Quantitative MRI in obesity & reno-cardiovascular function

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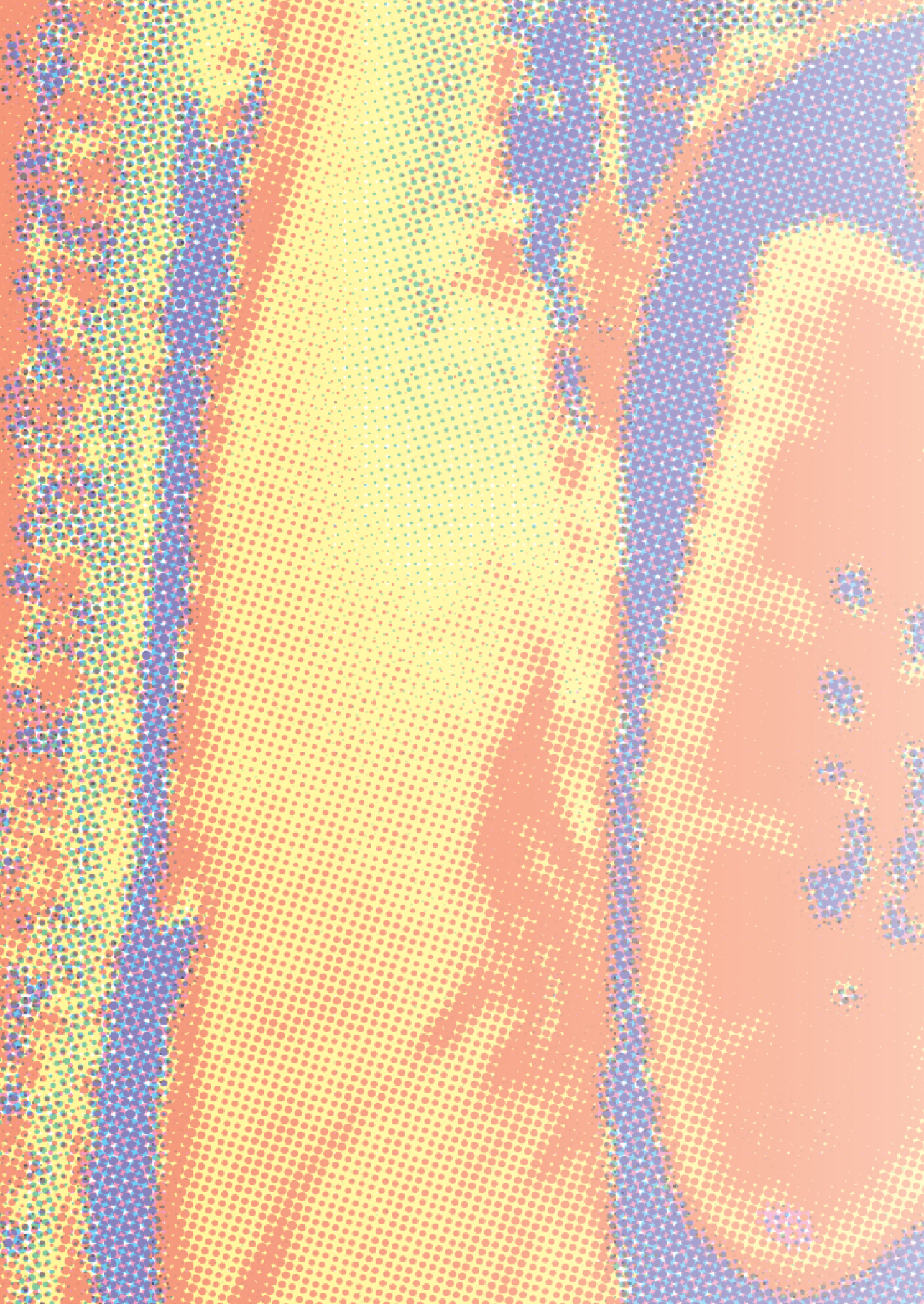

INTRODUCTION

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General introduction and thesis outline

INTRODUCTION

In the past century, medical imaging has undergone several great transformations. First, from diagnosing pathologic conditions based on distinguishing abnormal opacities and lucencies on chest X-rays, to a discipline that is focused on defining and locating such conditions based on cross-sectional imaging by computer tomography (CT) and magnetic resonance imaging (MRI). The introduction of MRI has made it possible to diagnose diseases based on anatomical location of particular abnormalities, combined with contrast between "affected" and "normal" tissues due to differences in relaxation times of hydrogen atoms (e.g. longitudinal and transverse relaxation times) based on the underlying biophysical properties of the tissue of interest. The introduction of these techniques has radically changed the practice of medicine, making medical imaging essential in diagnostics as well as in the evaluation of therapeutic efficacy. In the 21st century, radiology is expected to evolve into a specialty that has integrated artificial intelligence with human interpretation to increase consistency and reduce errors in image analysis (1). This requires a new level of quantitative measurement metrics as conventional MRI is intrinsically insensitive to detect diffuse changes affecting the imaged tissue or organ of interest. The use of quantitative MRI based metrics allows for less biased and more reproducible measures compared to qualitative interpretations, and can be used for statistical modelling and longitudinal evaluation (2). The fields of neuroimaging and cardiovascular imaging were among the first to adopt quantitative imaging metrics, and in cardiovascular imaging the use of quantitative measures is considered part of standard clinical care. In body imaging however, the clinical application of quantitative MRI is less wide spread and in renal MRI only used in research settings, whilst these organs are particular vulnerable for diffuse disease to which conventional MRI is intrinsically insensitive. In addition, conditions that could potentially affect multiple organ systems, such as the metabolic syndrome, diabetes and obesity, could in particular be evaluated using multi-organ quantitative MRI metrics. The use of quantitative MRI allows for the comparison of individual measurements with normative values obtained from healthy populations. In the clinical setting, these quantitative MRI metrics could be utilized for monitoring treatment effect.

Aims of this thesis

The aims of this thesis are to evaluate quantitative MRI techniques in reno-cardiovascular health, and to study the links between obesity and reno-cardiovascular health using quantitative MRI metrics. Furthermore, we aim to address novel insights on the safety of contrast media with regard to the use of gadolinium.

Magnetic resonance imaging

MRI is based on the phenomenon of nuclear magnetic resonance, and MR images are constructed by measuring signals emitted from spinning anatomic nuclei (hydrogen in this thesis) in response to radiofrequency pulses with the same natural frequency as the nuclei themselves (3). The location of the excited protons (^{1}H atoms) is determined via predefined applied magnetic field gradients, and information on amplitude, frequency and phase of MR signals are mapped in K-space that result in the final MR image after the Fourier transform (3). Magnetization relaxation rates T1, T2, and proton density (PD) are important tissue-specific parameters that are characteristic for different body tissues, with T1 representing the rate of regrowth of longitudinal magnetization, T2 the rate of decay of transverse magnetization after the start of the MR experiment, and PD reflecting the actual density of protons (4). For qualitative interpretation of MRI, the images are obtained at a time when the relaxation curves are widely separated for different body tissues, producing an image that has high contrast between these tissues (e.g. T1-weighted images) with signal intensities on an arbitrary scale. Parametric maps however, are calculated matrices from two or more images of the same tissue of interest that have individual pixel values with numerical meaning (such as T1 in ms for T1 mapping) (2). Although MR images are conventionally displayed as gray-scale images for qualitative interpretation, the MR signals can also be reconstructed in a different basic "readout" compared to MR imaging, namely as a spectrum rather than an image (5). This is the basis of MR spectroscopy (MRS), in which the MR spectrum consists of resonances or peaks that represent signal intensities as a function of frequency (designated in parts per million) within a voxel of interest (6).

There are different ways in which MRI can be used for quantification of different image-derived phenotypes. This quantification of MR images, referred to as quantitative MRI, can be defined as the extraction of quantifiable features from medical images for the assessment of normal or the severity, degree of change, or status of a disease, injury, or chronic condition relative to normal (7). Quantification using MRI can broadly be done in four different approaches. First, quantification can be done on visual borders of anatomical structures using 'qualitative' MR images, such as in volumetric analysis. Second, quantification is possible via direct measurement of specific nuclear MR characteristics within a certain tissue-of-interest reflecting the tissue specific relaxation properties or tissue microstructure, as in parametric mapping and diffusion tensor imaging respectively. Third, specific organ function can be measured by changes in position of spins over time, as used in phase imaging and arterial spin labelling, or changes in magnetic susceptibility over time as in blood oxygen level-dependent imaging. Fourth, concentrations of different metabolites of a voxel of interest can be measured by MRS using the constructed MR spectrum.

Quantitative MRI in renal imaging

The global burden of kidney disease is considerable, as over 10 percent of the global adult population suffers from chronic kidney disease, and more than 2 million individuals annually endure acute kidney injury in developed countries (8,9). Currently, most kidney disorders are usually diagnosed by biochemical serum and urine analysis (e.g. serum creatinine). As biochemical analyses alone often provide insufficient information for classifying disease, renal biopsies commonly remain required for making a definitive diagnosis (10). Recent advances in new MRI techniques enable the measurement of biophysical tissue properties that have been linked to fibrosis, inflammation, tissue edema, perfusion, filtration and tissue oxygenation that can be used to study renal disease in patients non-invasively over time (11). As such, quantitative measurement of these renal biophysical tissue properties might contribute to earlier diagnosis, treatment-monitoring, and for evaluating the pathophysiology of potential risk factors of CKD and AKI. Quantification of tissue relaxation is a promising technique in renal imaging as it potentially enables the measurement of biophysical properties linked to fibrosis, analogous to imaging of myocardial scar in cardiac imaging or cirrhosis in liver imaging. In **Chapter 2**, we discuss the clinical application and technical considerations of multi-parametric of the kidney. Importantly, before the clinical application of novel quantitative MRI protocols can be further explored for the kidney, evaluation of the reproducibility of these new quantitative renal MRI protocols is needed first. As such, we explored the reproducibility of renal native T1 mapping and renal proton MR spectroscopy (^{1}H-MRS) in **Chapter 3**, and **Chapter 5** respectively. As renal quantitative MRI is a novel field, there is a need for a standardized approach to improve comparability of results by different research groups and to establish a common benchmark to evaluate future developments. To facilitate these aims, we developed an expert-based consensus imaging protocol for renal T1 mapping using the Delphi method, which is described in **Chapter 4**. Finally, we performed a clinical study evaluating the biomarker potential of renal triglyceride content measured by ^{1}H-MRS, which is described in **Chapter 6**.

MRI in epidemiological research

Epidemiology involves the study of the distribution and determinants of disease frequency (12). Prospective cohort studies are, as exposures can be assessed before they are affected by treatment or disease (thus avoiding recall bias and minimizing reverse causation), suited for identification and quantification of risk factors for disease (13). Prospective cohorts can be based on either a large amount of data on a small number of participants (e.g. the Framingham Heart Study, with extensive phenotyping of 5000 participants (14)), or a relatively small amount of data on a large number of participants (e.g. the Million Women Study, with questionnaire data on 1.3 million women (15)). In the recent decades, MRI has because of its non-invasive nature, increasingly been applied to population cohorts,

also referred to as population-based imaging studies. With the rapidly increasing sample sizes of population-based imaging studies, it can be considered as an emerging field with widespread applications and enabling multi-organ assessment (heart, liver, brain, vessel, kidney etc.) during one imaging session (16). Technical advances in image acquisition, optimized imaging sequences and automated post-processing of imaging data are among the major drivers of these rapid developments in population imaging (16). In the second part of this thesis, we present population-based imaging studies using quantitative MRI, in which **Chapter 7** to **Chapter 9** are based on the imaging data of the Netherlands Epidemiology of Obesity (NEO) study and **Chapter 10** is based on the UK Biobank. The NEO study (https://neostudie.nl) is a population-based cohort study in 6,671 men and women aged 45 to 65 years from the greater Leiden area, with an oversampling of individuals with a BMI of 27 kg/m^2 or higher (17). The NEO study is designed to investigate pathways that lead to common diseases and conditions, and the studies presented in thesis involve cross-sectional analyses of the baseline data of the NEO study. The UK Biobank Study (https://ukbiobank.ac.uk) is a large population-based cohort study in 503,325 men and women aged 45 to 69 years who were recruited across the United Kingdom (18). The study in this thesis based on UK Biobank data is a cross-sectional analysis of the imaging data of a consecutive subset of participants who underwent additional MRI scanning.

Quantitative MRI in cardiovascular imaging

Global cardiovascular mortality is increasing due to aging and population growth. Despite gains in cardiovascular health (19), it has been estimated that 40-55% of the decline in coronary heart disease in high-income countries can be attributed to the effects of medical and surgical treatments (20). The utilization of cardiovascular imaging tests including cardiac MRI is rapidly increasing in order to assist in clinical decision making (21). The possibility to quantify various aspects of the cardiovascular system (e.g. anatomy, function, flow, and perfusion) in different phases of the cardiac cycle under different conditions (rest and stress), makes cardiac MRI a promising tool for accurate and reliable assessment of cardiovascular risk. In **Chapter 2**, an overview is given on the similarities and differences of quantitative multiparametric imaging in cardiac, liver, and renal disease. **Chapter 7** and **Chapter 8** present the use of different quantitative metrics on left ventricular (LV) geometry, LV function and vascular function based on cardiac MRI in population-based studies evaluating the associations between renal and cardiovascular function.

Quantitative MRI in obesity

The disease burden related to obesity has increased significantly over the last decades, making excess body weight one of the most challenging public health problems of our time (22). Cardiovascular disease is globally the leading cause of death and disability

related to a high body mass index (BMI), followed by diabetes, and chronic kidney disease for BMI-related death and disability respectively (22). Increasing evidence indicates that global microvascular dysfunction is the underlying common pathway of obesity-related disease, leading to dysregulation of vascular tone, insulin resistance, and altered levels of paracrine and inflammatory factors (23). Subsequently, these changes could lead to impaired organ function and perfusion, predisposing obese individuals to the development of chronic kidney disease, microvascular dementia, and heart failure with preserved ejection fraction (23), see **Fig. 1**. BMI is currently used to classify overweight (25-30 kg/m^2) and obesity (>30 kg/m^2), however since BMI poorly differentiates between body fat, muscle mass, and water, this could lead to misclassification of cardiometabolic health risks (24,25). This limits the use of BMI as a clinical tool to identify overweight and obese individuals with excess visceral fat (who represent the subgroup of individuals at highest cardiometabolic risk), which has led to various strategies for the quantification of body fat distribution (26).

One of the unique capabilities of MRI is the detection of lipids based on its specific nuclear MR characteristics, making MRI ideal for the non-invasive visualization and quantification of fat. Lipids are stored in large vacuoles within adipocytes which consist for 99% of triglycerides and less than 1% of cholesterol, phospholipids, and free fatty acids (27). The MR signal obtained when exitating adipose tissue consists of signal based on protons from lipids (>80% of the signal), and signal based on protons from water molecules located within the loose connective tissue (<20% of the signal) of white fat (27). The ability of MRI to depict lipids against background water content stems from the intrinsic differences in the rate of nuclear spin relaxation (T1), with the T1 of fat being shorter than the T1 of water (27). These intrinsic differences in T1 are used in relaxometry based approaches, which are applied to quantify visceral and subcutaneous fat depots. Another difference between water and fat is that protons in water have a slightly different local magnetic field than protons in a lipid molecule, resulting in a "chemical shift" (difference in effective magnetic field induced by electron shielding) which leads to a slight difference in precessional frequency between water- and lipid-bound protons (6). Because of these differences in nuclear MR characteristics between water and fat, it is possible to accurately, precisely, and reliably quantify fat distributions throughout the body and inside organs (28). Chemical shift is widely used in different MR sequences such as frequency selective and water-fat MR imaging techniques, however also MR spectroscopy is based on the same principles of chemical shift imaging. Since ^{1}H-MRS enables the analysis and quantification of the chemical composition of a tissue volume of interest, this technique is very well suited for the quantification of low amounts of ectopic lipids.

MR imaging and spectroscopy can be used to accurately quantify different body fat distributions, i.e. visceral fat, subcutaneous fat, and intra-organ ectopic lipid accumulation, which is highly relevant in obesity studies since the distribution of fat accumulation

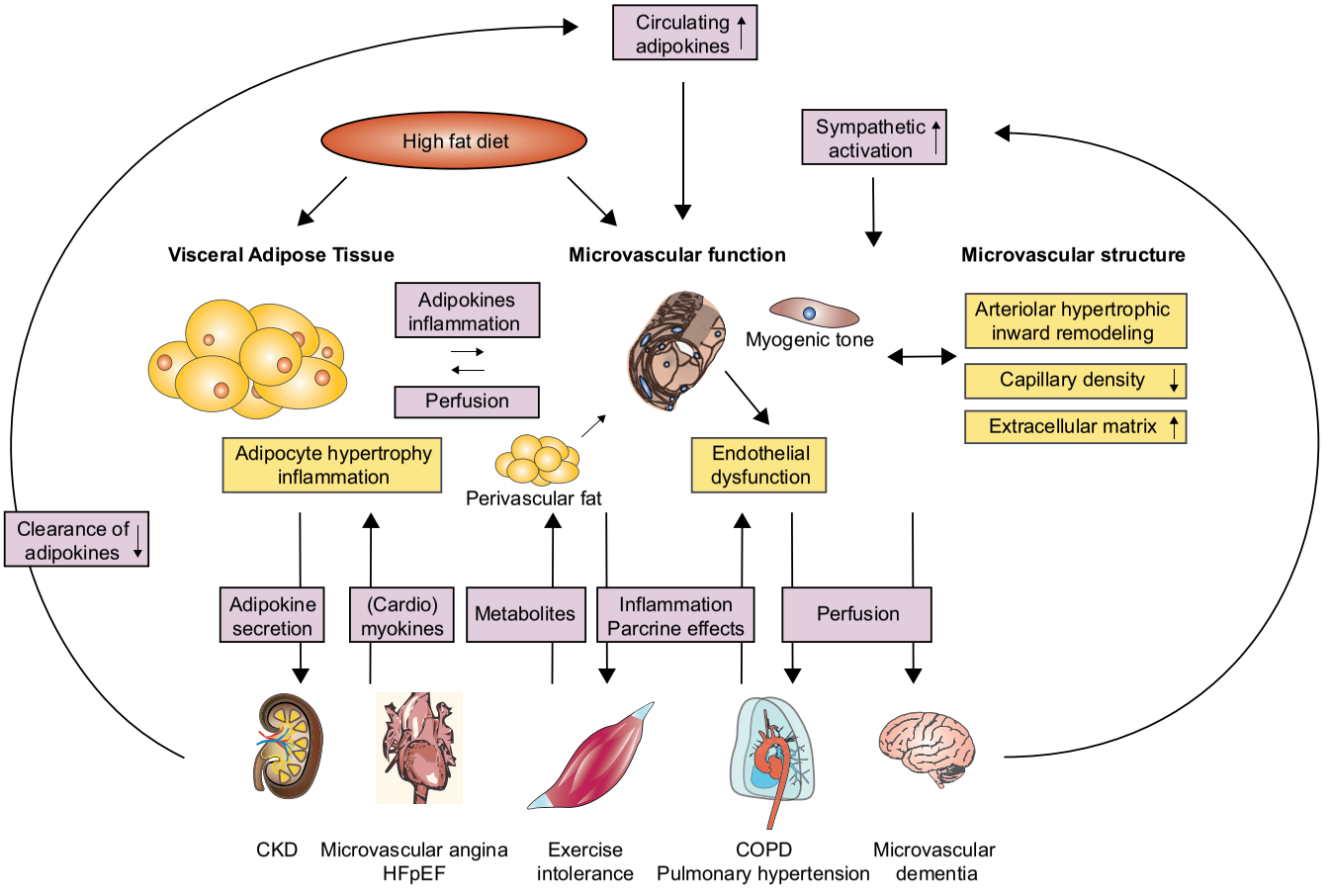

Figure 1. overview of proposed mechanisms of obesity-related global microvascular dysfunction predisposing to multi-organ disease, adapted from Sorop et al. (23).

is strongly related to metabolic risk (29,30). In addition, quantitative MRI can be used to study obesity in a holistic approach (e.g. to assess the inter-organ relation and multi-organ impact of obesity). In this thesis, we studied the negative health effects of obesity on a several organs using MRI. In **Chapter 5** and **6**, we explore the application of ^{1}H-MRS for the quantification of renal steatosis. In **Chapter 9**, we describe a population-based study that evaluates the associations between visceral adipose tissue, liver triglyceride content and renal function. In addition, considering obesity has been associated with an increased risk of dementia (31), we investigated whether measures of obesity were associated with brain morphology and microstructure in **Chapter 10**.

Contrast media safety

Gadolinium containing contrast agents (GCCAs) are used in MR imaging for improved lesion detection, and characterization for various indications such as in evaluation of malignancies, infections, inflammation, and vascular diseases. The safety profile of GCCAs is based on the strong binding properties of the chelate to the paramagnetic gadolinium ion (Gd^{3+}) to assure nearly complete renal excretion (33). GCCAs can be classified based on structure (linear or macrocyclic), and charge (ionic or nonionic), where macrocyclic chelates have demonstrated higher in vivo stability, and are thus considered safer than linear agents (33). The identification of nephrogenic systemic fibrosis (NSF) as a rare but serious adverse reaction to (mainly) linear GCCAs led to a new perception of the safety profile of GCCAs, and restricted the use of GCCAs in patients with an estimated renal filtration rate below 30 ml/min/1.73m^2 (34). Recent findings on accumulation of miniscule amounts of gadolinium in the human body have spurred further reassessments of the safety profile of GCCAs, which in July 2017 led to the recommendation of suspension of marketing authorization of linear chelates by the European Medicine Agency (EMA). In **Chapter 11**, we provide an overview of the safety profile of all GCCAs, and reflection of the EMA recommendations.

THESIS OUTLINE

This thesis is structured as follows. First, we evaluate the reproducibility and clinical validity of T1 mapping and ^{1}H-MRS in renal imaging, and provide consensus-based technical recommendations for renal T1 and T2 mapping (**part 1**). Second, we study the associations between obesity and reno-cardiovascular health, and multi-organ impact of obesity in population-based imaging studies using different quantitative MRI metrics (**part 2**). Finally, we contemplated contrast media safety with regard to the use of gadolinium (**appendix**).

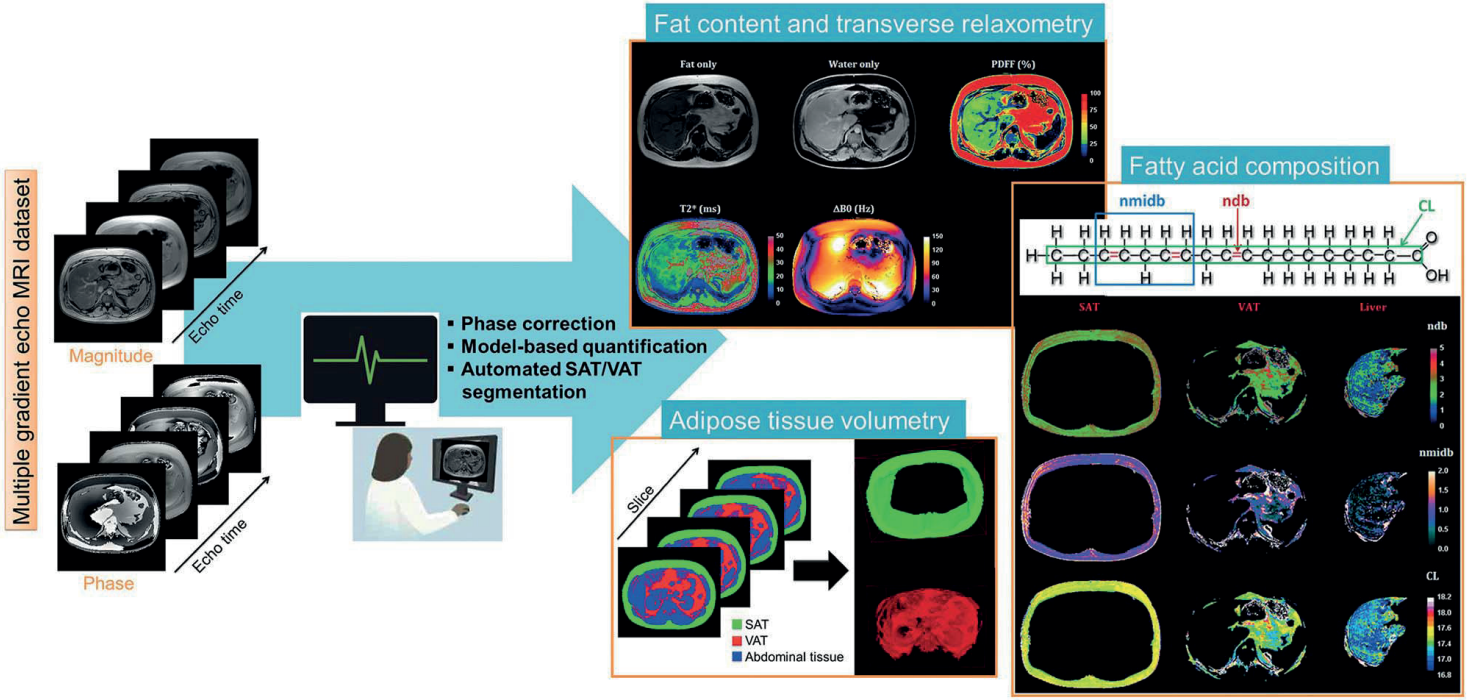

Figure 2. Different MRI approaches for the quantification of body fat distribution (32).

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