similar to prior findings in PIVUS [69], it was much higher than that in MESA [70]. These differences may be due to demographics (ICELAND-MI participants were older with a higher prevalence of cardiac risk factors) and the study design (MESA excluded individuals with baseline clinical cardiovascular disease).

In addition to identification of fibrosis, CMR with IV gadolinium allows for myocardial perfusion imaging, a technique that allows to reliably detect coronary artery disease (CAD) when compared to other non-invasive imaging modalities [71] as well as invasive studies including coronary angiography and fractional flow reserve [72]. Perfusion CMR was performed in a subset of the MESA patients at rest and during adenosine-induced hyperemia to determine the perfusion reserve (the ratio of myocardial blood flow during hyperemia to rest)[73]. In a MESA study of participants without known coronary heart disease (CHD), several well-known risk factors of CHD, including hypertension and higher LDL cholesterol, were associated with lower perfusion reserve [73]. These findings were extended by another study showing that higher coronary artery calcium scores are inversely correlated with perfusion reserve, again population-based imaging can help identifying subclinical disease and high risk individuals [74], an implication further corroborated by the finding that lower perfusion reserve is associated with decreased regional systolic function even in asymptomatic participants [75].

IMAGING BIOMARKERS AND OUTCOME PREDICTIONS

MESA, ICELAND-MI, and the Framingham Heart Study have studied clinical outcomes following CMR. It has repeatedly been shown that an elevated LV mass and LVH are associated with incident heart failure, coronary heart disease, and cardiovascular death [76–78], a finding that is in line with prior studies using echocardiography [79]. Conversely, a normal CMR has been associated with a lower risk of incident heart failure [80]. Peters et al. [81] recently extended prior reports by showing that individuals with LVH and positive serum biomarkers of myocardial strain constitute the group at highest risk for new asymptomatic LV dysfunction, heart failure, and cardiovascular death.

Interestingly, despite the differences seen in cardiac remodeling over time between men and women as detailed above, the association of LV mass or LV mass/volume with incident cardiovascular disease did not differ between men and women [77]. There is, however, evidence for racial differences. Akintoye et al. [82] found that the relationship between LV mass and incident cardiovascular disease was strongest among Chinese and Hispanics, and weakest for non-Hispanic Whites.

An analysis of the Framingham Heart Study Offspring Cohort [78] showed, similar to the MESA studies, that higher LV mass is associated with a higher incidence of cardiovascular disease. LV wall thickness was also associated with the clinical outcomes in that study, while LV wall/volume ratio was only borderline significant. Further, the study highlighted how, in addition to trying to find causal relationships, large population-based studies that use advanced imaging techniques can improve the prediction of clinical outcomes, an application that has also been described using MESA [83].

More recently, CMR tagging, late gadolinium enhancement, and T1 mapping as described above have also been associated with clinical outcomes [68,84,85]. An ICELAND-MI study [68] examined the association of ischemic and non-ischemic myocardial fibrosis identified using late-gadolinium enhancement and heart failure hospitalization and death from any cause. Patients with an MI had, on average, a higher amount of fibrosis. Despite this, the group with major non-ischemic fibrosis had the highest rates of heart failure hospitalizations compared to patients with ischemic fibrosis, minor non-ischemic fibrosis, or no fibrosis after adjustment for confounders. The authors highlight the important implication that the pathophysiologic processes leading to non-ischemic fibrosis are not captured by the traditional risk factors they adjusted for in the analysis.

ASSOCIATIONS WITH RV STRUCTURE AND FUNCTION

One of the biggest strengths of CMR is its ability to accurately characterize the right ventricle (RV), which has made it possible to investigate risk factors associated with RV dysfunction and remodeling: Cross-sectional analyses of the Framingham Heart Study Offspring Cohort [86] and MESA [87] have shown that RV mass decreases with age and that men have greater RV mass and larger RV volumes, but lower RV EF. Aaron et al. [88] demonstrated that physical activity is associated with higher RV mass and volume. And while obesity has also been found to be associated with higher RV mass and volume [89], the RV EF was lower in obese than in lean individuals.

One of the risk factors specifically linked to RV dysfunction is pulmonary dysfunction. While it has been known from other cohort studies that chronic pulmonary disease is associated with a higher rate of adverse cardiac outcomes [90], population-based studies using CMR have helped to identify underlying pathways and to characterize subclinical changes in cardiac structure and function. One MESA study sought to examine the association of emphysema with RV changes using the lung density on cardiac CT scans to determine the severity of the emphysema [91]. Greater percent of emphysema was associated with lower RV end-diastolic volume, stroke volume, cardiac output, and mass. The magnitude of those changes was greater among current and former smokers compared to never smokers. Thomson et al. [92] extended those findings by showing that reduced forced expiratory volume (FEV_1) and forced vital capacity (FVC) are associated with lower RV end-diastolic volume, end-systolic volume, and lower stroke volume in a sample of the UK Biobank cohort without known cardiorespiratory disease.

Similar to the LV, the RV structure and function has also been associated with several commonly used medications. Histamine 2 (H2) receptor antagonists were associated with a lower RV mass and smaller RV volume, while the ejection fraction was unchanged [93]. These results remained significant after adjustment for left ventricular mass, indicating a potential favorable effect on RV morphology that is independent of the effect on the LV described above. Selective serotonin reuptake inhibitors (SSRIs), on the other hand, have been found to be associated with larger RV stroke volume without a change in RV EF [94]. Interestingly, RV mass and RV end-diastolic volume were higher in men on SSRIs, a finding that is unexpected given a the expected protective effect of SSRIs against serotonin induced pulmonary hypertension [95]. The cross-sectional design and lack of adjustment for length of therapy, however, are considerable limitations. The association between angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) and RV structure and function remains similarly unclear. While a MESA study found significant associations with RV mass and volumes [96], the study failed to adjust for the high number of tests performed and adjusted for LV measures which are possibly on the causal pathway given the known effect of ACE inhibitors and ARBs on LV morphology and function.

NOVEL APPROACHES TO IMAGE ANALYSIS – AUTOMATION IN POPULATION-BASED STUDIES

A major challenge for population-based studies is the analysis of the large amount of imaging data. The analysis of the CMR scans in clinical practice and the population-based studies discussed above heavily relies on manual approaches to identify cardiac chambers and blood vessels. This process is prone to subjective variation and is very time-consuming, requiring up to 30 minutes for a single CMR analysis of the left and right ventricular volumes. However, population-based studies may at the same time offer a solution to the problem by providing large datasets that help to improve machine learning algorithms. While the overall number of participants is still small compared to other specialties, population-based studies are currently the closest we can get to big data in a controlled environment in medical imaging and may allow for the development of algorithms for data analytics at large. The following sections will discuss the analysis process, which can be divided into a pre-analytical, an analytical, and a post-analytical part.

Pre-analysis quality control

Prior to segmentation and measurement of cardiac structure and function, it is necessary to ensure adequate CMR image quality. Incomplete myocardial coverage, suboptimal angulation or slice position, motion artefacts due to breathing or arrhythmia, aliasing, and truncation artifacts are some of the issues that may impair the subsequent analysis [97,98]. Initial image quality assessment is usually performed by radiographers to ensure that the patient does not leave the scanner before diagnostically interpretable images have been obtained. However, this process may be subjective and error-prone, and potentially time consuming [99]. Several studies have aimed to define standardized criteria for quality control through visual inspection in cardiovascular imaging using MRI [100,101], but the process remains very time consuming and challenges such as inter-

and intra-reader variability persist. These issues are further compounded when large amounts of data are obtained for population-based studies because of different imaging centers involved and a lag in time between image acquisition and analysis [102].

In an effort to overcome these limitations, Zhang et al. [102] recently proposed an algorithm for the automatic assessment of full left ventricular coverage. The method was validated in 5,000 CMR scans from the UK Biobank. The algorithm's error rate was just below 5% and demonstrated good agreement with a human expert. Tarroni et al. [103] proposed a strategy based on the identification of cardiac landmarks (apex and mitral valve) to estimate heart coverage that was able to identify cases in the UK Biobank with insufficient coverage with 88% sensitivity and 99% specificity. In addition, their quality control algorithm was designed to assess inter-slice motion detection and image contrast estimation in the cardiac region. Motion-corrupted cases were detected with a sensitivity and specificity of 85% and 95%, respectively. The complexity of motion detection that is caused by respiratory variation alone has been outlined extensively [104,105] and is one of the areas where further research is needed to improve automated quality control techniques. Others include identification and correction for suboptimal angulation and slice position and automated approaches to predicting results from slices that have poor quality of what the results would have been with good image quality.

Analysis

The analysis part includes the identification, localization, and segmentation of cardiovascular contours, enabling an automated quantification of the cardiac structure and function. A number of (semi-) automated LV segmentation algorithms have been described that include a wide range of different techniques [106–111]. There are, however, only a few studies evaluating segmentation

algorithms for more advanced techniques such as T1 mapping [112], late gadolinium enhancement MR images [113,114], aortic stiffness [115], or aortic flow [116]. In addition, most of them have been developed in small datasets, limiting their application in clinical practice or population-based studies.

The Siemens InlineVF was one of the first commercially available fully automated LV analysis tools and the results of the D13 version are available to researches as part of the original UK Biobank dataset. A study comparing automated analyses using the D13 as well as the advanced E11C InlineVF versions to manual assessments [117] showed that the best precision obtainable with the automated analysis was about two to three times that of the manual analysis for ventricular volumes and mass. The study also highlighted conditions where misdetection is more common: If the aorta is very bright or pulsating, if the contrast between blood and myocardium is weak, and if the gray level distributions of the different regions cannot be modeled correctly due to unexpected intensities and contrast in the images.

Also using the UK Biobank, Bai et al. [118] recently developed a fully convolutional network to analyze the 4,875 CMR studies that have already been annotated by clinical experts. The automated analysis closely matched the analysis by clinical experts with Dice metrics >0.9. The mean differences between automated and manual assessment were only 6.9 for LV mass and <10 mL for all LV volumes. Automated algorithms have also been found to be able to reliably detect the localization of the ascending and descending aorta [119], a step that is vital for the calculation of aortic distensibility. Compared to the ground truth (established by visual assessment by 13 observers), the algorithm was able to detect the ascending and proximal descending aorta with an accuracy of 99.4% and 99.8%, respectively.

Novel algorithms may also help to provide tools for better quantification of the myocardial structure and function. As detailed above, current clinical assessment is mostly limited to ventricular mass and volume measures. The Cardiac Atlas Project (CAP) is an international collaboration to provide a population atlas of asymptomatic and pathological hearts [120–122], which has facilitated the development and sharing of advanced analysis techniques including statistical shape modeling. MESA contributed data from the baseline examination of 1,991 asymptomatic volunteers. Data has also been contributed from several other studies including Defibrillators to Reduce by Magnetic Resonance Imaging Evaluation (DETERMINE) [122].

Studies using the CAP data have shown that shape analysis techniques such as principal component analysis (PCA) can be used to quantify remodeling due to myocardial infarction [123,124] or congenital heart disease [125]. These approaches may help with identifying individuals with a certain pathology and, consequently, those at increased risk for adverse outcomes. However, the clinical interpretation of PCA shape components is often difficult as they are not designed to be related to any of the clinical parameters discussed above. Approaches that relate statistical modeling to clinical remodeling parameters might help to overcome this limitation [126].

In addition to currently available segmentation techniques for ventricular or atrial volumes, further research should focus on the development of highly accurate and precise segmentation tools for regional systolic function (strain analysis) and vascular analyses such as aortic stiffness measures and flow quantification. In addition, automated analysis algorithms are needed for advanced CMR techniques outlined above including late gadolinium enhancement, CMR perfusion, and mapping (including T1, T2, T2*, and extracellular volume).

Post-analysis quality control

Earlier work has relied on visual verification of segmentation results, which becomes impractical in large population-based studies. In addition to proposing a fully automatic method for initializing CMR segmentation, Alba et al. [127] proposed one of the first measures to identify incorrect segmentation without the need for visual assessment. Failure is detected using statistical, pattern, and fractal descriptors based on features computed on image intensity values of the blood pool and myocardium. Using CAP for verification, the accuracy of the segmentation quality control reached 96% in both asymptomatic individuals and in individuals with a prior MI.

Automated quality control in image segmentation has also been applied to the UK Biobank datasets. Robinson et al. [128] used Reverse Classification Accuracy (RCA) to predict the quality of segmentation on a case-by-case basis, allowing not only to identify the quality of the segmentation, but also if the segmentation has failed. The algorithm was also successfully applied to a large dataset without ground truth and showed good agreement with visual quality control scores, simulating real life scenarios. A potential limitation of the approach is the runtime of 11 minutes as it limits immediate feedback.

Table 4. Automation and Quality Control.

	Pre-Analysis Quality Control	**Analysis**	**Post-Analysis Quality Control**
Challenges	- Incomplete myocardial coverage - Suboptimal angulation - Suboptimal slice position - Motion artifacts - Aliasing - Truncation artifacts	- Automatic quantification of cardiac structure and function - Segmentation algorithms for more advanced techniques (Mapping of T1 / T2 / T2* / extracellular volume, LGE, CMR perfusion, aortic stiffness, aortic flow) - Advanced analysis techniques such as statistical shape modeling	- Verify correct segmentation without need for visual assessment
Examples of Current Approaches	- Automatic assessment of full LV coverage [102] - Assessment of LV coverage based on cardiac landmarks [103] - Assessment of inter-slice motion [103]	- Siemens InlineVF LV analysis tool [117] - Fully convolutional networks for the analysis of LV mass and volume [118] - Statistical shape analysis using the datasets of the cardiac atlas project [123–126]	- Combination of statistical, pattern, and fractal descriptors based on blood poor and myocardium features [127] - Reverse classification accuracy [128]

LGE, Late gadolinium enhancement; CMR, Cardiac magnetic resonance; LV, Left ventricle.

FUTURE WORK

CMR in population-based studies offers a unique opportunity to bring together experts from different fields to combine approaches from medicine, epidemiology, engineering, and computer science. Improvements in image analysis, automation, and quality control will help advance our ability to identify cardiac risk factors and to correlate imaging characteristics with clinical outcomes, a process leading to precision medicine that will be most impactful if cohorts are combined and data are shared (Figure 1).

Exposures and Clinical Outcomes

Large population-based studies are ideal to study the effects of rare exposures or exposures that vary considerably among individuals of the target population. An example of this is the combination of cardiac imaging with genetics: In order to be able to identify new genes that are associated with certain cardiac characteristics at a population level, a large number of participants needs to be included. Further examples include various environmental exposures such as traffic, pollution, noise, or stress. In addition, population-based studies may help to show a benefit associated with new technologies aimed at promoting health such as the Apple Watch. Population-based studies using CMR may also allow the identification of unknown cardiac effects of various medications or even the correlation of findings from different imaging techniques. For example, the large number of cardiac and brain MRIs obtained on participants of the UK Biobank might allow to better understand which cerebral changes are associated with alterations in cardiac structure or function. There are many other organ interactions with the heart that are worth exploring in an aging population with increasing multi-morbidity and polypharmacy: e.g. respiratory-cardiac axis, liver-heart axis or bone-heart axis. All of these questions could be answered as soon as MRIs have been obtained on a critical number of participants of the target

population if a cross-sectional approach is used. Other questions that seek to answer which cardiac phenotypes are associated with certain clinical outcomes such as cardiovascular events, on the other hand, will require longer follow up periods.

Image Sequences and Analysis

The large number of study subjects in population-based studies, time consuming manual analyses, and significant inter-reader variability require the development of highly accurate, automated segmentation tools for standard measures such as ventricular mass and volume, and for various advanced CMR techniques including strain analysis, late gadolinium enhancement, CMR perfusion, and mapping. In addition to conventional segmentation of these sequences, further development of advanced analysis techniques may allow for a more precise identification of individual structural and functional characteristics.

A very promising example of an advanced analysis technique is the extraction of a large number of quantitative features from digital images. This process, in combination with the storage in shared databases to facilitate subsequent hypothesis generation or testing, is known as radiomics [129,130]. While radiomics has thus far mostly been used in the field of oncology [131,132], it can be applied to many conditions and will undoubtedly help advance precision medicine by identifying and verifying new imaging biomarkers. The process of radiomics as outlined previously [129] includes image acquisition, identification of the volume of interest, segmentation, extraction and qualification of descriptive features from the volume, and population of a searchable database. Application of radiomics to CMR data on a population level will not only allow to better characterize subtle changes in the cardiac phenotype which are not immediately obvious using standard measures such as LV mass or volume, but it will also allow to improve the prediction of

outcomes and thereby potentially provide the means to identify individuals who are most likely to respond to a certain intervention.

Finally, the large number of datasets may offer the opportunity to develop algorithms to predict the results of sequences which were not directly obtained during an MRI scan. For example, early synthetic gadolinium enhancement has been shown to agree with conventional late gadolinium enhancement for assessing myocardial scar [133], a finding that may allow to shorten CMR acquisition time. Further helpful approaches could for example include the prediction of CMR perfusion scans if perfusion imaging was not performed.

Quality Control

The challenges associated with quality control are outlined above. Further research may focus on the detection of and correction for respiratory motion artifact and suboptimal angulation and slice position. In addition, further development of automated quality control of segmentation and other analysis results is needed. Quality improvement projects using quasi-experimental designs demonstrating the impact of regular automated quality information feedback to radiographers on quality of image acquisition could demonstrate the potential of such an approach in population studies but also in clinical practice.

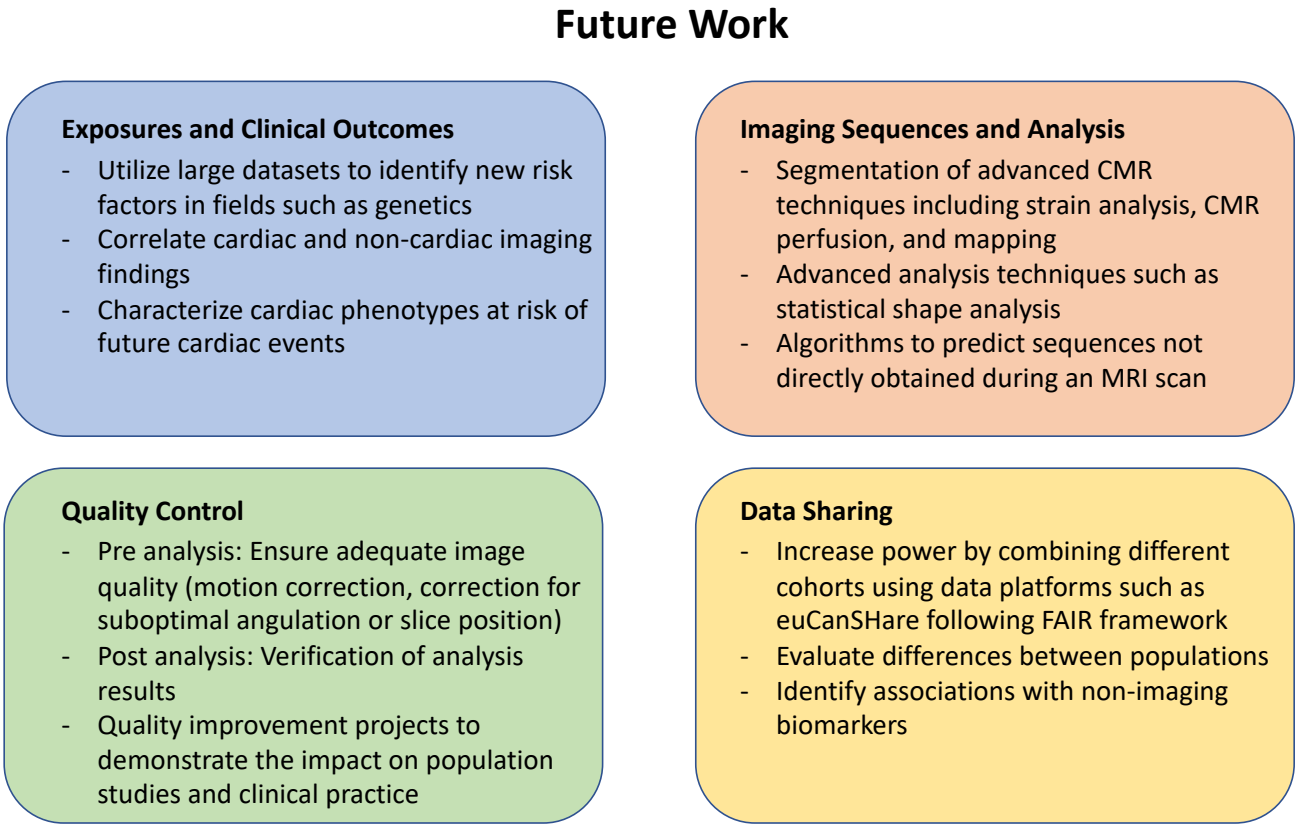
Data Sharing

Despite the large number of participants in each individual study, the clinical goals outlined above will only be achieved with a multi-cohort approach that not only allows the inclusion of participants from different backgrounds, but also facilitates the link of clinical, laboratory, molecular, and clinical data. So far, CAP has helped to establish a large-scale, online accessible

database of CMR datasets with associated clinical data [120]. While extremely important, the total number of datasets currently included is fewer than 3,000. Therefore, other approaches have been developed, most notably euCanSHare [134]. EuCanSHare is a joint EU-Canada project to establish a cross-border data sharing and multi-cohort cardiovascular research platform. It currently aims to integrate 35 Canadian and European cohorts, making up over 1 million records [134]. Future efforts should focus on the development of similar platforms for other regions or, ideally, the integration of other cohort studies within euCanSHare.

Sharing and reuse of data and interpretations, particularly in the setting of large-scale population datasets, are, however, surrounded by several challenges. Specifically, data must be Findable, Accessible, Interoperable, and Reusable, summarized as the FAIR guiding principles recently agreed upon by different stakeholders at a Lorentz workshop and summarized by Wilkinson et al. [135,136]. These high-level principles are in line with previous work such as the Joint Declaration of Data citation Principles [137] or the 'Data Seal of Approval' [138], but specifically focus on machine actionability – the ability of machines to find and use data, thereby supporting its reuse by individuals[139]. Future efforts to share data and make results reproducible should attempt to follow this framework and to quantify the level of FAIRness based on 14 defined metrics [140].

Figure 1. Future Work.



CONCLUSIONS

CMR is the reference standard for the assessment of LV and RV anatomy and function. Since the start of MESA in 2000, CMR has been used in several large population-based studies, which has helped to advance our understanding of the effects of various cardiovascular risk factors on myocardial structure and function. The relatively low prevalence of cardiac risk factors and outcomes in a general population, however, requires large sample sizes. Two ongoing studies, the UK Biobank and the German National Cohort, may help to overcome this limitation due to their significantly higher number of CMR scans.

CMR protocols differ between the individual studies. CMR tagging, T1 mapping, and late gadolinium enhancement are not universally performed, but have helped to detect subclinical disease such as missed MI and have been shown to improve prediction of future cardiovascular events.

The reliable and timely analysis of the large number of scans remains an ongoing challenge. While automated analyses have been developed that closely match the performance of clinical experts, further advances are necessary considering the large sample sizes of the currently ongoing large population-based studies.

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