

Rapid Body Composition Measurements Reveal Detailed Metabolic Changes in Large Scale Population Studies

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Introduction

Body composition measurements, such as adipose tissue compartments, muscle volumes, and muscle tissue composition are increasingly important in research and clinical context. Up until recently many MR-protocols in combination with analysis methods for segmenting muscle and fat compartments in the body were laborious and time-consuming. This has hindered implementation in large cohorts and in clinical applications. In this article we present a rapid and robust MR-protocol for body composition profiling and initial clinically relevant findings. This MR-protocol enables accurate measurements of visceral adipose tissue, abdominal subcutaneous adipose tissue, thigh muscle volumes, as well as other specific biomarkers such as liver and intra-muscular fat content. The MR-protocol and analysis method were applied and quality assured in the vast UK Biobank imaging cohort showing excellent results in terms of compliance and scan precision.

The UK Biobank imaging study

The UK Biobank is a very large and detailed prospective study following about 500 000 volunteers in the UK for over 25 years. Participants were aged from 40 to 69 when recruited between 2006 and 2010. The ambitious study collects data ranging from questionnaires and physical measurements to genome-wide genotyping. In 2014 an imaging sub-study was added to the biobank and the plan is to scan 100 000 participants by 2021. Participants are illegible for imaging if they have metal or electronic implants, had surgery within six weeks before imaging, or if they have medical conditions that would make it difficult to conduct the imaging, such as hearing or breathing problems. The UK Biobank imaging sub-study includes detailed MR examinations of the brain, heart, abdomen, and body (neck to knee), as well as ultrasound and dual-energy X-ray absorptiometry (DXA). The North West Multicentre Research Ethics Committee (MREC), UK, approved the study and written informed consent was

	First slab (neck region)	Slabs two to four (torso region)	Slab five (upper leg region)	Slab six (lower leg region)
Repetition time (ms)	6.69	6.69	6.69	6.69
Echo time (ms)	2.39 & 4.77	2.39 & 4.77	2.39 & 4.77	2.39 & 4.77
Bandwidth (Hz)	440	440	440	440
Slices (-)	64	44	72	64
Voxel size (mm ³)	2.23 x 2.23 x 3	2.23 x 2.23 x 4.5	2.23 x 2.23 x 3.5	2.23 x 2.23 x 4
Matrix size (-)	224 x 168	224 x 174	224 x 162	224 x 156
Breath-hold time (s)	-	17	-	-

Table 1: Summary of the 6-minute Dixon VIBE-based neck to knee body composition MR-protocol presented per region.

obtained from all participants prior to study entry [1, 2]. The research presented in this communication has been conducted using the UK Biobank Resource under Application Number 6569.

A body composition MR-protocol

All eligible participants were imaged using 1.5T MAGNETOM Aera MR-scanners (Siemens Healthcare, Erlangen, Germany). The participants were imaged in supine position with the arms along the sides, initial isocentering was performed with the laser crosshair on the participant’s clavicles and no localizer sequence was used. The MR-protocol was based on T1-weighted VIBE Dixon and had a total cranio-caudal coverage of of 1.1 m divided over six overlapping slabs of axial 3D spoiled gradient dual-echo images. The acquired images covered a region between the neck and the knees. Detailed protocol

parameters are presented in Table 1 and the parameters differed between the slabs depending on which anatomical region was being imaged. Over the torso region (slabs two to four) imaging was performed during 17 s expiration breath-hold. The total time for the MR body composition protocol was about 6 minutes. Reconstruction of Dixon water and Dixon fat images was performed using the integrated scanner software. Examples of the reconstructed water and fat images are shown in Figures 1A, B for two participants.

Body composition profiling

The body composition profile of all participants was based on quantifying fat and muscle compartments such as visceral adipose tissue, abdominal subcutaneous adipose tissue, and thigh muscle volumes as well as intra-muscular and liver fat content (hepatic proton-

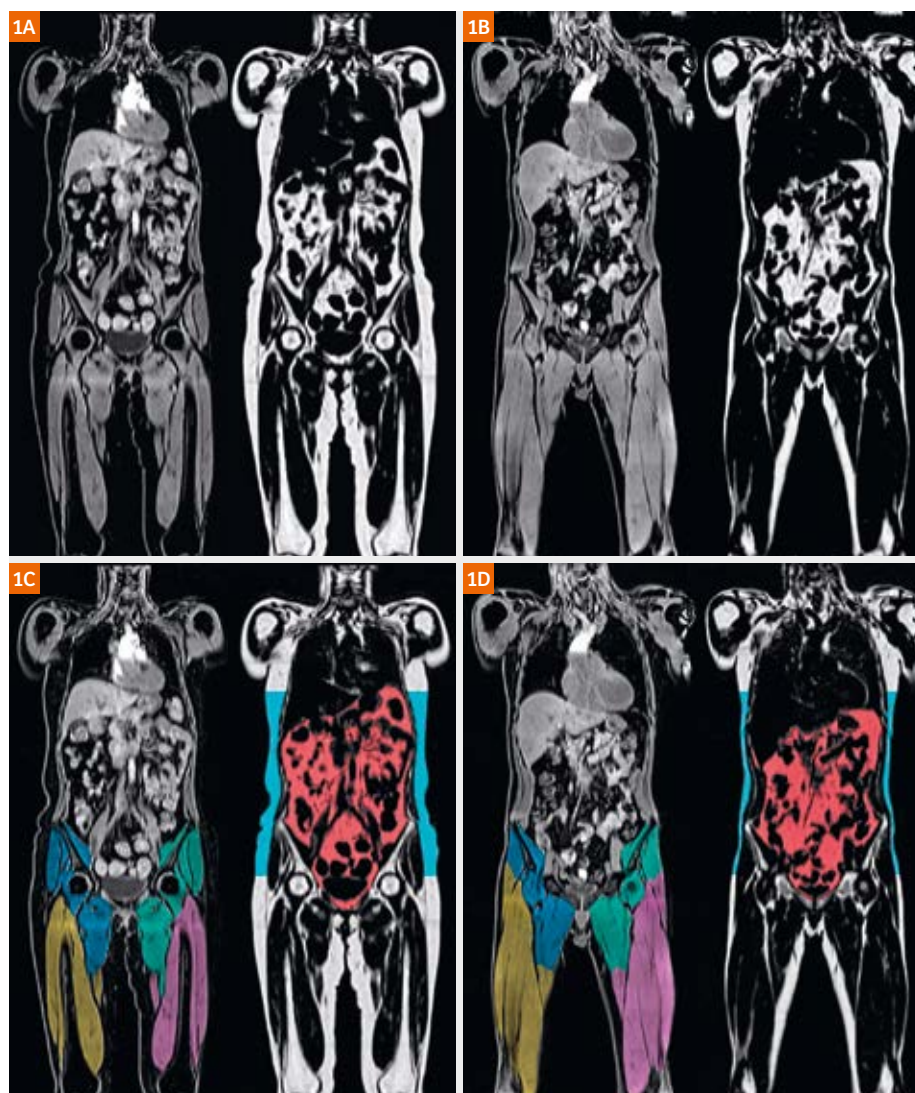


Figure 1: Top row shows sample reconstructed water- and fat-volumes from the Dixon VIBE-based neck to knee MR-protocol for a female (1A) and male (1B) participant.

Sample segmentation results are shown in the bottom row for the female (1C) and male (1D) participants.

In the water images (left) the segmented thigh muscles are presented in false color and in the fat images (right) the segmented visceral (red) and subcutaneous (blue) adipose tissues are shown.

density fat fraction; PDFF). Body composition profiling was performed using the commercially available service AMRA® Profiler (Advanced MR Analytics AB, Linköping, Sweden). The profiling consisted of the following steps:

1. automatic image calibration,
2. automatic labeling and registration of fat and muscle regions to the acquired image volumes,
3. quality control of anatomical regions and MR-data performed by trained analysis engineers at Advanced MR Analytics, and
4. quantification of fat and muscle volumes based on the calibrated images.

Full details of the body composition profiling can be found in [2].

The semi-automated methods for analysing the body composition profile have up to now been shown to provide high repeatability and accuracy for adipose abdominal tissue volume, thigh muscle volumes, and liver fat content Proton Density Fat Fraction [3, 4]. Examples of segmented and labeled fat and water images are presented for two participants in Figures 1C–D, and four participants with normal BMI but different body composition profiles are presented in Figures 2A–D.

Feasibility of using the MR-protocol in a large population study

Quality control of the MR-protocol was analyzed in depth on the first 3 000 participants of the imaging study of UK Biobank. Of those first cases 2 995 (99.83%) were analysable for body fat, 2 775 (92.50%) were fully analysable for body fat and both thigh muscles. The main reasons for the dataset not being analysable were missing slabs in the acquisition, or improper positioning so that large parts of the volume were outside the field-of-view. Most types of artifacts were infrequently observed and water-fat swaps were uncommon. The conclusion was that the short Siemens MR-protocol was well tolerated by most participants and was sufficiently robust to achieve a very high success-rate for body composition profiling in a large population study [2].

Initial clinical findings

Obesity is a worldwide epidemic associated with significant costs. The traditional definition of obesity, based on body mass index (BMI), lacks detailed information on fat distribution. Moreover, the diseases relating to the metabolic syndrome may also affect muscle volumes and fat accumulation in organs such as the liver. Thus we sought to explore how the detailed body composition profile acquired in the UK Biobank imaging study is

associated with important disease manifestations. In the analyses discussed below the visceral, total abdominal, and subcutaneous adipose tissue volumes were normalized with the square of the height.

In 2016 an analysis of the first 3 900 participants was presented. From these we analyzed 194 participants with diagnosed type 2 diabetes mellitus with age and gender matched controls and reported a strong association between type 2 diabetes and high visceral and total abdominal adipose tissue volumes, increased liver fat content, and low muscle ratio (defined as the total lean thigh muscle volumes normalized with body weight). When BMI was also included in the matching criteria the association of visceral adipose tissue volume and liver fat content to type 2 diabetes remained [5]. Cardiovascular disease is another disease relating to the metabolic syndrome. When we explored the body composition profiles for 213 participants with a history of cardiovascular events (angina, heart attack, or stroke) with age and gender matched controls with high blood pressure a strong disease association was found for multiple body composition parameters. Specifically, the visceral and total abdominal adipose tissue volume as well as liver fat content was significantly higher in the cardiovascular disease group whereas the muscle ratios were found to be lower, the association between visceral fat and cardiovascular disease remained when BMI was also included in the matching criteria [6].

As the inclusion in the UK Biobank imaging study continued we explored a larger group in 2017 (6 021 participants) and we found that the visceral adipose tissue volume and intra-muscular fat content were significantly associated with prior hospitalization [7]. An obese sub-population in this large group was further explored for the association to previous cardiovascular events and type 2 diabetes. In this case we found that visceral adipose tissue volume was significantly higher for both the diabetic and cardiovascular event groups. The participants that had reported previous diabetes had a lower muscle ratio and higher intra-muscular fat content than the participants without previous diabetes or cardiovascular events. The liver fat content was significantly higher in the diabetic group compared both controls and the cardiovascular event groups, no significant differences were observed comparing controls to the cardiovascular event group [8].

The non-alcoholic fatty liver disease spectrum is of growing concern and multiple pharmaceutical companies and research groups are working diligently to explore potential treatments to this worldwide epidemic. The disease spectrum is initially characterized by increased liver fat content (hepatic steatosis) and in the obese sub-population we explored if a fatty liver was associated

with increased health care burden (defined by the accumulated hospital nights). This analysis was slightly more complex as the association was significantly negative when controlling for visceral and total abdominal adipose tissue volumes (the models were also adjusted for age, sex, smoking, alcohol intake, and physical activity). The observation suggested that hepatic steatosis may have a link to visceral adiposity in participants with an increased health care burden in a phenotype presenting with high visceral adipose tissue volume together with low liver fat content [9].

Sarcopenia is a common problem in the aging population as well as in certain disease states, such as non-alcoholic steatohepatitis. In the UK Biobank imaging study DXA, which is typically used to diagnose sarcopenia, is also acquired and in 2016 we explored the relationship between the body composition profile derived from the MR-exami-

nation and the DXA-based biomarker for sarcopenia. We found that the total lean thigh muscle volume divided by the square of the height could be used to identify sarcopenic participants with an AUROC of 0.96. This suggests that sarcopenia can be characterized from this Siemens MR body composition protocol with high sensitivity and specificity [10].

Conclusions

In this article we have presented a robust and rapid neck to knee MR-protocol for Siemens MR-scanners that can deliver high technical success rates in large scale population studies. We have also presented initial clinical findings based on analysing the body composition profile in such a large population. We believe that this is a widely applicable method in a clinical and research setting investigating metabolic disease, muscle degenerative

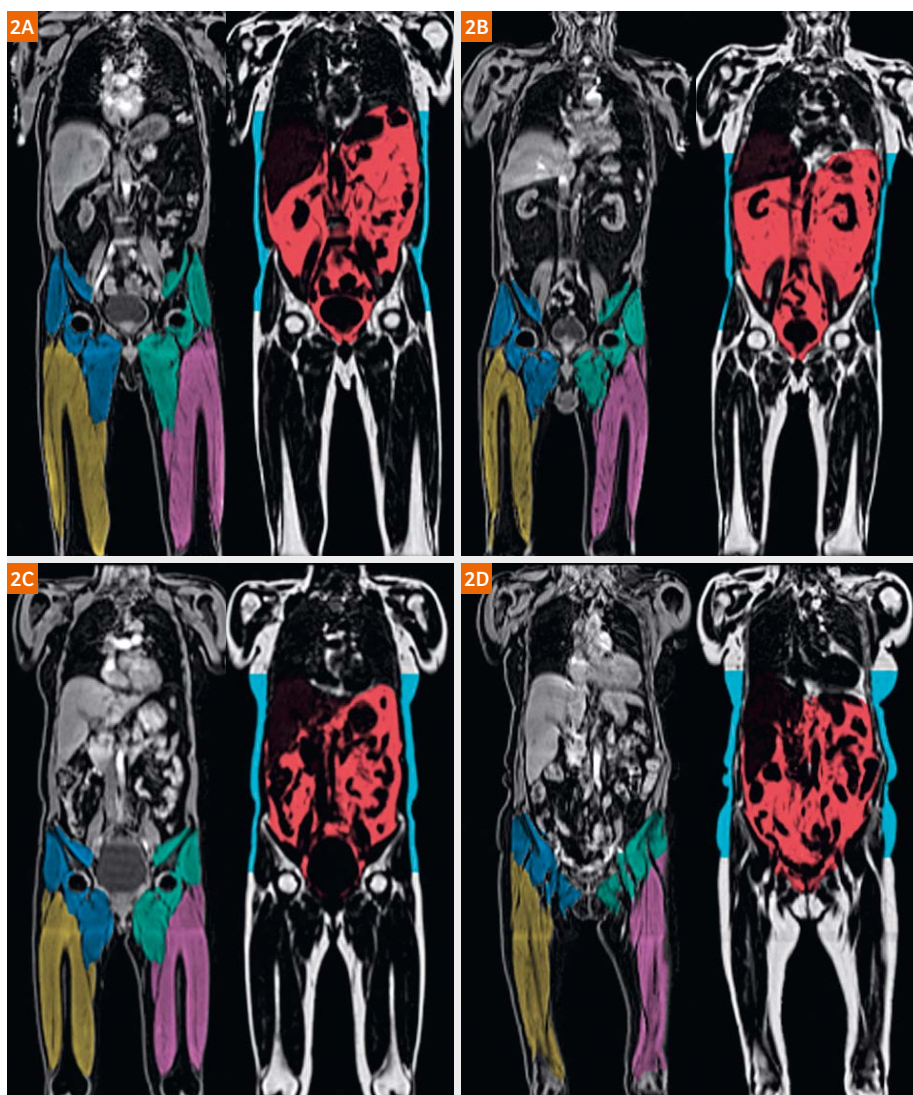


Figure 2: Four sample reconstructed water- and fat-volumes from the Dixon VIBE-based neck to knee MR-protocol for participants with normal BMI but different body composition profile. In the water images (left) the segmented thigh muscles are presented in false color and in the fat images (right) the segmented visceral (red) and subcutaneous (blue) adipose tissues are shown. The panels show (2A) a 63-year-old male with a BMI of 22.7 kg/m², (2B) a 67-year-old male with a BMI of 24.9 kg/m², (2C) a 55-year-old female with a BMI of 21.9 kg/m², and (2D) a 70-year-old female with a BMI of 23.9 kg/m².

disease, as well as metabolic components of other diseases. The simultaneous assessment of multiple important fat and muscle compartments increase the understanding of the complex interplay between disease development and metabolic processes.

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