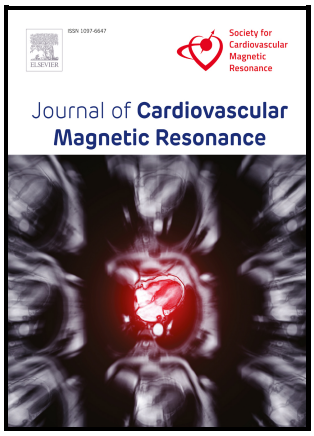
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Myocardial Native T1 Mapping in the German National Cohort (NAKO): Associations with Age, Sex, and Cardiometabolic Risk Factors

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Myocardial Native T1 Mapping in the German National Cohort (NAKO): Associations with Age, Sex, and Cardiometabolic Risk Factors

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Abstract

Background: In cardiovascular magnetic resonance (CMR), myocardial native T_1 mapping enables quantitative, non-invasive tissue characterization and is sensitive to subclinical changes in myocardial structure and composition. However, data on the association between cardiometabolic risk and myocardial alterations are still limited. We therefore investigated how age, sex, and cardiometabolic risk factors are associated with myocardial T_1 as a potential imaging marker of myocardial target-organ involvement in a population-based analysis within the German National Cohort (NAKO).

Methods: This cross-sectional study included 29,573 prospectively enrolled participants who underwent midventricular T_1 mapping using 3.0 T CMR along with deep clinical phenotyping. After artificial intelligence-assisted myocardial segmentation, a subset of 9,162 outlier cases was subjected to manual quality control according to clinical evaluation standards. Cardiometabolic risk factors were identified through self-reported, physician-diagnosed medical history, clinical chemistry, and blood pressure measurements. Associations with myocardial T_1 were evaluated using multiple linear regression models adjusted for age, sex, heart rate, imaging site, and comorbidities.

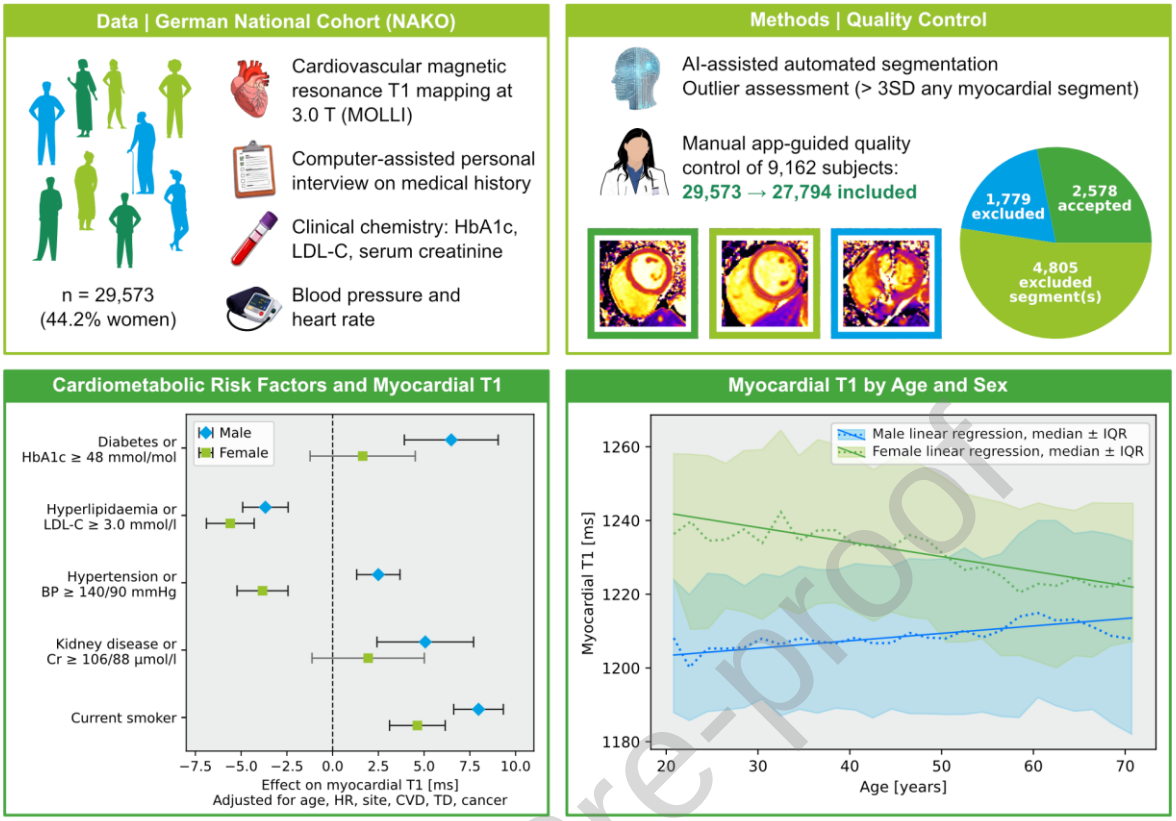
Results: After quality control, 27,794 participants (12,401 [44.6%] women; 20–75 years) were included. Mean T_1 was overall higher in women (1,231 ± 33 ms) than in men (1,209 ± 34 ms), with differences progressively declining with age. The sex difference was confirmed in a healthy subcohort (n = 3,910), whilst age interaction was less pronounced. In adjusted analyses, T_1 was significantly higher in individuals with diabetes, kidney disease, and current smoking. Conversely, hyperlipidaemia was significantly associated with lower T_1. Associations with hypertension showed strongly sex-specific patterns: women had lower T_1 values, while T_1 increased with hypertension severity in men.

Conclusions: Myocardial native T_1 varies by sex and age and shows distinct sex-specific associations with major cardiometabolic risk factors, supporting its role as a sensitive imaging marker of subtle myocardial alterations. Unexpectedly lower T_1 times in participants with hyperlipidaemia suggest a potential direct effect of blood lipids on the heart, which warrants further investigation.

Keywords

German National Cohort (NAKO); T_1 mapping; cardiovascular magnetic resonance; myocardium; cardiometabolic; cardiovascular disease

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Graphical Abstract: Associations of Age, Sex, and Cardiometabolic Risk Factors with Myocardial Native T_1 in the NAKO Study

Bottom left panel: unstandardized β coefficients and 95% confidence intervals from multiple linear regressions, stratified by sex. Bottom right panel: linear regression (solid line), median (dotted line), and interquartile range (shaded area) in 2-year age bins, stratified by sex. The last bin is defined as ≥ 70 years. MOLLI: modified look-locker inversion recovery; LDL-C: LDL-cholesterol, AI: artificial intelligence; SD: standard deviation; BP: blood pressure; Cr: serum creatinine; HR: heart rate; CVD: cardiovascular disease; TD: thyroid disease; IQR: interquartile range

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Abbreviations

AHA	American Heart Association
AI	artificial intelligence
BMI	body mass index
BP	blood pressure
CAD	coronary artery disease
CI	confidence interval
CMR	cardiovascular magnetic resonance
Cr	serum creatinine
CVD	cardiovascular disease
ESC	European Society of Cardiology
HR	heart rate
LDL-C	LDL-cholesterol
MAP	mean arterial pressure
MOLLI	modified look-locker inversion recovery
MR	magnetic resonance
NAKO	German National Cohort
SD	standard deviation
TD	thyroid disease

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Introduction

Myocardial native T_1 mapping by cardiovascular magnetic resonance (CMR) is a quantitative, non-invasive imaging marker of myocardial tissue composition [1,2]. The technique is sensitive to diffuse processes including inflammation, oedema, interstitial fibrosis or myocardial infiltration with iron or lipid deposits and has proven helpful in diagnosing and monitoring cardiovascular disease [3]. Importantly, T_1 mapping enables the detection of subclinical changes in myocardial tissue composition, potentially capturing early stages of cardiac pathology [4].

The German National Cohort (NAKO) is a population-based prospective study comprising over 100,000 women and 100,000 men aged 19 to 75 years with extensive phenotyping, aimed at investigating the causes of chronic diseases [5]. Its whole-body magnetic resonance (MR) imaging subcohort comprises 30,868 individuals who underwent standardized 3.0 T MR imaging at five centres across Germany with near-simultaneous clinical and laboratory assessments [6]. Given the high prevalence of cardiometabolic comorbidities and metabolic syndrome in the general population and the NAKO study [7], non-contrast CMR offers a promising tool for detecting myocardial alterations in these individuals.

Major cardiometabolic risk factors such as diabetes, hypertension, hyperlipidaemia, chronic kidney disease, and smoking are believed to promote adverse structural myocardial remodelling through mechanisms including low-grade inflammation and fibrosis [8–12]. Native T_1 mapping may therefore serve as a sensitive, albeit non-specific, imaging marker of myocardial target-organ involvement. In the UK Biobank, T_1 mapping at 1.5 T was found to be associated with prevalent cardiovascular disease and incident events in participants aged 44 to 84 based on hospital registry data [13]. However, large-scale prospective studies examining sex-stratified effects of cardiometabolic risk factors on myocardial tissue composition are still lacking, and data from younger individuals and from 3.0 T imaging remain limited. Moreover, while previous studies have reported sex differences of myocardial native T_1, the role of age remains inconsistent and insufficiently understood [13–15].

In this cross-sectional analysis of the NAKO MR cohort, we investigated how cardiometabolic risk factors, age, and sex are associated with native T_1 as a marker of myocardial tissue composition.

Methods

Study Population

This study leverages data from the NAKO at baseline [6] and included 29,573 participants (13,075 [44.2%] women) with a midventricular T_1 map obtained by CMR and corresponding data from self-questionnaires and clinical chemistry. Participants in the NAKO MR cohort were randomly selected from resident registers and scanned between 2014 and 2019 across five German imaging centres, ensuring uniform protocols and equipment (3.0 T MAGNETOM Skyra, Siemens Healthineers, Forchheim, Germany) [16]. A modified look-locker inversion recovery (MOLLI) 5(3)3 T_1 mapping technique was used to acquire a midventricular short-axis T_1 pixel map. Imaging parameters are reported in the Supplementary Material and include a voxel size of 1.4×1.4×8.0 mm and a flip angle of 35°. The average interval between clinical examination and MR imaging was 28 to 42 days.

Analysis and Quality Control

Automatic segmentation of the myocardium and identification of the right ventricular insertion point were performed using a deep learning-based research algorithm (Siemens Healthineers, Forchheim, Germany) [17,18]. Mean T_1 values were calculated globally and for the six midventricular segments defined by the American Heart Association (AHA) [19] using dedicated in-house research software [20].

After exclusion of repeated or failed T_1 mapping acquisitions, image quality and artificial intelligence (AI)-generated segmentations were reviewed manually by an experienced physician if the mean T_1 time of at least one myocardial segment differed by more than three standard deviations from age- (10-year groups) and sex-specific means. A custom Python tool enabled visual inspection of T_1 maps with overlayed contours alongside corresponding source images and metadata. In case of insufficient image quality due to inadequate breathing motion correction or co-registration of individual images, electrocardiographic trigger errors, incorrect orientation or other image artifacts [21] not limited to individual myocardial segments, the entire examination was excluded from analysis. If at most three segments had to be excluded, the mean myocardial T_1 time was calculated over the remaining segments weighted by their area. Manual quality control followed recommendations for clinical evaluation [1].

To validate the analysis pipeline, 100 cases were selected using random sampling (weighted for age, sex, as well as cardiovascular and metabolic condition prevalence) and were reanalysed manually in CE-certified medical software for comparison with results from automated segmentation.

Statistical Analysis

Statistical analyses were carried out in Python 3.12 using statsmodels 0.14.4 and following recommendations for analysing NAKO data [22]. Variables of interest included: age, sex,

body mass index (BMI), blood pressure, heart rate, self-reported cardiovascular or metabolic diseases, current smoking, and laboratory parameters (HbA1c, LDL-cholesterol, serum creatinine). Medical history was collected via standardized computer-assisted personal interview limited to physician-diagnosed conditions. Variables were primarily sourced from the clinical examination, with age extracted from DICOM metadata.

Mean T_1 relaxation time was analysed by sex and myocardial segment. Since lateral segments generally exhibit more artifacts and lower T_1 values, all statistical analyses were additionally performed for the two septal segments only and are reported in the Supplementary Material. A healthy subcohort was defined as follows: none of the diseases listed in Table 1, no current smoking, BMI between 18.5 and 30.0 kg/m^2, blood pressure < 140/90 mmHg, LDL-cholesterol < 3.0 mmol/l (116 mg/dl), HbA1c < 48 mmol/mol (6.5%) and serum creatinine < 106 µmol/l (1.2 mg/dl) for men or < 88 µmol/l (1.0 mg/dl) for women. By combining reported conditions and clinical chemistry, we aimed to exclude both treated patients with controlled disease and undiagnosed diseased participants.

Ordinary least squares linear regression was used to examine the associations of age, sex, and their interaction (age×sex) with myocardial T_1 in the full cohort. Heart rate and imaging site were included as covariates due to the potential sensitivity of the MOLLI sequence to heart rate [1,23] and minor variations between sites (Supplementary Figure S1). Age was mean-centred to aid interpretation and reduce collinearity. Unstandardized regression coefficients β with 95% confidence intervals are reported to facilitate direct interpretation in the unit of T_1 (ms). We observed a strong sex dependency that varied by age. This relationship was visualized using linear regression, median and interquartile range in 2-year bins. Heart rate was linearly associated with T_1 (β = 0.35 [0.31–0.38] ms/bpm; $p < 0.001$). The five imaging sites revealed small but statistically significant differences (all $p \leq 0.008$). Accordingly, all subsequent analyses were adjusted for heart rate, imaging site, age, sex, and their interaction; where appropriate, analyses were also stratified by sex.

To evaluate the association between cardiometabolic risk factors and myocardial T_1 relaxation times, we used multiple linear regression models with T_1 as the dependent variable. Independent variables of interest comprised the presence of self-reported diabetes or elevated HbA1c, reported hyperlipidaemia or elevated LDL-cholesterol, reported hypertension or elevated measured blood pressure, reported kidney disease or elevated creatinine levels, and current smoking. The limits for blood parameters corresponded to those defined for the healthy subcohort. For LDL-cholesterol, the target value for low-risk populations (< 3.0 mmol/l) specified by the European Society of Cardiology (ESC) and European Atherosclerosis Society was used [24]. Other cardiovascular disease (myocardial infarction, coronary artery disease, heart failure, arrhythmia, peripheral artery disease) as

well as thyroid disease and cancer were included as covariates in the regression model. Detailed medication data were not available in the full cohort and could therefore not be included as covariates; the reported associations thus reflect cardiometabolic risk independent of specific treatment effects.

In a sub-analysis, blood pressure was categorized according to the ESC hypertension classification [25] into grade I (≥ 140/90 mmHg), grade II (≥ 160/100 mmHg), grade III (≥ 180/110 mmHg), and isolated systolic or diastolic hypertension. We calculated sex-stratified linear regression models with myocardial T_1 as the dependent variable and hypertension category as the main independent variable, adjusting for all other variables from the primary model. In a further linear regression analysis restricted to participants with self-reported hyperlipidaemia, the influence of lipid-lowering therapy was examined, adjusting for all covariates from the previous models.

Variance inflation factors remained below 2.0, indicating no relevant multicollinearity. Subjects with missing values were omitted from the respective analyses. BMI was excluded from the regression models as it may act as a mediator in the causal pathway from lifestyle or metabolic factors to cardiometabolic conditions such as hypertension and diabetes. Adjusting for BMI in this context could attenuate the observed effects of these conditions on myocardial T_1.

Nonlinear associations between BMI, mean arterial pressure (MAP) and heart rate with myocardial T_1 were explored separately using locally estimated scatterplot smoothing stratified by sex. Medians and 95% confidence intervals were bootstrapped for equal-width bins, and sex-stratified density plots were displayed along the same horizontal axis for each variable.

Ethics

This study was approved by the NAKO Use and Access Committee, based on the participants' informed consent and consistency with the objectives of the NAKO. Ethical approval for the NAKO study was obtained from the responsible local ethics committees of all study centres. The study was conducted in accordance with the Declaration of Helsinki and subsequent amendments.

Results

Quality Control

Of the 29,573 available T_1 maps, 9,162 images with corresponding myocardial segmentation were selected for manual quality control, following the criteria outlined above. Among these,

1,779 subjects were excluded entirely from the analysis, while 4,805 cases involved the exclusion of one to three individual myocardial segments. The quality control procedure and results are illustrated in Figure 1. Artifacts were most frequently found in the inferolateral (n = 3,631) and inferior (n = 2,757) myocardial segments (Supplementary Table S1). The exclusions reduced the standard deviation of the overall mean T_1 in the final dataset from 48 ms to 35 ms, while the mean itself remained unchanged (difference < 0.1 ms). Following quality control, a total of 27,794 (12,401 [44.6%] women) participants were included in the final analysis. Manual validation showed excellent agreement with automated results (intraclass correlation ICC(3,1) = 0.96 [0.94–0.97]; $p < 0.001$; Supplementary Figure S2).

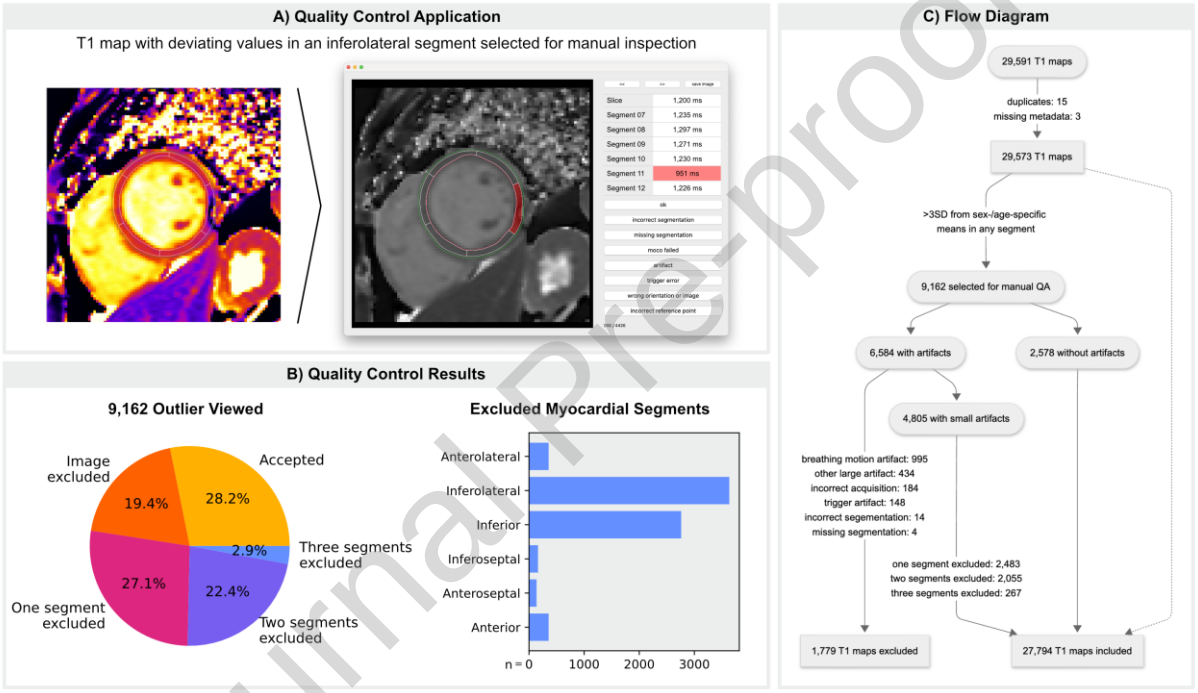


Figure 1: Manual Quality Control

A) T_1 maps with abnormal values that deviate by more than three standard deviations from age- and sex-specific means in at least one myocardial segment are displayed together with the artificial intelligence-generated segmentation in a Python-based interface. Individual segments with artifacts can be excluded from the analysis by clicking on the respective area. B) Results from manual quality control. C) Flow diagram of participants' inclusion and exclusion criteria.

Participant Characteristics

Participant characteristics and the prevalence of self-reported conditions are summarized in Table 1. Following the definition outlined above, 3,910/27,794 (14.1%) participants were assigned to the healthy subcohort (Supplementary Table S2). For the combination of self-reported medical history and elevated blood parameters, 1,341/27,794 (4.8%) participants reported diabetes or had elevated HbA1c, 18,263/27,794 (65.7%) reported hyperlipidaemia or had elevated LDL-cholesterol, 10,363/27,794 (37.3%) reported hypertension or had

elevated blood pressure, and 1,147/27,794 (4.1%) reported kidney disease or had elevated serum creatinine levels.

Table 1: Basic Characteristics of Participants and Prevalence of Self-Reported Conditions

	Men (n = 15,393)	Women (n = 12,401)	Missing Values
Age [years]	48.3 ± 12.4 [20–75]	49.0 ± 12.2 [20–74]	0/27,794 (0.0%)
BMI [kg/m²]	26.8 ± 4.1 [15.6–52.3]	25.8 ± 5.2 [14.9–54.6]	352/27,794 (1.3%)
Heart rate [bpm]	68.8 ± 10.8 [24–147]	70.8 ± 10.1 [28–120]	15/27,794 (0.1%)
Systolic BP [mmHg]	131.0 ± 14.6 [83–218]	122.9 ± 16.3 [81–234]	15/27,794 (0.1%)
Diastolic BP [mmHg]	80.4 ± 9.8 [49–136]	76.8 ± 9.7 [48–129]	15/27,794 (0.1%)
HbA1c [mmol/mol]	36.0 ± 6.5 [15–131]	35.7 ± 5.6 [6–127]	651/27,794 (2.3%)
LDL-cholesterol [mmol/l]	3.4 ± 0.9 [0.4–8.0]	3.2 ± 0.9 [0.7–9.9]	664/27,794 (2.4%)
Serum creatinine [µmol/l]	80.8 ± 14.5 [7–641]	64.7 ± 10.8 [11–347]	544/27,794 (2.0%)
Self-reported, physician-diagnosed medical history			
Diabetes	659/15,393 (4.3%)	505/12,401 (4.1%)	31/27,794 (0.1%)
Hyperlipidaemia	3,470/15,393 (22.5%)	2,608/12,401 (21.0%)	192/27,794 (0.7%)
Hypertension	3,903/15,393 (25.4%)	2,594/12,401 (20.9%)	57/27,794 (0.2%)
Kidney disease	245/15,393 (1.6%)	261/12,401 (2.1%)	46/27,794 (0.2%)
Current smoker	2,954/15,393 (19.2%)	2,169/12,401 (17.5%)	537/27,794 (1.9%)
Myocardial infarction	67/15,393 (0.4%)	19/12,401 (0.2%)	24/27,794 (0.1%)
CAD or angina pectoris	157/15,393 (1.0%)	60/12,401 (0.5%)	68/27,794 (0.2%)
Arrhythmia	958/15,393 (6.2%)	940/12,401 (7.6%)	146/27,794 (0.5%)
Heart failure	205/15,393 (1.3%)	168/12,401 (1.4%)	94/27,794 (0.3%)
Peripheral artery disease	152/15,393 (1.0%)	99/12,401 (0.8%)	61/27,794 (0.2%)
Thyroid disease	1,326/15,393 (8.6%)	4,061/12,401 (32.7%)	95/27,794 (0.3%)
Cancer	654/15,393 (4.2%)	810/12,401 (6.5%)	61/27,794 (0.2%)

Values are mean ± standard deviation [min-max] or count (%). Missing values were omitted for the regression models. BMI: body mass index; BP: blood pressure; CAD: coronary artery disease

Age and Sex Dependence of Myocardial T_1

The mean myocardial T_1 relaxation time for 27,794 participants was 1,219 ± 35 ms at 3.0 T. Septal T_1 (1,237 ± 40 ms) was significantly ($p < 0.001$ by two-sided paired t-test) higher than in lateral segments (1,200 ± 46 ms). Inferolateral and inferior segments had the highest variance in T_1 values (Figure 2).

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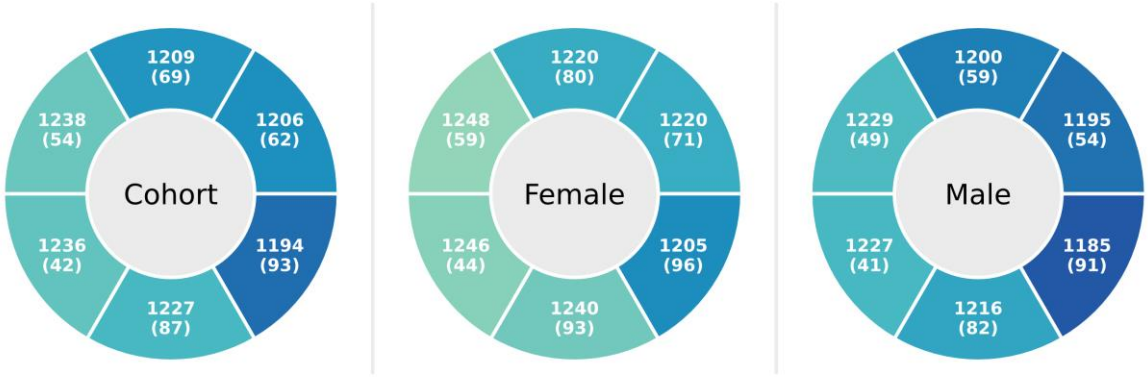


Figure 2: Polar Plots for Mean Myocardial T_1 per AHA Segment

Values are given as the mean and average standard deviation of T_1 within each segment (i.e., the mean of the standard deviations of individual pixel values). AHA: American Heart Association

In adjusted linear regression models, sex was significantly associated with myocardial T_1 relaxation time (β = 20.96 [20.18–21.74] ms at the mean age of 48.6 years; $p < 0.001$). However, the effect of sex varied with age and showed a significant interaction ($p < 0.001$). While T_1 increased with age in male participants (β = 0.20 [0.16–0.24] ms/year; $p < 0.001$), the age dependence was even stronger but inverse for women (β = −0.37 [−0.42 to −0.33] ms/year; $p < 0.001$) when stratified by sex. Mean values are shown in Table 2 by 10-year age groups (with the last bin covering ages 60 to 75). Corresponding values for septal segments only are provided in Supplementary Table S3.

Table 2: Mean Myocardial T_1 by Age Group and Sex

Age	Men		Women	
Group	mean ± SD	n	mean ± SD	n
20-29	1,205 ± 28	1,532	1,235 ± 33	1,167
30-39	1,207 ± 30	2,082	1,238 ± 34	1,427
40-49	1,208 ± 31	4,246	1,235 ± 32	3,445
50-59	1,210 ± 35	4,348	1,227 ± 31	3,643
60-75	1,213 ± 38	3,185	1,224 ± 32	2,719
Total	1,209 ± 34	15,393	1,231 ± 33	12,401

Two-way analysis of variance: age group $p < 0.001$; sex $p < 0.001$; age group-sex interaction $p < 0.001$. SD: standard deviation; n: number of subjects

In the healthy subcohort, the mean T_1 time was 1,220 ± 36 ms for 3,910 participants. Healthy women (1,237 ± 34 ms) had higher T_1 than healthy men (1,205 ± 30 ms). Visually, the age dependency appeared less pronounced in the healthy subcohort (Figure 3), which was statistically confirmed by a significant sign-reversed three-way interaction term ($p = 0.009$).

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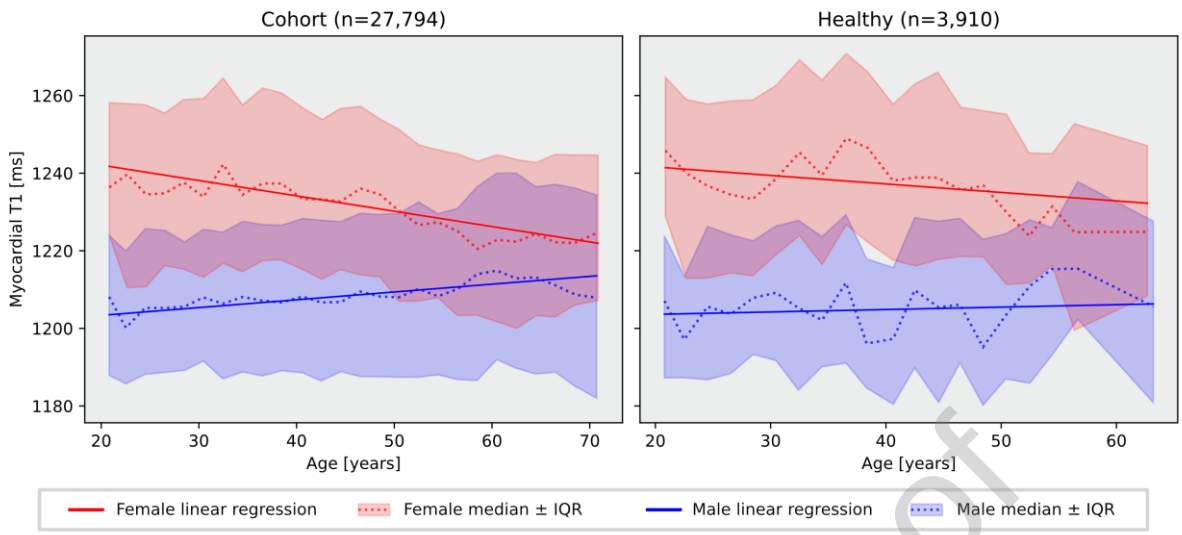


Figure 3: Age and Sex Dependence of Myocardial T_1

Linear regression (solid line), median (dotted line), and interquartile range (shaded area) shown in 2-year age bins, stratified by sex. The last bin is defined as ≥ 70 years for the whole cohort and ≥ 58 years for the healthy subcohort.

Associations of Cardiometabolic Risk Factors with Myocardial T_1

Multiple linear regression analyses adjusted for age, sex, age×sex, heart rate, imaging site, and relevant comorbidities yielded the following results: Self-reported diabetes or elevated HbA1c (β = 4.14 [2.23–6.06] ms; $p < 0.001$) and kidney disease or elevated serum creatinine levels (β = 3.64 [1.63–5.64] ms; $p < 0.001$) were both associated with significantly higher T_1 times in the overall cohort. When stratified by sex, both associations remained significant in men ($p < 0.001$) but not in women ($p = 0.263$ and $p = 0.215$, respectively). Current smoking was associated with elevated myocardial T_1 (β = 6.60 [5.59–7.62] ms), while hyperlipidaemia or elevated LDL-cholesterol was significantly associated with lower myocardial T_1 values in the overall cohort (β = −4.69 [−5.59 to −3.79] ms) and in both sexes (all $p < 0.001$). Sex-specific effects were observed for reported hypertension or elevated blood pressure, with a significant positive β in men (β = 2.50 [1.31–3.68] ms; $p < 0.001$) and a significant negative β in women (β = −3.83 [−5.22 to −2.44] ms; $p < 0.001$). In the entire cohort, the association was not significant ($p = 0.931$). Corresponding regression coefficients and confidence intervals are illustrated in Figure 4 and provided in Supplementary Table S4. A confirmatory analysis restricted to septal segments rendered comparable results (Supplementary Figure S3). Among participants with hyperlipidaemia, lipid-lowering therapy was associated with a nonsignificant, small decrease in myocardial T_1 (β = −0.92 [−2.99 to 1.14] ms; $p = 0.381$).

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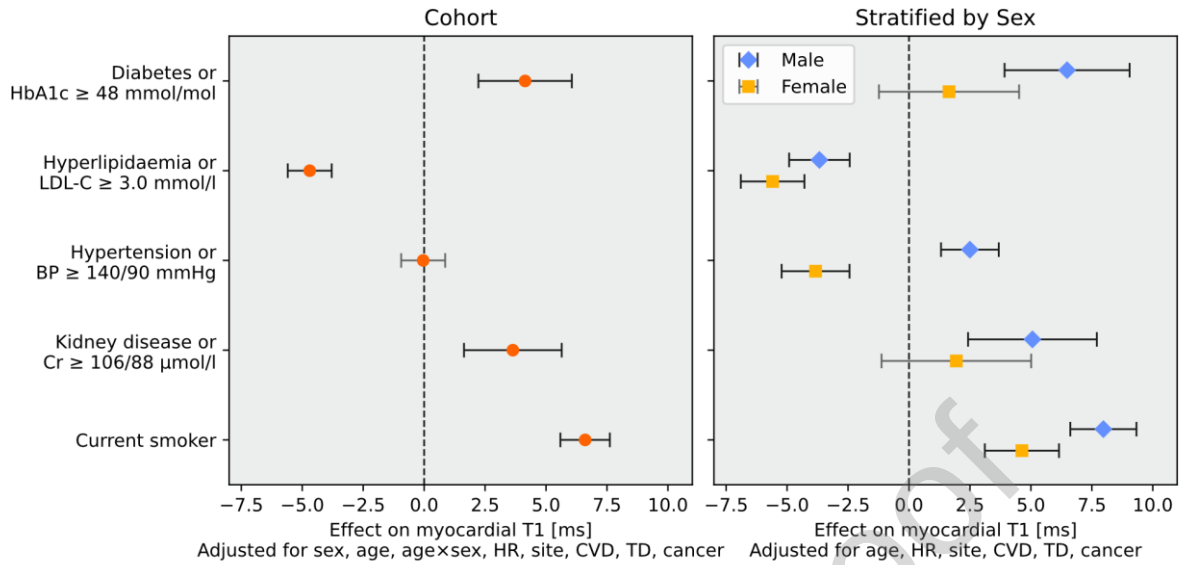


Figure 4: Associations of Cardiometabolic Risk Factors with Myocardial T_1

Unstandardized β coefficients and 95% confidence intervals from adjusted multiple linear regressions for the whole sample (left panel) and stratified by sex (right panel). Covariates included sex, age, age×sex, heart rate (HR), imaging site, cardiovascular disease (CVD), thyroid disease (TD), and cancer. LDL-C: LDL-cholesterol; BP: blood pressure; Cr: serum creatinine

Body mass index exhibited a nonlinear, U-shaped relationship with myocardial T_1, with higher T_1 values observed in both underweight and overweight individuals (Figure 5). Consistent with the findings from the regression model, there was a pronounced and unexpected negative correlation at low blood pressure values (MAP < 90 mmHg) in female participants, while blood pressure was almost linearly positively correlated in male participants. The heart rate showed an approximately linear positive relationship to T_1 for both sexes.

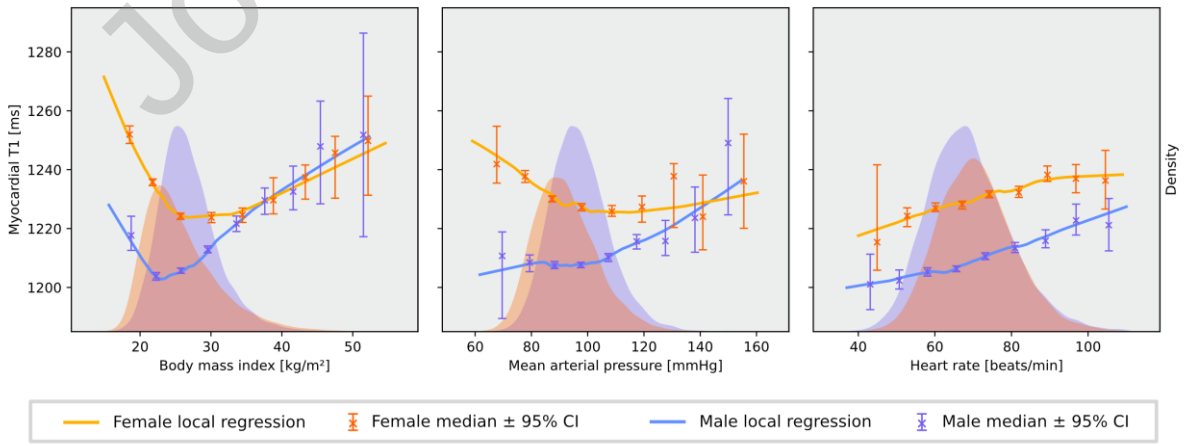


Figure 5: Local Regressions for Body Mass Index, Mean Arterial Pressure and Heart Rate

Locally estimated scatterplot smoothing, stratified by sex. Median and 95% confidence interval (bootstrapped with 1,000 iterations) are shown for nine equal-width bins. Values below the 0.1st or above the 99.9th percentile for

heart rate were excluded. Two outliers were excluded for mean arterial pressure. Kernel density plots for men (blue) and women (orange) are displayed on a secondary y-axis along the same horizontal axis. CI: confidence interval

Association of Hypertension Severity with Myocardial T_1 by ESC Classification

In the sex-stratified, adjusted sub-analysis based on the ESC classification of measured blood pressure (Figure 6), a progressive association between hypertension severity and myocardial native T_1 time was observed in men. Compared with normotensive individuals, T_1 gradually increased in men from grade I (β = 3.05 [0.93–5.17] ms; p = 0.005) to grade III hypertension (β = 8.21 [2.40–14.02] ms; p = 0.006), while isolated diastolic or systolic hypertension showed no significant trends (p = 0.551 and p = 0.300, respectively). Among women, isolated diastolic hypertension (β = −3.89 [−7.27 to −0.52] ms; p = 0.024) and isolated systolic hypertension (β = −3.10 [−5.36 to −0.83] ms; p = 0.007) were significantly associated with lower myocardial T_1 time, while no significant associations were observed for grade I (p = 0.236), grade II (p = 0.418), or grade III hypertension (p = 0.715).

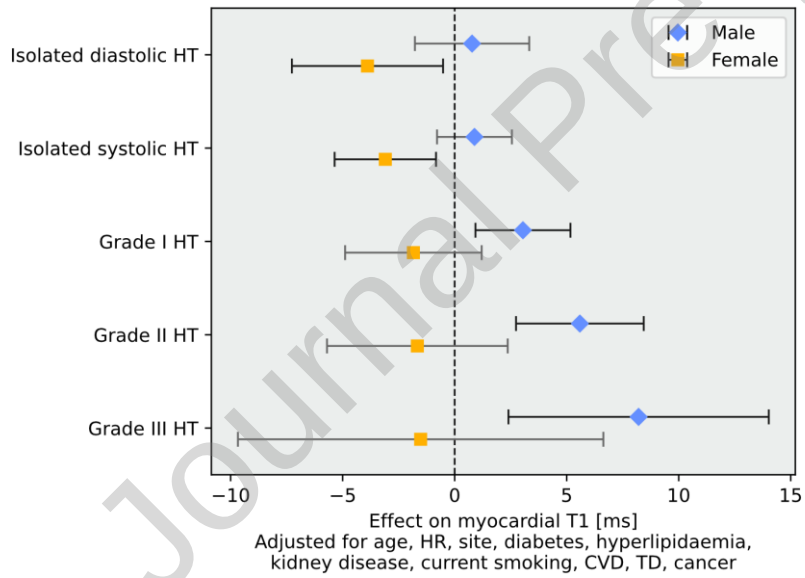


Figure 6: Sex-Stratified Associations of ESC Hypertension Categories with Myocardial T_1

Unstandardized β coefficients and 95% confidence intervals from adjusted multiple linear regression, stratified by sex. Covariates included age, heart rate (HR), imaging site, diabetes, hyperlipidaemia, kidney disease, current smoking, cardiovascular disease (CVD), thyroid disease (TD), and cancer. Definitions for diabetes, hyperlipidaemia and kidney disease were based on medical history and clinical chemistry. HT: hypertension

Discussion

Summary of Key Findings

In this large-scale analysis of 3.0 T CMR-based T_1 mapping in the NAKO study, we report associations between age, sex, and cardiometabolic risk factors with myocardial native T_1 in

27,794 participants. Women exhibited overall significantly higher T_1 values, with the sex difference progressively decreasing with age. Notably, we discovered an inverse relationship between hyperlipidaemia and myocardial T_1 and found sex-specific associations for cardiometabolic risk factors, especially hypertension.

Sex and Age Dependence of Myocardial T_1

The observed sex differences in T_1 are consistent with previous findings [13–15,26,27]. While the influence of age remains controversial in the literature [14,26], our analysis aligns with results from healthy participants in the UK Biobank [13]. The broader age distribution in the NAKO cohort allowed inclusion of younger adults and the capture of the menopausal transition, which may contribute to the observed sex-age interactions. Although thinner myocardial walls in women [28] might increase sensitivity to partial-volume effects, this alone is unlikely to account for the marked difference. The confirmatory analysis for septal segments further supports the internal validity of our findings. In the healthy subcohort, the age dependency was less pronounced and may therefore encompass differences in age-specific prevalence of diseases between sexes. Overall, the T_1 values in our cohort were slightly higher than those reported in the literature when using a 5(3)3 MOLLI sequence at 3.0 T (Supplementary Table S5).

Hyperlipidaemia and Myocardial T_1

The significant association of elevated blood lipids with lower myocardial T_1 is a novel and unexpected finding. Hyperlipidaemia typically promotes fibrosis via atherosclerotic pathways [29] and would therefore be more consistent with prolonged T_1 times [1]. Our results suggest additional mechanisms, with possible explanations including altered myocardial lipid metabolism or myocardial steatosis, as fat deposits are known to reduce T_1 times. There is growing evidence that serum lipids may accumulate and have direct effects on the heart independent of atherosclerosis [12]. Adipocyte infiltration of the myocardium has been described in obesity [30,31]. Moreover, MR spectroscopy has shown that triglyceride accumulation in the myocardium can also occur in otherwise healthy individuals, e.g. during fasting [32]. Hyperlipidaemia could therefore contribute to lower myocardial T_1 values through lipid accumulation in the heart. However, our data do not provide insights into the underlying mechanisms. While statin therapy has been reported to reduce extracellular volume expansion [33], lipid-lowering medication showed only a weak and nonsignificant association with myocardial T_1 in our analysis.

Sex-Specific Association of Hypertension with Myocardial T_1

The observation that hypertension is associated with elevated myocardial T_1 in men and lower values in women, indicates a potentially sex-specific cardiac response to pressure overload. One possible explanation lies in sex-specific hormonal and genetic regulation of

blood pressure and target-organ damage [34]. The observed difference aligns with one study reporting greater strain impairment in hypertensive men [35], but contrasts with another [36], where female sex was independently associated with structural left ventricular remodelling. Differing results may be related to women losing the cardioprotective effects of oestrogen in the context of obesity and diabetes, potentially influencing the myocardial response to hypertension [34,35]. Furthermore, technical factors could play a role as hypertension-related thickening of the heart muscle may reduce partial-volume effects and thus contribute partly to the lower T_1 values measured in women [37]. In men, the observed progressive increase in native T_1 values across hypertension grades I to III suggests a dose-response relationship, where higher blood pressure levels are associated with greater myocardial tissue alterations.

Diabetes, Kidney Disease, and Smoking

Our findings of elevated myocardial T_1 in individuals with diabetes, kidney disease or current smoking likely reflect known pathophysiological mechanisms: In recent studies, diabetes was independently associated with higher native T_1 values, indicating potential subclinical myocardial dysfunction before structural remodelling occurs [13,38]. Higher T_1 values in individuals with diabetes may reflect expanded intracellular water volume in hypertrophied cardiomyocytes [38]. Additionally, advanced glycation end-products increasingly form in the presence of chronic hyperglycaemia and are linked to oxidative stress and coronary artery disease [39]. Diffuse myocardial fibrosis, as measured by myocardial native T_1 and extracellular volume, has also been reported in early-stage chronic kidney disease [9] and is a recognized pathophysiological factor in haemodialysis patients [40,41]. Smoking is a well-established driver of systemic inflammation, oxidative stress, and atherosclerosis [11].

Clinical Implications

Our findings demonstrate measurable myocardial changes associated with key components of the metabolic syndrome, suggesting that cardiometabolic comorbidities have subtle but detectable effects on the composition of myocardial tissue. Unlike previous studies that modelled T_1 as a predictor of disease risk [13], our analysis considers T_1 as the response variable to reflect structural sex-specific effects associated with cardiometabolic risk. The reported β coefficients thus represent average group-level shifts in tissue composition. Since not all individuals with a given risk factor show myocardial involvement, population heterogeneity dilutes mean group differences. However, even moderate effect sizes may reflect an increased prevalence of individuals with pathologic myocardial changes within exposed subgroups. To illustrate this, we performed a distributional analysis (Supplementary Figure S4) showing the proportion of participants with T_1 values above or below one standard deviation from age- and sex-matched reference distributions. Even small mean differences correspond to a measurable enrichment in the distribution tails: for instance, 20.8%

(279/1,341) of participants with diabetes had T_1 values above one standard deviation compared with 15.1% (591/3,910) in healthy individuals. Recognizing myocardial tissue alterations in individuals with reversible cardiometabolic risk factor burden may facilitate the early identification of cardiac involvement and inform preventive strategies, even before the onset of symptomatic cardiovascular disease. At the same time, our analysis indicates that comorbidities such as diabetes or smoking do not limit the diagnostic capability of T_1 mapping, as the magnitude of differences overall remains far below those seen in key indications for T_1 mapping such as amyloidosis or Fabry disease [42,43]. Finally, clinical interpretation of myocardial native T_1 should consider sex-specific differences, as women show significantly higher baseline values [44].

Limitations

Medical history in the NAKO cohort was collected via self-reported questionnaires, which may introduce recall or reporting error. To mitigate these limitations, self-reports were complemented with measured elevations in relevant blood biomarkers to reduce potential biases in the primary variables. While the population-based study design supports generalisability of the observed association patterns, absolute T_1 values may not be directly transferable to different imaging settings or ethnically diverse cohorts. Our study does not provide causal explanations for the observed associations and is intended to inspire future mechanistic studies, including joint CMR analyses alongside cardiac function and morphology. While reader-AI agreement was assessed, inter-reader variability was not evaluated.

Conclusions

Our analysis provides large-scale population-based evidence linking cardiometabolic risk factors to myocardial native T_1 time. Diabetes, kidney disease and smoking were associated with prolonged T_1 times, indicating structural changes in myocardial tissue composition. Conversely, hyperlipidaemia was negatively associated with T_1, requiring further mechanistic investigation. We observed dynamic, age-dependent differences in native T_1 time between women and men, with particularly pronounced sex differences before the age of 50. While our findings for cardiometabolic risk factors underscore the complex interplay between metabolic and myocardial health, the overall moderate effect sizes support the clinical utility of T_1 mapping as a diagnostic marker of overt disease in the presence of cardiometabolic comorbidities.

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Data Availability

Data is available by application to the NAKO transfer office (https://transfer.nako.de).

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Competing Interests

FB and the Working Group on CMR receive research support from Siemens Healthineers. FB and CLS have received honoraria from the speaker's bureau of Siemens Healthineers. All other authors declare no competing interests.

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Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Janis M. Nolde reports financial support was provided by Berta-Ottenstein-Programme for Clinician Scientists. Richard Hickstein reports financial support was provided by German Research Foundation. Fabian Bamberg reports a relationship with Siemens Healthineers AG that includes: funding grants and speaking and lecture fees. Working Group on CMR reports a relationship with Siemens Healthineers AG that includes: funding grants. Christopher L. Schlett reports a relationship with Siemens Healthineers AG that includes: speaking and lecture fees. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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