Radiology

Whole-Body MR Imaging in the German National Cohort: Rationale, Design, and Technical Background[1]

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For the German National Cohort MRI Study Investigators

Purpose: To detail the rationale, design, and future perspective of implementing whole-body magnetic resonance (MR) imaging in the German National Cohort, a large multicentric population-based study.

Materials and Methods: All institutional review boards approved the study, and informed consent is obtained before study enrollment. Participants are enrolled from a random sample of the general population at five dedicated imaging sites among 18 recruitment centers. MR imaging facilities are equipped with identical 3.0-T imager technology and use uniform MR protocols. Imager-specific hardware and software settings remained constant over the study period. On-site and centralized measures of image quality enable monitoring of completeness of the acquisitions and quality of each of the MR sequences. Certified radiologists read all MR imaging studies for presence of incidental findings according to predefined algorithms.

Results: Over a 4-year period, six participants per day are examined at each center, totaling a final imaging cohort of approximately 30 000 participants. The MR imaging protocol is identical for each site and comprises a set of 12 native series to cover neurologic, cardiovascular, thoracoabdominal, and musculoskeletal imaging phenotypes totaling approximately 1 hour of imaging time. A dedicated analysis platform as part of a central imaging core incorporates a thin client-based integrative and modular data handling platform to enable multicentric off-site image reading for incidental findings. Scientific analysis will be pursued on a per-project hypothesis-driven basis.

Conclusion: Population-based whole-body MR imaging as part of the German National Cohort will serve to compile a comprehensive image repository, will provide insight into physiologic variants and subclinical disease burden, and has the potential to enable identification of novel imaging biomarkers of risk.

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The implementation of advanced imaging techniques in large cohort studies has been an increasingly used approach in epidemiologic research (1). Traditionally, longitudinal studies have relied on the clinical assessment of established and novel risk factors at baseline and their relation to the incidence of clinically overt events, such as stroke, myocardial infarction, or death over the follow-up period (2). While this design has served us well in the identification of many now-established risk factors for various disease states, its power is limited to the number of overt events in the source population. Over the past two decades, imaging has increasingly been implemented in population-based cohorts to obtain information on the presence and extent of subclinical disease burden, allowing for a more comprehensive assessment of development of disease states. This has resulted in improved understanding of complex disease processes, as well as identification of novel imaging biomarkers as a precursor for overt disease states. Prominent examples include the Rotterdam study (3), the Framingham Heart study (4), the Multi-Ethnic Study of Atherosclerosis (5), the Heinz Nixdorf Recall study (6), the Study of Health in Pomerania (7), and the Atherosclerosis Risk in Communities study (8). Examples of novel imaging-based markers of risk include coronary calcification with computed tomography (CT) (9,10), assessment of left ventricular function/fibrosis or hepatic steatosis with magnetic resonance (MR) imaging (11,12), and evaluation of intimamedia thickness with ultrasonography (13).

There are substantial advantages of using imaging-based measures of subclinical disease to identify the disease prior to clinical signs and symptoms in studies on disease etiology. Early detection of subclinical disease may enable more efficient and effective initiation of preventive measures and treatment interventions at early stages as compared with later stages of disease. Also, cross-sectional and case-control analyses may be less susceptible to recall bias or bias due to reverse causation related to treatment if the outcome is defined by subclinical disease as detected with imaging instead of with clinical endpoints (5). Finally, imaging biomarkers, with their potentially continuous scale of most subclinical measures (continuous measures of volume, diameter, and extent), yield significantly higher statistical power compared with dichotomous discrete measures of clinical disease (presence or absence) (1). Besides being used to assess subclinical disease burden, advanced imaging modalities may enable identification of a large set of normal variation and variants, which may be of particular interest to the scientific community and may signify susceptibility for a certain disease development. In case any risk factor role can be detected, one may hypothesize that it may serve as a tool to identify subjects who may benefit from primary prevention strategies.

MR imaging has advanced to a stage that allows nonionizing visualization of morphologic and functional processes without the need to administer a contrast agent. Its capability to perform examiner-independent, multiregion and whole-body MR imaging in clinical routine is a recent development (14,15) with a potentially high value for comprehensive phenotyping in a population-based imaging setting. Technical improvements, such as the introduction of multichannel radiofrequency receiver architecture (16), parallel acquisition techniques (17–19), continuous table movement techniques, and pulse sequence developments (20) enable the examination of different organ systems in a whole-body approach within a reasonable imaging time (21,22). Also, unenhanced MR imaging–based angiography has been shown to be an alternative modality that yields images of high quality in participants who are not amenable to contrast material administration (23,24). As a consequence, these novel developments

Advances in Knowledge

- The MR study of the German National Cohort will enroll approximately 30 000 asymptomatic participants from the German general population at five imaging sites and will include a comprehensive whole-body MR imaging protocol of approximately 1 hour.
- Standardized procedures of quality control and quality assurance, as well as algorithms for the management of incidental findings and basic integrative and modular data-handling strategies, have been incorporated.
- The highly stabilized set-up of the German National Cohort MR imaging study will be used to understand the natural history of a broad set of diseases and to potentially identify novel imaging biomarkers of risk.

Implication for Patient Care

- Large prospective cohort studies are required to determine the prognostic value of techniques such as whole-body MR imaging in the identification of participants in the general population who are at increased risk for overt disease development.

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Abbreviations:
SOP = standard operating procedure
3D = three-dimensional

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Conflicts of interest are listed at the end of this article.

enable comprehensive quantitative assessment of adipose tissue distribution; characterization of brain and cardiac function and morphology, as well as characterization of thoracic and abdominal organs; and quantification of changes in the musculoskeletal system.

The German National Cohort is designed to address research questions concerning a wide variety of possible causes and mechanisms for the development of frequent chronic diseases (25). The major objective of the German National Cohort is to identify risk factors and protective factors for population-relevant diseases and age-related declines in health to improve our understanding of disease etiology and to provide new information that can eventually be translated to primary prevention measures. The main diseases of interest include cardiovascular diseases, diabetes mellitus, cancer, neurologic and psychiatric diseases, and respiratory, infectious, and musculoskeletal diseases. Special research emphasis will be given to the association and interactions between biomarkers, subclinical disorders, and their predictive value for future clinical manifestation of disease. Given these general broad objectives of the German National Cohort, whole-body MR imaging may be a unique modality with which to serve these objectives by enabling assessment of subclinical disease and normal variants of the different organ systems within one comprehensive examination with high spatial and temporal resolution. However, while the scientific potential of implementing MR imaging in large cohort studies is substantial, there are numerous ethical and procedural challenges associated with a multicenter study on whole-body imaging in predominantly asymptomatic participants, especially in the case of unintended detection of clinically relevant incidental findings. To be qualified to serve as a scientific reference standard, it is essential to establish high-quality and standardized MR imaging data across different imaging sites over a few years of baseline data collection. At the same time, it has to be ensured that the applied scientific procedures do not compromise the interests and the human dignity of research participants with detectable incidental findings (26,27). Also, the acquisition, storage, and processing of large amounts of imaging data acquired at different sites requires established workflow and data management structures. In sum, all of the described challenges in these comprehensive acquisitions warrant dedicated resources and management algorithms.

In the present report, we describe the rationale and design of the MR Imaging Study of the German National Cohort. Also, we detail the developed and implemented procedures with respect to image quality assurance, data management, study logistics, training, and management of incidental findings.

National Cohort Description

Study Objectives

The primary objective of this research effort is to establish a comprehensive morphologic and functional imaging repository; this will be achieved by implementing whole-body MR imaging in a large subset of the participants of the German National Cohort.

The imaging repository serves as a reference for the following research aims of the study: *(a)* to determine the predictive value of findings on whole-body MR images for the incidence of chronic diseases over the follow-up period, *(b)* to determine pathways for the prevalence of subclinical disease states by studying associations with similarly obtained biologic and socioeconomic markers at baseline, *(c)* to perform cross-section assessment of the prevalence of subclinical disease states and normal variants in the general population, and *(d)* to develop methods that are suitable for application in future screening and intervention studies with which to characterize risk factors among asymptomatic persons.

General Design of the German National Cohort

The German National Cohort is a joint interdisciplinary endeavor by scientists from the Helmholtz Association, from universities, and from other German research institutions (25). Its objective is to study the causes and identify the risk factors of major chronic diseases (cardiovascular diseases, cancer, diabetes mellitus, neurodegenerative and psychiatric diseases, and pulmonary, musculoskeletal and infectious diseases) and to identify the subclinical stages and functional implications of these diseases. In 18 study centers across Germany, a representative sample of the general population will be randomly drawn to include a total of 200 000 male and female participants between 20 and 69 years of age. In addition to interviews and questionnaires, the baseline assessment includes a series of medical examinations, such as neurocognitive function tests, tooth count, blood pressure measurement, pulse wave velocity, spirometry, accelometry, and the collection of a diverse set of biomaterials, such as blood (plasma, serum, DNA, RNA, and red blood cells), saliva samples, nasal swabs, and feces (level I assessment, 2.5-hour program). In 20% of the participants, an intensified assessment program is implemented (level II assessment, additional 1.5 hours of examination time) that includes examinations such as 10-second electrocardiography, three-dimensional (3D) echocardiography, oral glucose tolerance testing, spirometry and FeNo analysis, ophthalmologic measurements, olfactory tests, and musculoskeletal examinations.

After the baseline examination, all participants will be invited for reassessment after 4 to 5 years. The reassessment will obtain information on incident outcomes, and part of the level I and II examinations (described previously) will be performed again. In addition to the reassessment after 4 to 5 years, data on incident outcomes will be collected more frequently via postal follow-up questionnaires and linkage to external databases (population registries, health authorities, health insurance companies, etc).

Funding is ensured for recruitment and reassessment and for the first rounds of postal follow-up (each

2–3 years), which should be achieved within the first 10 years.

MR Imaging Study Design

No industry funding was received for this study. Scientific collaborations exist, including collaborations with industry partners (Siemens Healthcare, Erlangen, Germany). One author (T.N.) is the chief executive officer of MR Imaging TOOLS (Berlin, Germany). Another author (H.U.K.) is a member of the advisory board of Siemens Healthcare and a consultant for Boheringer Ingelheim (Ingelheim, Germany). All other authors declare that they were neither employees of nor consultants for the industrial partners; the authors had full control of all data and information presented in this publication.

As part of the baseline examination of the German National Cohort study, a subset of approximately 30000 of the 200000 participants will be recruited to undergo whole-body MR imaging at one of five dedicated MR imaging centers (Fig 1) as an add-on to the standard examination program of the cohort (level I and II examinations, as described previously). These MR imaging centers are distributed across Germany and are located in Augsburg (Bavaria), Berlin (Berlin), Essen (North Rhine-Westphalia), Neubrandenburg (Mecklenburg-West Pomerania), and Heidelberg (Baden-Wurttemberg) to provide maximum generalizability with regards to sociodemographic characteristics, such as migration background, specific genetic predispositions, et cetera (Fig 2). Each MR imaging center will enroll and examine approximately 6000 participants over a 4-year enrollment period, with the MR examination being performed within a maximum of 12 weeks after the general baseline examination in the study center.

Sample Size Considerations for the MR Study

For the primary objective (ie, to establish an imaging repository), dedicated quality assurance algorithms and algorithms for the management of incidental findings have been implemented, but no dedicated sample size calculations have been performed (25).

Figure 1

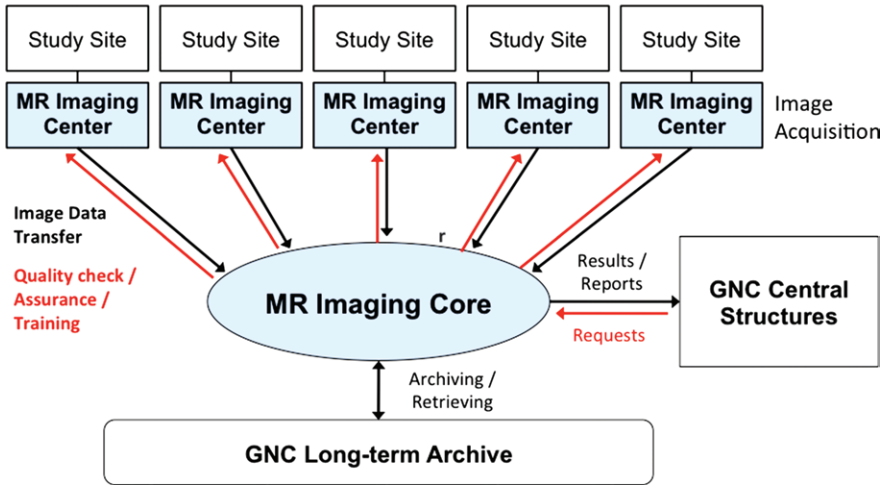

Figure 1: Flowchart shows general design of the MR imaging study of the German National Cohort *(GNC)*.

However, for the larger number of secondary aims (ie, scientific research questions), a total study population of 30000 participants will yield adequate statistical power to detect associations between common baseline MR imaging markers and incident outcomes (Fig 3). For example, in the case of highly prevalent subclinical disorders, such as hepatic steatosis, for which we expect a prevalence of over 20% (25), possible associations with incident cardiometabolic disorders can be detected with a statistical significance after a few hundred incident cases have been collected during the first years of follow-up. The study is also well powered for disorders that are less common. For instance, we expect a 3%–5% prevalence of MR imaging findings that are indicative of chronic pancreatitis (28). Hence, associations with a minimally detectable odds ratio of 1.7 in the presence of 400–600 cases will be detected, corresponding to an incidence of 1.3%–2.0%, as commonly observed in such a population (28).

All statistical analyses will be performed according to Good Epidemiologic Practice guidelines and will be reported in accordance with STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines (29,30).

Population and Recruitment Procedure

All institutional review boards at the five imaging sites approved the study, and informed consent is obtained before study enrollment. The study population is recruited from a random sample of the general population of the surrounding communities at each of the study sites. The MR imaging recruitment procedure is embedded within the recruitment procedure of the general cohort study. Participants in the general assessment program of the German National Cohort are randomly invited from the general population sampled from population registries, a municipal structure that mandatorily lists all inhabitants with residency in a municipal area. Inclusion criteria for the German National Cohort are provided in Table E1 (online) (25). The number of participants varies according to MR imaging study site, with 10000 participants each in Essen, Berlin, and Heidelberg and 20000 participants each in Augsburg and Neubrandenburg. Additional participants from adjacent study centers are invited to take part in MR imaging at the respective study center. At each of these sites, participants are approached for participation and are included if they consent to the MR imaging procedure and if no MR imaging exclusion criteria are present.

At each study site, approximately 6000 participants in the general cohort

Figure 2

Figure 2: Map of Germany shows the distribution of German National Cohort study centers and MR imaging centers.

will be included in the MR imaging examination. Participants not primarily assigned to level II will undergo these MR imaging examinations in addition to their level I examinations. Inclusion and exclusion criteria for the MR imaging study are listed in Table E1 (online).

Protection of Participants' Privacy and Access to Research Data

With respect to data safety, we implemented a central data management system that complies with relevant legislation. This includes a strict separation between personal data and all other information (eg, images and biomaterials collected from participants). All study variables are deidentified and kept in a central study database. For data linkage, an independent trust center has been established, which exclusively holds all identifying information. The trust center links follow-up information to the individual participants and replaces identifying variables with pseudonyms before they are included in the main study database.

The German National Cohort consortium is the legal owner of all data and biomaterials and will retain overall control of all access to the data and samples. The consortium strongly encourages researchers to use this scientific resource. Like all other data and biomaterials collected for the German National Cohort, the scientific use of MR imaging findings and images is dependent on an application approved by the use and access committee of the German National Cohort. Access to the deidentified data will be provided to the applicants via a transfer center as part of a planed analysis platform.

Cohort Surveillance and Follow-up for Events

Standard follow-up of the study population will be conducted within the main framework of the German National Cohort (25). This will include active follow-up via postal questionnaires every 2–3 years, supplemented with passive

Figure 3

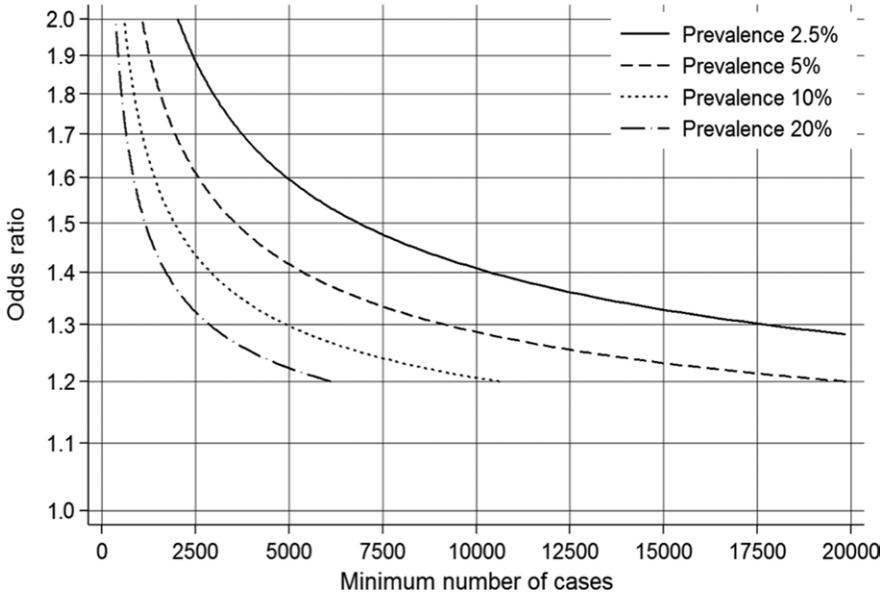

Figure 3: Power calculations. Graphs indicate the minimal detectable risks (α= 5%; statistical power, 80%) given a defined baseline prevalence of the exposure, number of incident cases (x-axis), and strength of associations (y-axis). Graphs indicate that the study size will be large enough to investigate, with high-power associations between common conditions (prevalence of 20% for hepatic steatosis or prostate hyperplasia, prevalence of 10% for left ventricular hypertrophy) and less common diseases (prevalence of 5% for cerebral microbleeds, prevalence of 2.5% for chronic pancreatitis) and incident outcomes. Over a 10-year follow-up period, we expect 2000 incident cancer cases, 5000 cases with incident cardiometabolic diseases, and 2500 deaths from all causes.

follow-up procedures. The latter will include contacting the participant's pertinent physician or physicians, hospitals at which they were treated, or both to collect further information on nonfatal or fatal diseases. Linkage between the German National Cohort and health insurance data and cancer registries will serve as additional health information resources. Information on vital status is collected annually from population registries. In case of death, health authorities are asked to provide death certificates. Also, German National Cohort data will be linked to the planned centralized German mortality registry.

Epidemiologic MR Imaging

General Consideration for Using MR Imaging

Population-based imaging requires a robust and comfortable modality that can be applied to a large number of consecutive study participants without major deviation, interruption, or examination cancellation. Such an imaging modality needs to be extremely safe because even very rare side effects and adverse events may occur due to the large sample size. The selected imaging modality should not alter the natural development of disease or potentially increase the risk for study end points (eg, radiation administration using CT and development of cancer). Also, a feasible population-based imaging modality should be able to include a large portion of the body and provide high spatial resolution to assess the variety of subtle pathologic changes of subclinical disease burden with respect to the different organ systems.

Advanced, native MR imaging technology combines most of these aspects, although known contraindications may limit the target population and introduce selection bias. While this bias needs to be measured prospectively, it can be assumed that a dedicated whole-body MR imaging protocol provides the most prolific means to assess subclinical disease and normal variants of the different organ systems within one comprehensive examination.

MR Imaging Examination and Components

Across all imaging centers, MR imaging will be performed by using identical 3.0-T MR technology with a 70-cm bore (Magnetom Skyra; Siemens Healthcare, Erlangen, Germany). Despite being more expensive and associated with a higher likelihood of artifacts, a magnetic field strength of 3.0 T was selected to leverage the improved signal-to-noise ratio, enhanced spatial resolution, parallel imaging techniques, and predicted future MR imaging standard in a clinical environment. Examination time is restricted to approximately 1 hour to increase participant compliance. It will be ensured that MR hardware and software will remain constant over the study period for reasons of data consistency and reproducibility, with the exception of safety-relevant updates and upgrades, which will be provided by the MR vendor. Each MR imaging site will be connected with the central MR imaging core to assure high protocol adherence and constant high image quality. The MR examination protocol comprises four dedicated components of approximately 15 minutes of examination time each, covering *(a)* cerebral morphology and function, *(b)* cardiovascular morphology and function, *(c)* body adipose tissue distribution, thoracoabdominal organ morphology and composition, and *(d)* musculoskeletal spinal and hip morphology (Table). Because of the very small but present risk of allergic reactions to the contrast agent, necessary assessment of kidney function, and complexity of the intravenous line positioning in this asymptomatic population, no gadolinium chelate will be administered. Examples of MR images obtained with selected MR imaging sequences are provided in Figures 4–7.

Morphologic and functional imaging of the brain.—Morphologic imaging

MR Protocol in the German National Cohort Covering Neurologic, Cardiovascular, Thoracoabdominal, and Musculoskeletal Sequences

MR Sequence	Imaging Parameters	Anatomic Coverage	Major Phenotypic Focus
	Neurodegenerative Focus		
T1-weighted 3D MPRAGE	1.0 × 1.0 × 1.0 mm (isotropic) voxel; sagittal orientation; repetition time msec/echo time msec/inversion time msec, 2300/2.98/900; 9° flip angle	Whole brain and upper spinal cord	Regional gray matter structure; volumetry
2D FLAIR	4.0-mm section thickness; axial orientation; 0.9 × 0.9 mm voxel size in-plane; 9000/100/2500; 150° flip angle	Whole brain	White-matter integrity/hyperintensities
Resting-state EPI BOLD	3.1 × 3.1 × 3.1 mm (isotropic) voxel; axial orientation; repetition time msec/echo time msec, 2000/30; 90° flip angle	Whole brain	Functional architecture and connectivity at rest
	Cardiovascular Focus		
MR angiography 3D SPACE STIR	2.5-mm section thickness; coronal orientation; 1.2 × 1.2 mm voxel size in-plane; 4000/102/220; 150° flip angle	Lung apices to diaphragm	Vascular morphology
Cine SSFP LAX	6.0-mm section thickness; 1.5 × 1.5 mm voxel size in-plane; 40/1.46; 50° flip angle	Four-, three-, and two-chamber views	Ventricular function
Cine SSFP SAX	6.0-mm section thickness; 1.5 × 1.5 mm voxel size in-plane; 63/1.46; 50° flip angle	12 stacks covering base to apex	Ventricular function and mass
MOLLI SAX	8.0-mm section thickness; 1.4 × 1.4 mm voxel size in-plane; 325/1.12/209; 35° flip angle	One midventricular stack	T1 relaxation maps
	Thoracoabdominal Focus		
T2-weighted HASTE	5.0-mm section thickness; axial orientation; 1.4 × 1.4 mm voxel size in-plane; echo time, 81 msec	Shoulder to epigastric region	Organ volumetry, inflammation
T1-weighted 3D VIBE two-point Dixon	3.0-mm section thickness; axial orientation; 1.4 × 1.4 mm voxel size in-plane; repetition time, 4.36 msec; CAIPIRINHA	Neck to knee	Total and local fat depots, organ volumetry
Multiecho 3D VIBE	4.0-mm section thickness; axial orientation; 1.6 × 1.6 mm voxel size in-plane; six echo times, 1.23, 2.46, 3.69, 4.92, 6.15, and 7.38 msec	Epigastric region, including liver and pancreas	Liver and/or pancreas fat, iron content
	Musculoskeletal Focus		
PD FS 3D SPACE	1.0 × 1.0 × 1.0 mm (isotropic) voxel; coronal orientation; variable flip angle, target tissue T1 of 940 msec and T2 of 100 msec	Pelvis, including iliosacral joint and both hips	Osteoarthrosis, inflammatory joint disease
T2-weighted 2D fast spin-echo	3.0-mm section thickness; sagittal orientation; 0.9 × 0.9 mm voxel size in-plane; echo time, 126.0 msec	Lumbar, thoracic, and cervical spine	Disk degeneration, osteochondrosis, osteoporosis

Note.—BOLD = blood oxygen level–dependent, CAIPIRINHA = 3D parallel technique for breath-hold abdominal imaging, Dixon = method of acquiring in- and out-of-phase images (ie, two echoes) and calculating water-only and fat-only images, EPI = echo-planar imaging, FLAIR = fluid-attenuated inversion recovery, FS = fat saturation, HASTE = half-Fourier acquisition single-shot turbo spin-echo, LAX = long axis, MOLLI = modified look-locker inversion recovery, MPRAGE = magnetization-prepared rapid acquisition gradient echo, PD = proton density, SAX = short axis, SPACE = sampling perfection with application contrast using different flip angle evolution, SSFP = steady-state free precession, STIR = short inversion time inversion recovery, VIBE = volumetric interpolated breath-hold examination.

will be performed by using *(a)* a T1-weighted three-dimensional magnetization-prepared rapid gradient-echo, or MPRAGE, sequence as a well-established approach to volumetric and morphometric analysis of regional brain structure (31) and *(b)* a predominantly T2-weighted fluid-attenuated inversion recovery sequence to detect white matter abnormalities mainly due to cardiovascular diseases (32). To characterize brain function, resting-state functional MR imaging data will be acquired by using a blood oxygen level–dependent gradient-echo echo-planar imaging sequence, which will enable investigation of the functional organization of brain areas and their connectivity in a task-free state (33,34). These parameters not only show relevant changes during the process of aging (35) but also might be promising risk parameters with which to assess dementia and psychiatric and neurologic disorders (36,37).

Morphologic and functional imaging of the cardiovascular system.—The cardiovascular MR protocol comprises

Figure 4

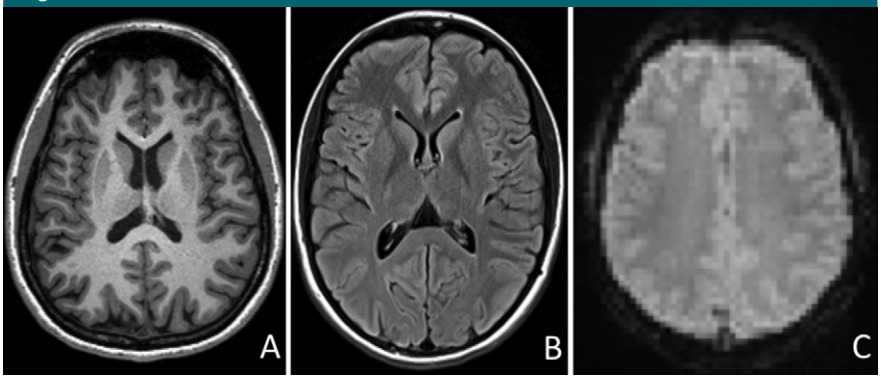

Figure 4: MR images obtained as part of the neurologic MR imaging protocol. *A,* T1-weighted 3D magnetization-prepared rapid acquisition gradient-echo sequence. *B,* Two-dimensional fluid-attenuated inversion recovery sequence. *C,* Two-dimensional gradient-recalled-echo echo-planar imaging blood oxygen level–dependent sequence (for resting-state functional MR imaging).

Figure 5

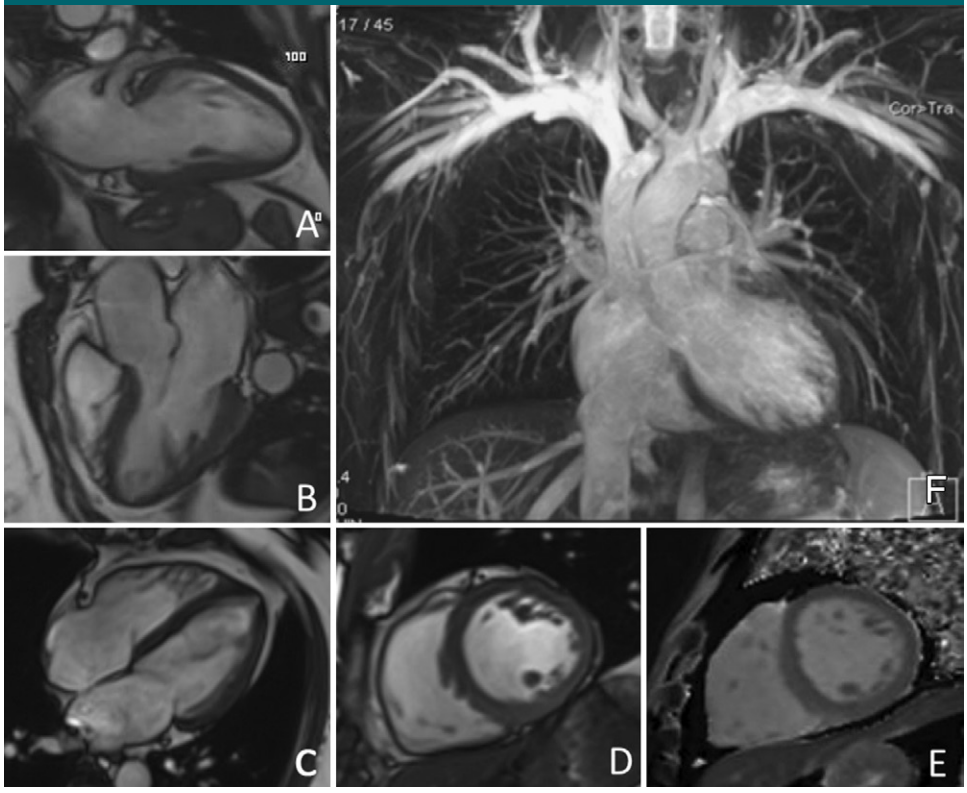

Figure 5: Examples of MR images acquired as part of the cardiovascular protocol: *A–C,* Long-axis MR images obtained with the cine steady-state free precession sequence. *D,* Short-axis MR image obtained with cine steady-state free procession sequence. *E,* MR image obtained with T1 mapping (modified look-locker inversion recovery). *F,* Native thoracic MR angiogram.

Figure 6

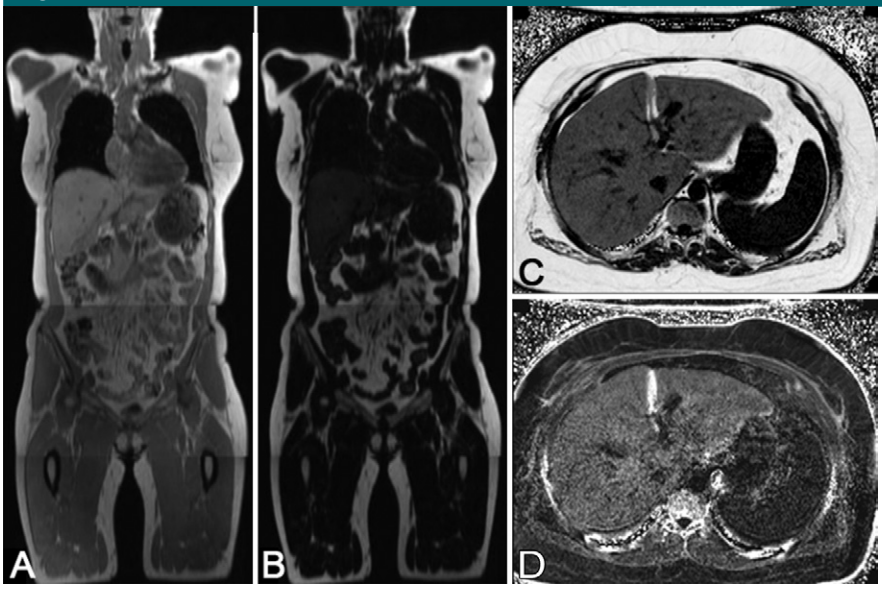

Figure 6: Image examples as part of the thoracoabdominal MR imaging protocol: *A,* T1-weighted 3D volumetric interpolated breath-hold examination (VIBE) image from the neck to the knees with coronal reconstructed images. *B,* Body fat can be assessed with the two-point Dixon-technique separated fat images. *C, D,* Multiecho VIBE images with six echoes yield percentage-scaled fat *(C)* and $R2_{eff}$ *(D)* images of the liver.

Figure 7

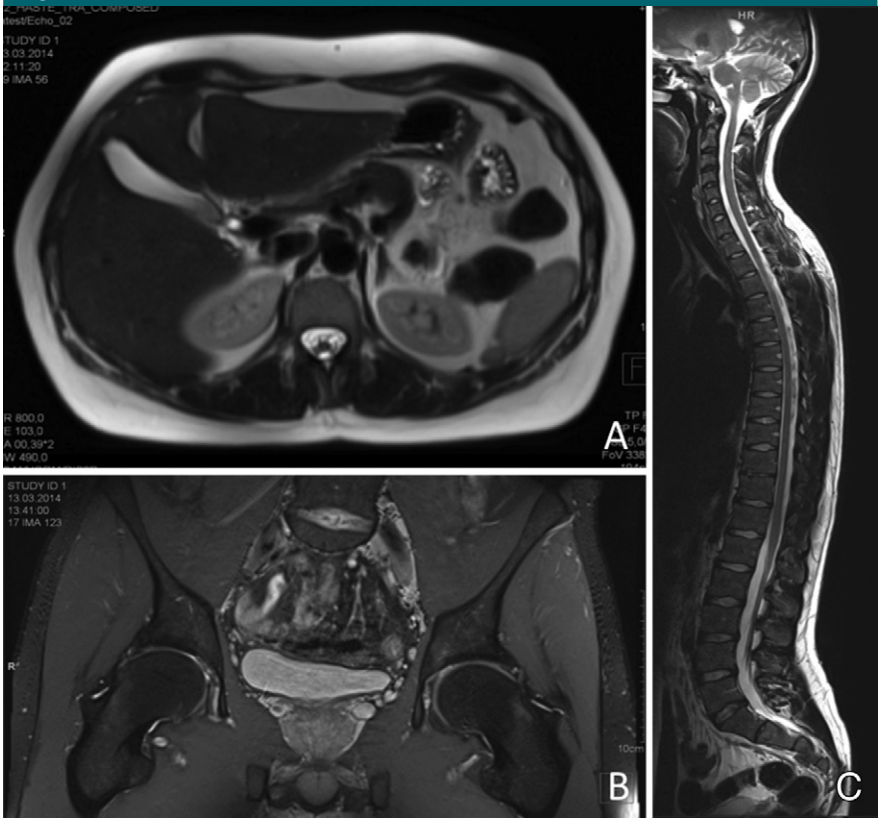

Figure 7: *A,* T2-weighted MR image of the thorax and abdomen obtained as part of the body protocol. *B, C,* MR images obtained as part of the musculoskeletal protocol (PD with fat saturation of the pelvis *[B]* and T2-weighted image of the entire spine *[C]*).

assessment of cardiac function, morphologic native MR angiography of the thorax, and parametric T1 mapping to assess myocardial tissue. For left ventricular function and mass as the most investigated parameters for cardiovascular outcomes, MR imaging is the established clinical reference standard (38). Reproducible standard long- and short-axis views of the heart will be acquired by using two-dimensional cine balanced steady-state free precession techniques (39). Steady-state free precession–based native angiography has been shown to be an alternative to contrast-based MR angiography (23) to cover the pulmonary arterial, venous, and aortic vasculature. Finally, the protocol will include parametric T1 mapping to detail myocardial tissue alterations through changes in T1 (40).

Thoracoabdominal imaging.—MR imaging, especially T1-weighted two-point Dixon techniques, enable reliable detection of fat and differentiation between adipose and lean tissue (41). Obese patients are at increased risk for many chronic diseases, including type-2 diabetes, cardiovascular disease, cancer, and osteoarthritis (42,43). Local adipose tissue depots play a pivotal role in the pathogenesis of metabolic and atherosclerotic diseases; for example, visceral fat is more important in the pathogenesis of insulin resistance than is subcutaneous fat because of its metabolic activity (44). Thus, quantification of not only total adipose tissue, but more importantly quantification of local adipose tissue depots, such as visceral or epicardial fat, has the potential to be a novel risk marker for metabolic and cardiovascular disease (45). With a dedicated multiecho sequence (46),

liver fat and iron content can be determined, which is an established prognostic marker in hepatic disease. This sequence can also be used to identify pathophysiological links to diabetes and other metabolic diseases (12). T2-weighted techniques enable imaging of free water and water content, such as in the process of inflammation or edema. Furthermore, it enables detection of chronic processes resulting in atrophy, cystic remodeling, or both as observed in the case of chronic pancreatitis, it improves visualization of dilated pancreatic or bile ducts and the decision between differential diagnosis of incidental findings (eg, between cystic and solid lesions), and it improves accurate segmentation of the different tissue types. Finally, both techniques enable volumetric measurements of organs and defined normal volume ranges within a healthy population.

Musculoskeletal imaging.—Musculoskeletal imaging will focus on the two major disease entities of osteoarthrosis (degenerative joint disease) and inflammatory joint disease. The protocol includes an established fat-suppressed 1-mm isotropic spatial-resolution 3D fast spin-echo with variable flip angle contrast proton-density sequence of the pelvis to assess the most relevant phenotypic parameters of osteoarthrosis and inflammatory joint disease. In addition to cartilage and labrum condition, potential osteophytes or subcondral cysts as markers of osteoarthrosis and femoroacetabular impingement can be assessed. Moreover, parameters for inflammatory joint disease, such as synovitis, joint effusion, articular bone marrow edema, and bursitis, will be imaged, and potential adjacent myopathies or tendinopathies can be visualized. Additionally, bone marrow lesions of the pelvic skeleton can be appreciated. Furthermore, the sacrum and the sacroiliac joints will be covered by the 3D fast spin-echo sequence so that signs of sacroiliitis will be detected. In addition, a two-dimensional T2-weighted fast spin-echo sequence of the entire spine will enable visualization and assessment of disc degeneration and disc herniations (protrusion, extrusion, sequestration). Moreover, possible osteochondrosis, spondylosis, osteoporosis with potential vertebral fractures, overall vertebral shape and potential endplate changes, spinal canal stenosis, and bone marrow changes in the examined participants will be appreciated. The MR protocol for musculoskeletal imaging overlaps anatomically in part with the protocol for thoracoabdominal imaging and therefore can extend the research foci; an example is the 1-mm isotropic 3D fast spin-echo sequence in the pelvis, which allows precise volumetric measurement of the prostate and its enlargement (47).

Quality Assurance

One of the major challenges of population-based imaging is to ensure high and identical image quality throughout the study period. In the MRI Study of the German National Cohort, a dedicated MR imaging core with different core units will serve as a central reference to address the challenges of quality assurance. All MR data acquired at each MR imaging center will be transferred to the central core, which in itself will provide long-term archived capacities.

The MR imaging core is designed as a distributed structure with a central coordination and training center (Munich, Germany), a dedicated MR data management center (Bremen, Germany), a quality assurance center (Greifswald, Germany), and a center for incidental findings (Heidelberg, Germany). The four centers are connected via a Web-based digital image management system that allows for *(a)* communication, *(b)* evaluation and monitoring of enrollment progress and image quality, *(c)* certification and evaluation of training status or readers, and *(d)* quality assurance and monitoring of the management of incidental findings.

Coordination and Training Center

The coordination and training center ensures coordination of the overall execution of the study, connects the imaging sites with the central MR imaging core, and ensures integration within the German National Cohort study. All study personnel will be centrally trained and certified in conducting fully standardized MR image acquisition and in on-site quality control. Respective adherence to trained procedures and standard operating procedures (SOPs) will be monitored by those at the coordination and training center via regular site visits. Image interpretation training will be coordinated with the centers for incidental findings and quality assurance in precisely defined tasks and closely interlinked roles, as will be described.

MR Data Management Center

The dedicated data management system provides the connection between the imaging sites, the imaging core centers, and the long-term data storage centers of the German National Cohort and the first steps of quality assurance. Basic automated quality assurance will include completeness of data, conformity of scan parameters and scan regions, and global image features that include signal-to-noise ratio and a universal image quality index (48). In detail, scores of program truth (complete MR examination) and protocol parameter truth (for each single MR protocol) are defined by cross comparison of each examination with a reference standard MR program covering a complete MR examination. Analysis of public and private Digital Imaging and Communications in Medicine header tags will enable extraction of order and timing information during the acquisition process and will reveal changes and deviations in relevant MR parameters. Subsequently, image volumes are evaluated by using automatically generated background and foreground image masks that offer position information, estimations of signal-to-noise ratio, image sharpness, structured noise, and N/2-ghosting level (49). The average assessment time for automated MR examination quality assurance is less than 60 minutes and is performed completely independent of the user and site.

The Web-based thin client tailored for the imaging program of the German National Cohort will provide additional capabilities of quality assurance

(visual image quality rating) and incidental finding readings at each of the MR imaging sites.

Center for Incidental Findings

This center is responsible for the management of incidental findings, which have been identified as a major challenge in population-based MR imaging (26,50–52). A particular challenge is attributed to the fact that the whole-body unenhanced MR protocol is designed for epidemiologic use with specific protocol parameters different from those used for clinical diagnostic imaging. From this protocol, results are obtained instead of diagnoses (eg, breast cancer cannot be observed with reasonable specificity). Further difficulties are the unavailability of clinical history, clinical imaging results, or laboratory information. It is not known whether the "participant" is a "patient" with an already known finding or disease. On the basis of clinical guidelines, recent research results, and ethical considerations (50), the most commonly expected incidental findings have been listed and categorized by expert panels into three groups according to clinical relevance and urgency as "actionable," "reportable," and "nonreportable."

Actionable results are those with a high likelihood to alter participants' well-being within a short time and to require urgent medical treatment to prevent adverse outcome; examples are pneumothorax, acute stroke, or intracranial hemorrhage. If these results are detected, the radiologist is required to get in direct contact with the participant and recommend immediate clinical work-up at the next available emergency department.

Reportable results are defined as follows: *(a)* the MR protocol allows high specificity for such a finding and *(b)* the finding has a reasonably high likelihood to alter participants' well-being. Both conditions must be applicable for a reportable result. Examples are an aortic aneurysm with a diameter of more than 5 cm or an abdominal mass with a diameter of more than 3 cm. The participant will be informed of the detected results via a standardized letter within approximately 10 working days after the examination.

All other nonreportable results are incidental findings without known clinical relevance or a high false-positive rate that will not be disclosed to the participants. The list of nonreportable findings is exemplary (cystic renal lesions, fatty masses, etc) and serves as a guideline for the reader to categorize other findings that he or she might observe.

The center has also defined a process pathway for incidental findings that are currently not listed but may have clinical relevance, as indicated by the local radiologists. It includes a committee of radiologists, general practitioners, epidemiologists, and ethicists who will determine whether a finding is actionable, reportable, or nonreportable based on the current clinical and scientific knowledge.

Together with the MR data management center, the center for incidental findings has developed a tool to mark and report incidental findings within the Web-based thin-client viewer. The center will keep all reporting algorithms updated and will include clinical developments during the entire study period. It will serve as a contact for local radiologists′ inquiries in unclear cases.

To ensure the highest quality standards, the center will oversee all readings, perform an overreading of a subset of data sets regarding the incidental findings, and provide mandatory standardized training for all local incidental finding readers, who can be nominated by the local MR sites (eligible are medical doctors who passed the National Board of Radiology examination and who are certified according to the internal quality assurance procedures). Reader certification involves personal on-site or Web-based training to ensure compliance with the SOPs. For certification of local radiologists, whole-body MR images with available reference standards must be assessed by the potential readers, and incidental findings must identified, marked, and reported in the same manner as during the study and according to SOPs. If the radiologists successfully pass the certification process, they will be granted access to the MR images via a personalized login. The access can be limited by study site, date, and login used.

The overreadings are performed by a senior radiologist from the center for incidental findings. The first five cases are reevaluated for each newly certified local radiologist and the first 20 cases for each newly activated MR site. In case of SOP deviations, direct contact is established to allow for corrective measures and repeat training, if necessary. Additionally, during the course of the study, overreading will be performed in a subset of 10% of all cases per site using stratified random sampling with oversampling participants in whom incidental findings have been detected.

Quality Assurance Center

To address the challenge of multicenter whole-body MR imaging, the quality assurance center will *(a)* monitor reader certifications, *(b)* monitor mean prevalence of incidental findings per reader and per site over time, and *(c)* perform reevaluation of the MR cases in regard to image quality to ensure highest adherence to the SOPs. The reevaluation of MR cases in regard to image quality is conducted in a random subset of 10% of all cases. Systematic deviations between sites, between individual readers, and/or over time are summarized and detected in comprehensive quality assurance reports, which provide comparative summaries of all previously outlined measures. Quality assurance reports are published quarterly throughout the entire data collection phase. The center initiates corrective measures, such as retraining of technical or medical personnel.

Furthermore, the quality assurance center coordinates all local and central procedures of quality assurance, such as the development and maintenance of SOPs and local quality assurance measures. This will be achieved in collaboration with the coordination and training center, which will develop procedures for and conduct site monitoring concerning SOP adherence in all

aspects of data acquisition. The quality assurance center is embedded into the quality management structure of the overall German National Cohort (25).

Summary

The MR Imaging Study of the German National Cohort will establish a large image repository and will eventually yield comprehensive phenotypic information from a large European population. It can be anticipated that relevant new information concerning the development of subclinical disease, overt disease states, and the relevance of findings on whole-body MR images will be derived. The derived MR data will complement the clinical, biochemical, and genetic factors in major pathophysiologic domains and will be available to the national and international scientific community.

To date, whole-body MR imaging has been used in smaller study cohorts and in the SHIP (Study of Health in Pomerania) project, a recently published population-based study comprising 3400 participants who underwent MR imaging in Germany (53). Implementation of larger MR imaging studies has been hampered by labor-intensive time-consuming acquisition techniques, which recently have changed greatly. However, it is still obvious that with limited imaging time available, applying whole-body imaging rather than organ-specific imaging (eg, neurologic imaging) represents a compromise between the achievable level of morphologic and functional details and a broad general coverage of the different body areas. In fact, this has resulted in the omission of many clinically and scientifically relevant pulse sequences (eg, vascular pulse sequences of the neurocranium or diffusion-tensor imaging). Also, without the use of a gadolinium chelate as a contrast agent, the diagnostic accuracy of native imaging is particularly limited with respect to oncologic disease detection and accurate assessment of the lungs, liver, pancreas, and kidneys.

In the setting of the German National Cohort, with a general focus on population-based disease states, the applied whole-body imaging protocol may represent a balanced and suitable approach to population-based imaging, exploiting recent advances in MR imaging technology and covering major organ systems simultaneously. Similar approaches currently are being undertaken in other large-scale cohort studies (54).

It is expected that the study results will be applicable to clinical practice through identification of novel imaging-based biomarkers that enable us to best predict individual risk. To date, evidence on whole-body MR imaging as a disease screening modality is limited and has been associated with overdiagnosis and risk of false-positive findings (55) while its clinical value in the diagnosis of systemic oncologic or inflammatory diseases is more established (56). In the setting of such large studies, the obtained high-contrast imaging information will be primarily used to assess the prevalence of subclinical disease states and normal variants and to understand pathophysiologic pathways in the natural history of disease development, but it will also be used to identify novel imaging biomarkers of risk due to the longitudinal study design. If the results are positive, these data may form the scientific basis to justify dedicated research (ie, cost-effectiveness analysis) to establish whole-body MR imaging in the setting of a broader risk assessment and screening. While particularly relevant to the potential role of whole-body MR imaging in a future screening context, the management of incidental findings, which are expected to occur in up to one-third of participants, poses an immediate major challenge to the conduct of the study (51). On the one hand, imaging findings may result in identification of early and potentially treatable disease (50). On the other hand, a patient's life could be affected by unnecessary work-up, including a follow-up examination or invasive procedures in the case of false-positive findings. Either possibility could introduce scientific bias to the initial study objectives. Within this spectrum of ethical considerations, the MR imaging study of the German National Cohort will use standardized algorithms and reporting systems for the various incidental findings. Board-certified radiologists will review all MR imaging data, and study participants will be notified if clinically relevant incidental findings are detected. However, as practicing clinicians know, there is a large category of findings with low or unknown importance for the health of the participants that will not be disclosed. While this approach is being closely followed by an expert panel, only the knowledge gained in the study will help redefine and optimize these management strategies for incidental findings.

Although existing cohort studies including imaging components have resulted in substantial advances in knowledge and have helped establish novel markers of risk, they have been limited in their ability to enable detection of smaller effect modification between groups and associations because of the small sample size. Thus, the relatively large sample size of the multicenter design of the German National Cohort covering major areas of a large European country will be particularly useful to elucidate smaller differences in the prevalence of subclinical disease between different regions and participants' distinct sociodemographic characteristics, such as migration background, specific genetic predispositions, or both. However, despite the relatively large sample size and detectable small differences between groups (Fig 3), there is the remaining risk that observed differences may not be identified with statistical confidence, especially with respect to genetic associations. Thus, the study is similarly tailored to enable pooling of MR imaging data with other European and non-European cohorts to identify even small observable variations between subgroups of participants.

Notably, assessment of smaller differences and variations requires one to take into account variability of every MR imaging phenotype of interest. While this has been accomplished for more established techniques, such as measurement of coronary calcification (57), these measures of accuracy are very limited in the field of whole-body MR imaging due to recent development

of the technique, and dedicated research will be necessary. However, applying identical MR imaging techniques and protocols throughout the imaging program of the German National Cohort will result in the lowest achievable variability.

In conclusion, population-based MR imaging as part of the German National Cohort represents not only a research opportunity to study the relationship between exposure and disease in a general European population with numerous scientific ramifications but also a challenge with respect to quality assurance, data postprocessing, and management of incidental findings. The implementation of identical MR imager technology and imaging protocols, as well as central imaging core structures, are critical to establish a comprehensive MR imaging data repository that will serve as a valuable source to advance our current understanding of major disease states and will eventually result in more tailored imaging-driven disease prevention strategies. Large prospective population-based cohort studies, such as the German National Cohort MR imaging study, are required to establish imaging-based biomarkers of risk.

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