Cardiovascular Diabetology

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Sex differences in myocardial flow reserve among individuals with type 2 diabetes: insights from the DiaHeart study

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Abstract

Background Type 2 diabetes is a stronger risk factor for cardiovascular disease (CVD) in women compared with men possibly due to higher susceptibility to develop myocardial microvascular dysfunction. We investigated sex-dependent effects of risk factors on myocardial blood flow (MBF) and myocardial flow reserve (MFR) in individuals with type 2 diabetes without overt CVD.

Methods Cross-sectional analysis of a prospective study including 901 individuals recruited between 2020 and 2023. All participants underwent a cardiac 82-Rubidium positron emission tomography/computed tomography scan to quantify MBF at rest and during pharmacologically induced stress, allowing for calculation of MFR. Linear regression, with/without interaction terms for sex, was used to test whether sex modified the association between MFR/MBF and risk factors.

Results Mean (SD) age was 65 (8.9) years, diabetes duration was 14 (8.4) years, and 266 (29.5%) were women. Women had higher MBF at rest and stress but had lower MFR (mean (SD) 2.44 (0.67) vs. 2.59 (0.77), $p=0.003$) than men. A similar proportion of men and women (21.1% vs. 23.7%) had an MFR < 2. The decline in predicted MFR with age differed between sexes. At age 55, women had a mean MFR that was 0.29 lower than men (95% CI: − 0.44 to − 0.14), but by age 75, this difference had nearly disappeared (− 0.04, 95% CI: − 0.19 to 0.11). However, after adjustment for other risk factors, the interaction between sex and age was not statistically significant ($p=0.057$). No other risk factors exhibited significant sex-dependent interactions.

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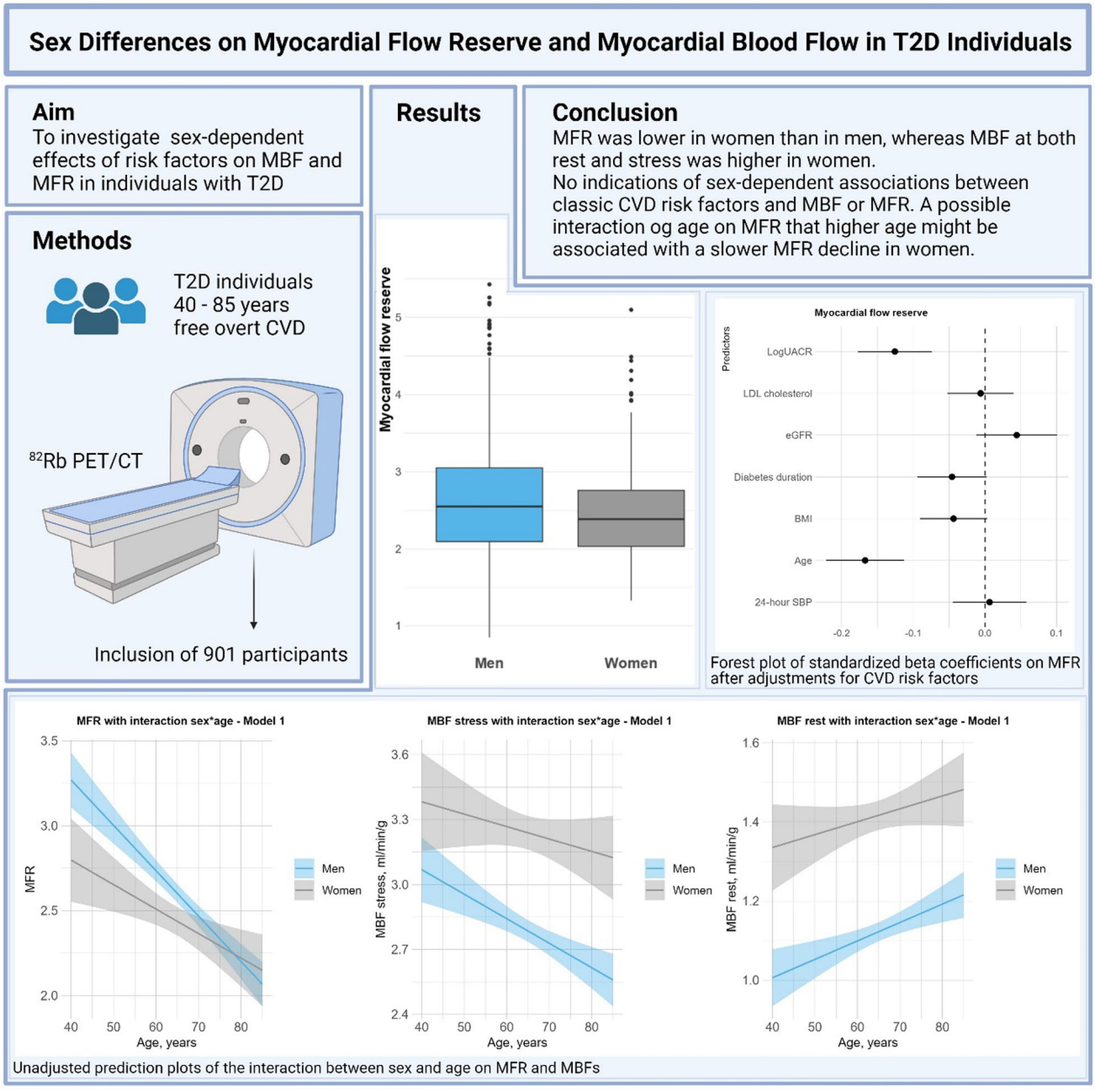
Conclusions In individuals with type 2 diabetes without overt CVD, women exhibited lower MFR than men, primarily due to higher MBF at rest, suggesting sex-related differences. While MFR declined in both sexes, the sex difference was more pronounced in younger individuals and diminished over time. These findings underscore the need for further research into sex-specific thresholds for MFR in cardiovascular risk stratification.

Graphical abstract



Keywords Sex-differences, Type 2 diabetes, Microvascular complications, Cardiovascular imaging

Introduction

Cardiovascular disease (CVD) is the leading cause of death in individuals with type 2 diabetes, posing significant risks to both men and women [1]. However, the distribution of cardiovascular risk is not equal between the sexes. Women with type 2 diabetes experience a disproportionately higher relative risk of adverse cardiovascular outcomes compared to men [2]. A meta-analysis

revealed a 30% higher relative risk of cardiovascular mortality in women with diabetes compared to men with diabetes [3]. This increased vulnerability in women with diabetes remains incompletely understood and is not fully explained by traditional risk factors, suggesting that other mechanisms contribute to the observed disparities [4–6]. One potential contributor is myocardial microvascular dysfunction, commonly observed in individuals with diabetes and which may exacerbate cardiovascular risk. The myocardial microvasculature, comprising the small blood vessels supplying the heart muscle, may respond differently to diabetes in men and women. Sex-specific differences in myocardial microvascular function could help explain why women with diabetes, despite having a similar burden of traditional cardiovascular risk factors as men, experience worse outcomes. Considering that asymptomatic CVD is prevalent among individuals with diabetes, especially women, there is a significant need for enhanced risk stratification within this population [7].

The myocardial flow reserve (MFR), a non-invasive measure derived from quantitative cardiac positron emission tomography (PET), quantifies the ability of the myocardial circulation to increase blood flow under stress conditions, reflecting the combined function of the epicardial arteries and the microcirculation [8]. MFR has proven to be a valuable prognostic marker in assessing cardiovascular risk [9–11]. While evaluation of MFR is increasingly used for risk stratification in clinical practice, current diagnostic cut-offs are not sex-specific and limited research has focused on potential sex-dependent differences in MFR and their implications for risk stratification, especially in asymptomatic populations. The appropriateness of the current MFR thresholds for both men and women remains uncertain. Understanding these sex differences could facilitate the development of more tailored and effective risk assessment strategies. The aim of this paper is to investigate potential differences in MFR between men and women with type 2 diabetes free of overt CVD evaluated using 82-Rubidium Positron Emission Tomography/Computed Tomography (82Rb PET/CT) in individuals included in the DiaHeart study. Additionally, potential sex-dependent effects of other cardiovascular risk factors on MFR will be explored. Participants in the DiaHeart study will be prospectively followed through registries for mortality and development of CVD. Here we report findings from the baseline examination.

Methods

Design

This was a multicenter study including individuals with type 2 diabetes according to the WHO criteria but free of overt CVD and without any symptoms of CVD. Eligible individuals were identified and recruited through electronic health records and advertisements in local newspapers. Potential participants attended a screening visit at the Steno Diabetes Center Copenhagen (SDCC), Zealand University Hospital, or Holbaek Hospital, Denmark. Participants were aged between 40 and 85 years and able to understand and provide informed consent. Individuals between 40 and 50 years were required to have at least two of the following additional cardiovascular risk factors: current smoking, hypertension, dyslipidemia, or family history of CVD. Exclusion criteria included: (i) history of stroke, coronary artery disease (CAD), or other CVD; (ii) non-diabetic kidney disease; and (iii) contraindications for cardiac 82Rb PET/CT. A flowchart of the participants included is presented in Supplemental Figure S1. The study included multiple visits depending on the recruitment site. For participants recruited from SDCC the study involved three visits: an initial visit at SDCC for written consent and clinical measurements, a second visit at Rigshospitalet Copenhagen for the cardiac 82Rb PET/CT scan, and a third visit at Gentofte Hospital for transthoracic echocardiography. For participants recruited from other regions of Zealand, written consent and clinical measurements were obtained at their respective recruiting centers, while both the 82Rb PET/CT scan and transthoracic echocardiography were performed during a single visit at Rigshospitalet Copenhagen.

Consent

The study was conducted from January 2020 to August 2023 and in accordance with the Declaration of Helsinki. All participants provided written consent, and the protocol was approved by the Danish National Committee on Health Research Ethics (H-19063311).

Clinical characteristics

Demographic information and details on medical history and treatment were collected through interviews and cross-checked against electronic medical records. Current smoking was defined as smoking one or more cigarettes, pipes, or cigars daily. Weight and height were measured, and body mass index (BMI) was calculated. Laboratory variables including lipid profile, HbA1c, C-reactive protein (hsCRP) N-terminal pro-brain natriuretic peptide (NT-ProBNP), pro-atrial natriuretic peptide (pro-ANP), Troponin T, and plasma creatinine, were assessed using standard methods. Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI equation [12]. A history of albuminuria was based on previous measures of urine albumin-to-creatinine ratio (UACR) where moderately and severely increased albuminuria was defined as an UACR level of 30–300 mg/g and >300 mg/g, respectively, in two consecutive measurements [13]. Current UACR levels was calculated as

the geometric mean of three consecutive morning urine samples, measured by an enzyme immunoassay. Office blood pressure was measured after 5 min of rest, and the average of three readings was calculated. 24-hour blood pressure was measured using a validated device (Takeda, TM2430, Japan) at 15-minute intervals during daytime (7 am–10 pm) and every 30 min during nighttime (10 pm–7 am).

Transthoracic echocardiography

The echocardiographic examinations were performed according to a standardized research protocol by trained investigators using GE Vingmed Ultrasound Vivid IQ (Horten, Norway). Echocardiographies were subsequently analyzed by experienced investigators blinded to study details using post-processing analysis software (EchoPac version 206). Left ventricular ejection fraction (LVEF) was measured from the apical 4- and 2-chamber views using a semi-automatic tool that traces the myocardial deformation and resulting volume changes throughout the cardiac cycle. Automated function imaging, a novel semi-automatic algorithm for speckle-tracking echocardiography, was used to measure global longitudinal strain (GLS) from the apical 4-, 2, and 3-chamber views.

Cardiac 82Rb PET/CT

The cardiac 82Rb PET/CT examinations were performed following the administration of 1,100 MBq of 82Rb, using the same hybrid PET/CT scanner in 3D mode (Siemens Biograph mCT 128, Siemens, Munich, Germany) and Bracco infusion system. The scan was performed at rest and stress conditions. To achieve the latter adenosine was infused at 140 mg/kg/min for 6 min to induce maximal myocardial hyperemia. Participants were instructed to pause phosphodiesterase 5 inhibitors for 72-h, and medications containing dipyridamole for 36-h and abstain from food and beverages containing caffeine for 18-h prior to the examination. The MBF was computed using the Siemens Syngo MBF 2.3 (Siemens Medical Solutions, Malvern, PA, USA) software, employing one-compartment tracer kinetic models for 82Rb along with the extraction curve introduced by Lortie et al. [14]. Frame-by-frame motion correction was performed for participants who exhibited high spillover fractions from blood to myocardium (greater than 0.65) in any coronary territory applied across the entire dynamic study. MFR was calculated as the ratio between the MBF during rest and stress, estimated globally in the myocardium. Global MFR was the primary variable of interest and was considered reduced when ≤ 2 [9]. For RPP correction, rest MBF was multiplied by the reference RPP (8500) and divided by the product of resting heart rate and systolic blood pressure. RPP-adjusted MFR was subsequently calculated. Coronary artery calcium score (CACS) was calculated as described by Agatston et al. [15] using commercial software (Syngo.via, Siemens Healthineers, Germany).

Statistics

Normally distributed continuous variables are presented as mean and standard deviation (SD), and non-normally distributed as median with interquartile range (IQR). Categorical variables are reported as number and percentages. To assess associations between MFR/MBF at rest and stress and cardiovascular risk factors, we performed multiple linear regression models in two steps. Missing values for variables included in the regression analyses were imputed using multivariate imputation by chained equations, 50 imputations (mice package, version 3.16.0). Continuous variables were imputed using predictive mean matching and categorical variables by polytomous logistic regression. Multicollinearity was assessed using the variance inflation factor (VIF), with a predefined threshold of 2 to identify potential collinearity issues. Adjustments in model 1 included sex and age. Adjustments in model 2 included sex, age, diabetes duration, BMI, LDL-cholesterol, smoking, HbA1c, 24-hour systolic blood pressure, eGFR, and current UACR. To investigate potential sex-dependent differential effects of cardiovascular risk factors, an interaction term with sex was added to the models: y = sex + risk factor of interest + covariates, and y = sex + risk factor of interest + sex*risk factor of interest + covariates. The UACR was log-transformed (natural logarithm) before analysis. Beta-coefficients with 95% confidence intervals (95% CI) are presented along with *P*-values. Supplementary analyses were performed to assess possible effects of reversible perfusion defects as well as treatment with beta-blockers. To assess whether the presence of irreversible perfusion defects influenced the results, a sensitivity analysis was performed by excluding participants with these defects ($n = 19$). The Model 1 for rest MBF was re-run in this subset to evaluate whether the exclusion altered the estimated effect sizes. A two-sided *P*-value of < 0.05 was considered statistically significant; the *P*-values were not adjusted for multiplicity. Statistical analyses were performed using the statistical software R (version 4.3.3, R Foundation for Statistical Computing, Vienna, Austria).

Results

Clinical characteristics

The cohort consisted of 901 participants, 266 (29.5%) were women. Mean (SD) age was 65.1 (8.9) years, and the mean diabetes duration was 13.7 (8.4) years. Table 1 summarizes clinical characteristics for the total population and stratified by sex. Total cholesterol, LDL-cholesterol, hsCRP levels, as well as higher LVEF and GLS estimates

Table 1 Clinical characteristics in the total population and stratified by sex

	Overall, *N* = 901	**Men, *N* = 635**	**Women, *N* = 266**	***P*-value**
Age (years)	65.1 ± 8.9	65.3 ± 9.0	64.5 ± 8.9	0.20
Ethnicity, n (%)				0.20
Caucasian	867 (96.2)	608 (95.7)	259 (97.4)	
Asian	18 (2.0)	13 (2.0)	5 (1.9)	
Other	9 (1.0)	8 (1.3)	1 (0.4)	
Known duration of diabetes (years)	13.7 ± 8.4	13.8 ± 8.1	13.5 ± 9.1	0.30
Body mass index (kg/m^2)	30.2 ± 5.4	30.0 ± 5.0	30.5 ± 6.3	0.40
24-hour systolic blood pressure (mmHg)	138 ± 13	139 ± 13	137 ± 14	0.059
Missing, n (%)	149 (16.5)	92 (14.5)	57 (21.4)	
Office systolic blood pressure (mmHg)	139 ± 16	140 ± 16	136 ± 16	**0.002**
HbA1c (mmol/mol)	55.7 ± 12.8	56.1 ± 12.8	54.7 ± 12.9	0.051
HbA1c (%)	7.2 ± 1.2	7.3 ± 1.2	7.2 ± 1.2	0.051
Total cholesterol (mmol/l)	3.9 ± 0.9	3.8 ± 0.9	4.1 ± 0.9	**< 0.001**
LDL cholesterol (mmol/l)	1.7 ± 0.8	1.7 ± 0.7	1.9 ± 0.8	**0.002**
eGFR (ml/min/1.73 m^2**)**	82.1 ± 21.8	82.1 ± 22.6	82.2 ± 19.7	0.50
HsCRP (mg/l)	1.3 (0.6, 2.7)	1.2 (0.6, 2.5)	1.5 (0.7, 3.1)	**0.006**
Missing, n (%)	77 (8.5)	55 (8.7)	22 (8.3)	
proANP (pmol/l)	247.0 (152.0, 384.0)	251.5 (150.0, 396.0)	237.0 (158.5,351.0)	0.30
Missing, n (%)	68 (7.5)	45 (7.1)	23 (8.6)	
NT-proBNP (pmol/l)	6.4 (3.0, 14.4)	6.1 (3.0, 16.0)	6.8 (3.0, 12.6)	0.80
Troponin T (ng/l)	9.7 (6.8, 14.3)	10.7 (7.9, 15.7)	7.1 (5.0, 9.9)	**< 0.001**
Urine albumin-to-creatinine ratio (mg/g)	7.7 (4.9, 19.9)	7.8 (4.6, 23.7)	7.3 (5.4, 13.2)	0.70
Historic albuminuria*, n (%)				**0.002**
Normal	582 (66.4)	391 (63.0)	191 (74.6)	
Moderately increased	225 (25.7)	171 (27.5)	54 (21.1)	
Severely increased	70 (8.0)	59 (9.5)	11 (4.3)	
Retinopathy, n (%)				0.12
None	629 (77.5)	430 (75.8)	199 (81.2)	
Simplex	126 (15.5)	91 (16.0)	35 (14.3)	
Proliferative	57 (7.0)	46 (8.1)	11 (4.5)	
Missing, n	89 (9.9)	68 (10.7)	21 (7.9)	
Smoking, n (%)				**0.006**
Non-smoker	382 (42.4)	249 (39.2)	133 (50.2)	
Former	408 (45.3)	300 (47.2)	108 (40.8)	
Current	110 (12.2)	86 (13.5)	24 (9.1)	
Family history of cardiovascular disease, n (%)	189 (21.1)	118 (18.8)	71 (26.7)	**0.008**
Medical treatment				
Lipid-lowering, n (%)	723 (80.3)	512 (80.8)	211 (79.3)	0.60
Antihypertensive drugs, n (%)	685 (76.0)	490 (77.2)	195 (73.3)	0.20
RAAS blockade, n (%)	610 (67.7)	435 (68.5)	175 (65.8)	0.40
Betablockers, n (%)	150 (17)	116 (18)	34 (13)	**0.044**
Aspirin, n (%)	270 (30.0)	204 (32.1)	66 (24.8)	**0.029**
Metformin, n (%)	730 (81.0)	525 (82.7)	205 (77.1)	0.050
Insulin, n (%)	366 (40.6)	260 (40.9)	106 (39.8)	0.80
SGLT-2i, n (%)	413 (45.8)	302 (47.6)	111 (41.7)	0.11
GLP-1 RA, n (%)	458 (50.8)	312 (49.1)	146 (54.9)	0.12
Both SGLT-2i and GLP-1 RA†, n (%)	256 (28.4)	183 (28.8)	73 (27.4)	0.70

Data are expressed as mean ± SD, median (interquartile range) or number (%) as appropriate. eGFR: estimated glomerular filtration rate. HbA1c: glycosylated hemoglobin. Hs-CRP: High-sensitivity CRP. ProANP: Pro-Atrial Natriuretic Peptide. NT-ProBNP: N-terminal pro-brain natriuretic peptide. RAAS: renin-angiotensin-aldosterone-system. SGLT-2i: sodium glucose transporter 2 inhibitor, GLP-1 RA: glucagon-like peptide-1 receptor agonist. Significant *P*-values are highlighted in bold. Numbers with missing values are reported if more than 5% were missing

*Albuminuria: Normal: UACR < 30 mg/g. Moderately increased UACR 30–300 mg/g. Severely increased: UACR > 300 mg/g, in two consecutive measures

†Participants receiving both medications are also included in the sum of each medication separately

from transthoracic echocardiography were higher in women than in men, and more women reported a family history of CVD. Men had a slightly higher systolic blood pressure, and higher levels of Troponin T compared with women, and a higher proportion of men had a history of moderately or severely increased albuminuria and were current smokers. Other characteristics did not differ between sexes.

In terms of medical treatment, most participants were treated with antihypertensive medication (76.0%), with renin-angiotensin-aldosterone system (RAAS) blockade being the most common (67.7%). Additionally, 80.3% were prescribed lipid-lowering and 30.0% were on aspirin treatment. The predominant antidiabetic treatment was metformin (81.0%), followed by glucagon-like peptide-1 receptor agonists (GLP-1RA) (50.8%) and sodium-glucose cotransporter-2 inhibitors (SGLT-2i) (45.8%). Notably, 256 (28.4%) were treated with both GLP-1RA and SGLT-2i. There were no significant sex differences in the prescription of medical treatment, except that a higher proportion of men were prescribed betablockers and aspirin.

Sex differences in cardiac PET/CT measurements

The results from the cardiac PET/CT scans are summarized in Table 2. The mean MFR for the total population was within the normal range 2.55 (0.73). Men had higher MFR than women (2.59 (0.77) vs. 2.44 (0.61); $P = 0.003$), but there was no significant sex difference in the prevalence of MFR below 2 or 1.7 ($P = 0.4$ for both). Despite having lower MFR, women had higher MBF both at stress and rest compared with men ($P < 0.001$). After correction for RPP, MBF at rest remained significant higher in women compared with men (1.28 ± 0.28 vs. 1.04 ± 0.24, $p < 0.001$), but MFR was no longer different between sexes ($p = 0.30$). The median [IQR] CACS was higher in men 209 [30,800] versus 53 [1,280] in women; $P < 0.001$, and the prevalence of reversible perfusion defects (> 5%) was higher in men (30.4% vs. 17.3%, $P < 0.001$). However, the median extent of perfusion defect was similar in men and women (7% [5,11] vs. (7% [5,10]; $P = 0.60$). The prevalence of irreversible perfusion defects (> 5%) was only 2.1%, with a nonsignificant difference observed between sexes (2.7% in men and 0.9% in women).

Table 2 Cardiac PET/CT and echocardiography measurements

	Overall, *N* = 901	Men, *N* = 635	Women, *N* = 266	*P*-value
MFR	2.55 ± 0.73	2.59 ± 0.77	2.44 ± 0.61	**0.003**
MFR < 2, n (%)	197 (21.9)	134 (21.1)	63 (23.7)	0.40
MFR < 1.7, n (%)	93 (10.3)	69 (10.9)	24 (9.0)	0.40
RPP corrected MFR	2.74 ± 0.81	2.76 ± 0.87	2.69 ± 0.67	0.30
MBF rest ml/min/g	1.21 ± 0.34	1.12 ± 0.31	1.42 ± 0.32	**< 0.001**
RPP corrected MBF rest ml/min/g	1.11 ± 0.28	1.04 ± 0.24	1.28 ± 0.28	**< 0.001**
MBF stress ml/min/g	2.92 ± 0.72	2.76 ± 0.70	3.30 ± 0.60	**< 0.001**
CACS	138 (13, 601)	209 (30, 800)	53 (1, 280)	**< 0.001**
CACS, n (%)				**< 0.001**
0	121 (13.7)	62 (10.0)	59 (22.4)	
1–99	278 (31.5)	182 (29.4)	96 (36.5)	
100–399	188 (21.3)	135 (21.8)	53 (20.2)	
> 400	296 (33.5)	241 (38.9)	55 (20.9)	
LVEF at rest (%)	66 ± 8	64 ± 8	72 ± 7	**< 0.001**
LVEF at stress (%)	72 ± 8	69 ± 8	78 ± 7	**< 0.001**
LVEF-reserve	5 ± 4	5 ± 4	5 ± 4	0.70
RPP at rest	9,409 ± 1,968	9,316 ± 1,944	9,629 ± 2,011	**0.027**
RPP at stress	10,897 ± 2,439	10,572 ± 2,377	11,676 ± 2,413	**< 0.001**
LVEF from echocardiogram	55 ± 6	54 ± 7	57 ± 5	**< 0.001**
GLS from echocardiogram	16.3 ± 2.7	16.0 ± 2.8	17.0 ± 2.2	**< 0.001**
Reversible perfusion defect (≥ 5%), n (%)	239 (26.5)	193 (30.4)	46 (17.3)	**< 0.001**
Eversible perfusion defect, (extent %)*	7.0 (5.0, 11.0)	7.0 (5.0, 11.0)	7.0 (5.0, 9.8)	0.60
Irreversible perfusion defect (≥ 5%), n (%)	19 (2.1)	17 (2.7)	2 (0.8)	0.067
Irreversible perfusion defect (extent %)†	6.0 (5.0, 8.0)	6.0 (5.0, 8.0)	5.5 (5.3, 5.8)	0.50

Data are expressed as mean ± SD, median (interquartile range) or number (%) as appropriate. MFR: Myocardial flow reserve, MBF: Myocardial blood flow, CACS: Coronary artery calcium score, LVEF: Left ventricular ejection fraction, RPP Rate pressure product. Significant *P*-values are highlighted in bold

*Calculated among the participants with a reversible perfusion defect

†Calculated among the participants with an irreversible perfusion defect

Associations between MFR and risk factors

Table 3 summarizes the associations between MFR and cardiovascular risk factors. After adjusting for multiple risk factors, female sex, higher age, and elevated UACR were significantly associated with lower MFR. In model 1, longer diabetes duration, higher BMI, and lower eGFR were also linked to lower MFR, but these associations were no longer significant after further adjustments in model 2. Interaction analysis revealed a statistically significant interaction between sex and age on MFR in model 1 ($P = 0.031$). However, this significance was not retained in model 2 ($P = 0.057$; Fig. 1, panels A and B). Additional adjustment for hsCRP for the interaction between sex and age on MFR in Model 2 did not change the results (β: 0.10, 95% CI − 0.01, 0.21, $p = 0.08$).

Associations between MBF at stress and rest and risk factors

In adjusted analyses (model 2), female sex, higher age and UACR was associated with higher MBF at rest, while female sex, higher eGFR, and lower age and 24-hour systolic blood pressure were associated with higher MBF during stress (Table 4). Figure 2 presents standardized beta coefficients for the associations between risk factors and MFR and MBF at rest and during stress in model 2.

No sex-dependent effects on MBF at rest and during stress were found in the interaction analyses ($P > 0.4$; Fig. 1: panel C–F).

Sensitivity analyses

A sensitivity analysis excluding the 19 participants with irreversible perfusion defects did not change the association between sex and rest MBF in Model 1, and the effect size remained identical (female sex β = 0.29 (95% CI: 0.25, 0.34), $p < 0.001$). Additionally, two sensitivity analyses were conducted to exclude potential effects of beta-blocker treatment and reversible perfusion defects (extent > 5%). Adding adjustment for beta-blocker treatment ($n = 150$) to model 2 did not alter the results (Supplemental Table S1). Similarly, the analyses adjusted for the presence of reversible perfusion defects confirmed the results; however, longer diabetes duration was significantly associated with lower MFR ($P = 0.045$) (Supplemental Table S1).

Discussion

In this large cross-sectional multicenter study including 901 participants with type 2 diabetes free of symptoms and without a history of CVD, we observed significant differences in MFR and MBF between men and women. Women had a lower average MFR than men, on a background of a higher MBF at both rest and stress. No significant interactions between sex and traditional cardiovascular risk factors were found for MFR. However, age appeared to influence MFR differently in men and women, with women showing a slower decline in MFR compared to men.

These findings confirm and extend previous studies [16, 17] by validating the results in a high-risk population with type 2 diabetes. The observed differences in MBF and MFR raise questions about whether current diagnostic thresholds are appropriate for both sexes.

Sex-dependent differences in myocardial blood flow and flow reserve

While most studies, agree that MBF at rest and during stress is higher in women than in men, the interpretation of MFR in relation to sex differences remains unclear. Some studies report similar MFR between the sexes [17–22], while others, including our study, show lower MFR in women compared to men [16, 23–26].

This finding prompts important clinical questions about the lower MFR in women, particularly in the context of diabetes. Studies in individuals with known or suspected CAD have shown that MFR is 7–8% lower in those with diabetes compared to those without [18, 23]. The difference in MFR between men and women in our study is comparable in magnitude to that associated with diabetes, suggesting that the sex difference may be clinically significant. The observed lower MFR in women is primarily driven by the higher MBF at rest. As MFR is defined as the ratio of stress to resting MBF, a higher resting MBF naturally leads to a lower MFR. Increased MBF at rest has been proposed as a compensatory mechanism of microvascular dysfunction. However, this may not necessarily indicate microvascular dysfunction itself, but instead reflect physiological differences between sexes, such as smaller epicardial arteries and a larger myocardial blood volume in women [27]. Factors such as estrogen levels, which influence coronary tone in women, may contribute to the observed sex differences in MFR [28, 29]. We do not have data on menopause status in our study. However, if estrogen were the primary factor driving sex differences, one might anticipate younger women to exhibit higher MFR values, comparable to those in men, when estrogen levels are at their peak and provide a protective effect. Conversely, MFR would be expected to decline more sharply after menopause as estrogen levels diminish. This speculation is supported by a study showing that adjustment for menopause status and hormone use did not reduce sex differences in MBF, suggesting that other factors may contribute to the observed sex differences [30]. It is important to recognize that the observed differences in MFR between sexes may not necessarily imply worse cardiovascular outcomes for women, but rather reflect inherent physiological variations in MBF [19, 25, 27]. However, this raises important questions: What causes the sex-dependent differences

Table 3 Associations between myocardial flow reserve and cardiovascular risk factors

Variable	No interaction						With interaction for sex					
	Model 1			Model 2			Model 1			Model 2		
	Beta	95% CI	*P*-value	Beta	95% CI	*P*-value	Beta	95% CI	*P*-value	Beta	95% CI	*P*-value
Age (decades)	− 0.23	− 0.28, − 0.18	**< 0.001**	− 0.19	− 0.25, − 0.13	**< 0.001**	− 0.27	− 0.33, − 0.21	**< 0.001**	− 0.22	− 0.29, − 0.15	< 0.001
Woman	− 0.17	− 0.27, − 0.07	**0.001**	− 0.14	− 0.29, − 0.09	**< 0.001**	− 0.96	− 1,70, − 0.23	**0.01**	− 0.89	− 1.62, − 0.16	0.016
Age* Woman							0.12	0.01, 0.24	**0.031**	0.11	− 0.00, 0.22	0.057
Diabetes duration (decades)	− 0.09	− 0.15, − 0.04	**< 0.001**	− 0.06	− 0.11, 0.00	0.061	− 0.01	− 0.02, 0.00	0.004	− 0.01	− 0.01, 0.00	0.13
Woman							− 0.19	− 0.38, − 0.01	0.041	− 0.19	− 0.37, − 0.01	0.039
Diabetes duration* Woman							0.02	− 0.10, 0.13	0.80	0.00	− 0.01, 0.01	> 0.9
BMI (pr. 1 kg/m^2)	− 0.01	− 0.02, 0.00	**0.016**	− 0.01	− 0.02, 0.00	0.069	− 0.01	− 0.02, 0.00	0.055	0.00	− 0.02, 0.01	0.40
Woman							− 0.18	− 0.71, 0.35	0.50	0.01	− 0.51, 0.52	> 0.9
BMI* Woman							0.00	− 0.02, 0.02	> 0.9	0.00	− 0.02, 0.01	0.60
24-hour SBP (pr. 10 mmHg)	− 0.03	− 0.06, 0.01	0.20	0.00	− 0.03, 0.04	0.80	− 0.03	− 0.07, 0.02	0.20	0.02	− 0.02, 0.06	0.40
Woman							− 0.28	− 1.3, 0.79	0.60	− 0.01	− 1.0, 1.0	> 0.9
24-hour SBP* Woman							0.01	− 0.07, 0.08	0.80	− 0.01	− 0.08, 0.06	0.80
LDL-cholesterol (pr. 1 mmol/mol)	− 0.01	− 0.07, 0.05	0.9	− 0.01	− 0.07, 0.05	0.80	0.00	− 0.07, 0.08	> 0.9	0.02	− 0.05, 0.09	0.60
Woman							− 0.12	− 0.37, 0.13	0.30	− 0.08	− 0.32, 0.16	0.50
LDL-cholesterol* Woman							− 0.02	− 0.15, 0.10	0.70	− 0.03	− 0.16, 0.09	0.60
HbA1c (pr. 5 mmol/mol)	− 0.02	− 0.03, 0.00	0.066	− 0.01	− 0.03, 0.01	0.33	− 0.02	− 0.04, 0.01	0.20	− 0.01	− 0.03, 0.02	0.60
Woman							− 0.13	− 0.57, 0.31	0.60	− 0.07	− 0.5, 0.35	0.70
HbA1c* Woman							0.00	− 0.04, 0.03	0.80	− 0.01	− 0.04, 0.03	0.80
Smoking												
Woman							− 0.09	− 0.24, 0.05	0.20	− 0.07	− 0.21, 0.07	0.30
Former	− 0.04	− 0.13, 0.06	0.50	− 0.03	− 0.13, 0.06	0.50	0.00	− 0.11, 0.12	> 0.9	− 0.01	− 0.12, 0.11	> 0.9
Former* Woman							− 0.12	− 0.34, 0.09	0.30	− 0.10	− 0.31, 0.11	0.30
Current	− 0.11	− 0.26, 0.04	0.15	− 0.09	− 0.24, 0.06	0.22	− 0.04	− 0.21, 0.13	0.70	− 0.06	− 0.22, 0.11	0.50
Current* Woman							− 0.29	− 0.64, 0.06	0.10	− 0.28	− 0.61, 0.06	0.11
eGFR (pr. 10 ml/min/1.73m^2)	0.05	0.02, 0.07	**< 0.001**	0.02	− 0.01, 0.04	0.17	0.05	0.03, 0.08	< 0.001	0.02	0.00, 0.05	0.10
Woman							0.08	− 0.33, 0.49	0.70	− 0.01	− 0.06, 0.04	0.60
eGFR*Woman							− 0.03	− 0.08, 0.02	0.20	− 0.01	− 0.06, 0.04	0.60
UACR (pr. dobling mg/g)	− 0.11	− 0.14, − 0.08	**< 0.001**	− 0.09	− 0.13, − 0.05	**< 0.001**	− 0.12	− 0.15, − 0.08	< 0.001	− 0.09	− 0.13, − 0.05	< 0.001
Woman							− 0.29	− 0.51, − 0.06	0.013	− 0.18	− 0.41, 0.04	0.11
UACR*Woman							0.04	− 0.05, 0.13	0.40	0.02	− 0.07, 0.10	0.70
Hs-CRP (pr. dobling (mg/l))	− 0.08	− 0.12, − 0.03	**< 0.001**	− 0.05	− 0.10, 0.0003	0.051	− 0.08	− 0.14, − 0.31	0.002	− 0.05	− 0.11, 0.007	0.09
Woman							− 0.16	− 0.26, − 0.05	0.004	− 0.18	− 0.29, − 0.08	< 0.001
Hs-CRP*Women							0.02	− 0.07, 0.12	0.64	0.002	− 0.10, 0.10	0.96

Beta (95% confidence intervals) and *P*-values for selected risk factors. Model 1: Adjustment for sex and age. Model 2: Model 1 + diabetes duration, BMI, 24-hour SBP, LDL-cholesterol, HbA1c, smoking, eGFR and current UACR

The * indicates the interaction between the relevant risk factor and sex. Significant differences are indicated in bold. BMI: Body mass index; SBP: Systolic blood pressure; eGFR: Estimated glomerular filtration rate; UACR: Urine albumin creatinine ratio

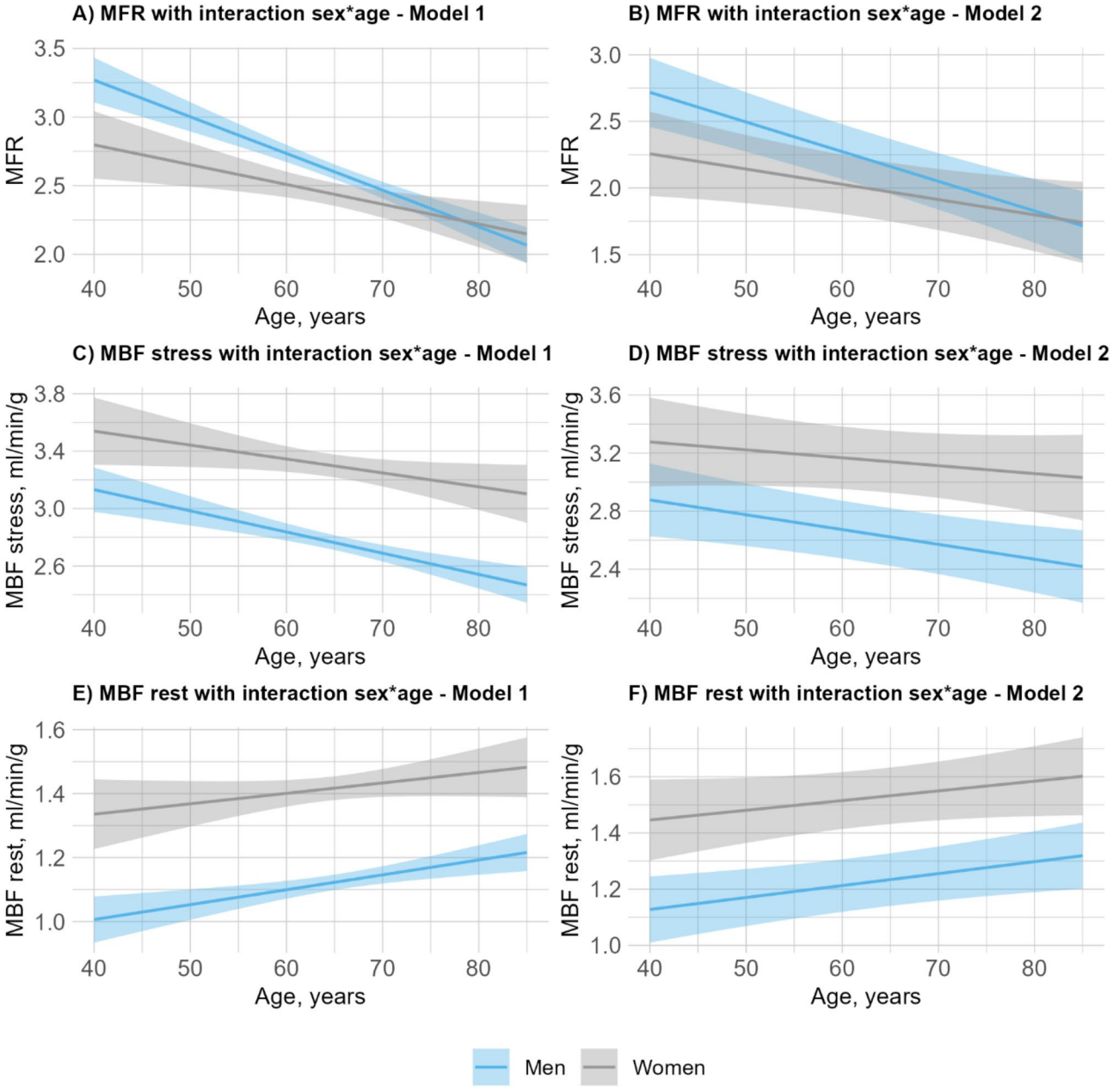


Fig. 1 Prediction plots for interaction between sex and age on myocardial flow reserve and myocardial blood flow at rest and stress. Model 1: Adjustment for sex and age. Model 2: Model 1 + diabetes duration, BMI, 24-hour systolic blood pressure, LDL-cholesterol, HbA1c, smoking, estimated glomerular filtration rate and current urine albumin creatinine ratio. MFR: Myocardial flow reserve. MBF: Myocardial blood flow

in MBF? Does a low MFR reflect the similar underlying physiology in men and women? And what are the implications for test interpretation and risk assessment? Currently, an MFR value < 2 is widely considered abnormal for both sexes, implying a similar risk level at this threshold [31]. However, it remains unclear whether an MFR < 2 has similar prognostic value for men and women, both overall and within specific patient groups, such as those with or without diabetes, as previous studies have reported mixed results [18, 32]. In a systematic review and meta-analysis, the risk of major adverse cardiovascular events related to MFR showed wide confidence intervals for both men and women, making firm conclusions impossible [9]. The MFR has been shown to be a stronger risk marker of cardiovascular mortality than the MBF at stress. One study found that individuals with impaired MFR but preserved MBF at stress had a cardiovascular mortality rate of 1.7% per year, with 70% of this group being women. In contrast, those with preserved MFR but impaired MBF at stress had a lower mortality rate of 0.9%

Table 4 Associations between myocardial blood flow at rest and stress and cardiovascular risk factors

Group	Variable	No interaction						With interaction for sex					
		Model 1			Model 2			Model 1			Model 2		
		Beta	95% CI	*P*-value	Beta	95% CI	*P*-value	Beta	95% CI	*P*-value	Beta	95% CI	*P*-value
MBF rest	Woman (man as reference)	0.29	0.25, 0.34	**< 0.001**	0.30	0.25, 0.34	**< 0.001**	0.39	0.06, 0.71	0.020	0.34	0.01, 0.67	0.041
	Age (decades)	0.04	0.02, 0.07	**< 0.001**	0.04	0.01, 0.07	**0.006**	0.05	0.02, 0.07	< 0.001	0.04	0.01, 0.07	0.012
	Age*Woman							− 0.01	− 0.06, 0.04	0.60	− 0.01	− 0.06, 0.04	0.80
	Diabetes duration (decades)	0.02	0.00, 0.05	0.10	0.01	− 0.01, 0.04	0.30						
	BMI (pr. 1 kg/m^2)	0.00	0.00, 0.01	0.20	0.00	0.00, 0.01	0.20						
	24-hour SBP (pr. 10 mmHg)	− 0.01	− 0.02, 0.01	0.40	− 0.01	− 0.03, 0.00	0.10						
	LDL-cholesterol (pr. 1 mmol/mol)	0.00	− 0.03, 0.02	0.90	0.00	− 0.03, 0.03	> 0.9						
	HbA1c (mmol/mol)	0.00	− 0.01, 0.01	0.60	0.00	− 0.01, 0.01	0.80						
	Smoking (non-smoking as reference)												
	Former	0.01	− 0.04, 0.05	0.70	0.01	− 0.04, 0.05	0.80						
	Current	0.02	− 0.05, 0.08	0.60	0.01	− 0.05, 0.08	0.70						
	eGFR (pr. 10 ml/min/1.73m^2)	− 0.01	− 0.02, 0.00	0.20	0.00	− 0.01, 0.01	0.90						
	UACR (pr. dobling mg/g)	0.02	0.01, 0.04	**0.007**	0.02	0.00, 0.04	**0.014**						
	Hs-CRP (pr.dobling (mg/l))	0.00	− 0.02, 0.02	0.67	− 0.04	− 0.09, 0.00	0.08						
MBF stress	Woman (man as reference)	0.53	0.44, 0.63	**< 0.001**	0.52	0.42, 0.61	**< 0.001**	0.20	− 0.49, 0.90	0.60	0.20	− 0.50, 0.90	0.60
	Age (decades)	− 0.13	− 0.18, − 0.08	**< 0.001**	− 0.09	− 0.15, − 0.03	**0.003**	− 0.15	− 0.21, − 0.09	< 0.001	− 0.10	− 0.17, − 0.04	0.003
	Age*Woman							0.05	− 0.06, 0.16	0.40	0.05	− 0.06, 0.16	0.40
	Diabetes duration (decades)	− 0.05	− 0.10, 0.00	0.074	− 0.03	− 0.08, 0.03	0.40						
	BMI (pr. 1 kg/m^2)	− 0.01	− 0.01, 0.00	0.13	0.00	− 0.01, 0.01	0.50						
	24-hour SBP (pr. 10 mmHg)	− 0.05	− 0.08, − 0.02	**0.003**	− 0.04	− 0.08, − 0.03	**0.023**						
	LDL-cholesterol (pr. 1 mmol/mol)	− 0.02	− 0.08, 0.03	0.40	− 0.02	− 0.08, 0.04	0.50						
	HbA1c (mmol/mol)	− 0.01	− 0.03, 0.01	0.20	− 0.01	− 0.02, 0.01	0.50						
	Smoking (non-smoking as reference)												
	Former	− 0.03	− 0.12, 0.06	0.60	− 0.03	− 0.12, 0.06	0.50						
	Current	− 0.10	− 0.24, 0.04	0.20	− 0.09	− 0.23, 0.05	0.20						
	eGFR (pr. 10 ml/min/1.73m^2)	0.04	0.02, 0.06	**< 0.001**	0.03	0.00, 0.05	**0.021**						
	UACR (pr. dobling mg/g)	− 0.08	− 0.11, − 0.05	**< 0.001**	− 0.03	− 0.07, 0.00	0.059						
	Hs-CRP (pr.dobling (mg/l))	− 0.07	− 0.11, − 0.02	**0.002**	− 0.04	− 0.09, 0.00	0.08						

Beta (95% confidence intervals) and *P*-values for selected risk factors. Model 1: Adjustment for sex and age. Model 2: Model 1 + diabetes duration, BMI, 24-hour SBP, LDL-cholesterol, HbA1c, smoking, eGFR and current UACR

The * indicates the interaction between the relevant risk factor and sex. Significant differences are indicated in bold. BMI: Body mass index; SBP: Systolic blood pressure; eGFR: Estimated glomerular filtration rate; UACR: Urine albumin creatinine ratio

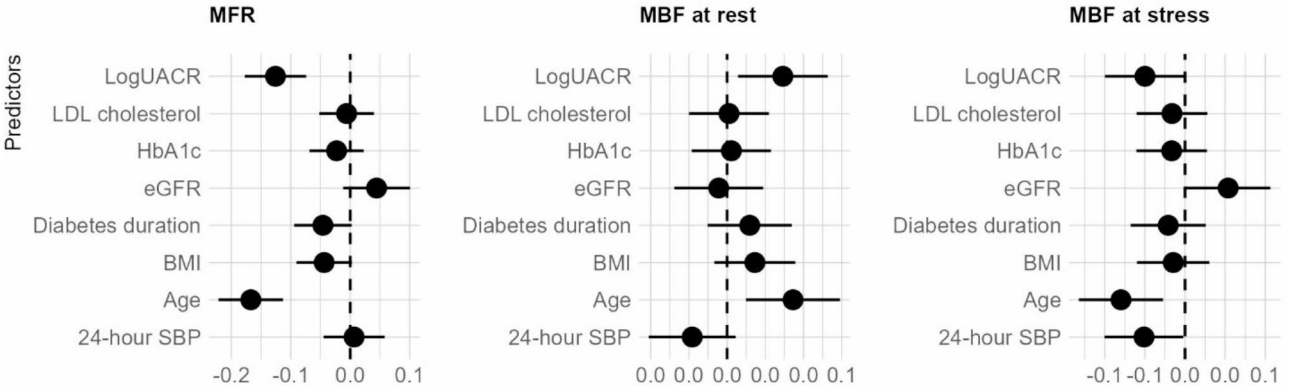


Fig. 2 Forest plots presenting standardized beta coefficients on myocardial flow serve and myocardial blood flow at rest and stress from model 2. Adjustments: Model 2: Sex + age + diabetes duration, BMI, 24-hour SBP, LDL-cholesterol, HbA1c, smoking, eGFR and current UACR. UACR was log-transformed with natural logarithm. MFR: Myocardial flow reserve. MBF: Myocardial blood flow. BMI: Body mass index. SBP: Systolic blood pressure. eGFR: Estimated glomerular filtration rate. UACR: Urine albumin creatinine ratio

per year [33]. In contrast, a recent study demonstrated that impaired stress MBF (< 1.94 ml/min/g) was associated with a higher risk of MACE than impaired MFR (< 1.98), indicating its potential superiority in risk stratification. These diverging results underscores the need for further studies to determine the most reliable metrics for assessing cardiovascular risk [34].

While MBF and MFR are known to be influenced by hemodynamic factors such as heart rate and blood pressure, the clinical relevance of correcting for RPP remains uncertain. After adjusting for RPP, MFR was no longer significantly different between sexes; however, this normalization should be interpreted with caution. RPP-correction is not routinely applied in clinical practice and lacks standardized reference values across populations [35]. Furthermore, recent evidence from Huck et al. demonstrated that RPP-corrected MFR does not improve prognostic discrimination compared to uncorrected MFR, neither in people with impaired nor preserved MFR [36]. Most importantly, adjusting for RPP may inadvertently obscure physiologically meaningful sex differences in cardiovascular physiology. In our cohort, women had higher RPP, likely reflecting physiological differences such as higher resting heart rate. This may in turn be related to differences in autonomic tone, vascular compliance, or metabolic demand. By correcting for RPP, these biological sex differences may be masked, limiting insights into pathophysiological mechanisms relevant to sex-related variation in myocardial vascular function.

Our results suggest that age might be considered when evaluating sex differences in MFR. The observed differences in MFR between men and women varied significantly with age, with the sex-related gap narrowing in older individuals; at 55 years the predicted MFR was − 0.29 (95% CI − 0.44 to − 0.14) lower in women, and at 75 years the difference had all but disappeared; − 0.04 (95% CI − 0.19 to 0.11) (Model 1 with interaction). Similar findings were recently published in a cohort of people without diabetes and CVD, showing that predicted MFR was higher in men than in women at younger ages, with the gap narrowing with increasing age [16]. Evaluating sex-dependent differences in MFR without considering age might explain the diverging results reported in the literature. The observed smaller decline in MFR with age in women may also explain why we find comparable proportions of men and women with an MFR < 2. These findings suggest that using sex- and age-specific cut-offs may be appropriate, as others have also recommended [16, 17, 19, 22]. The prospective follow up of our cohort will enable evaluation of the potential sex-dependent impact of MFR on cardiovascular and mortality risk.

Risk factors associated with MFR and influence of sex

The cardiovascular risk profile differed between men and women in our cohort, with men showing higher CACS, higher frequency of smoking, perfusion defects and proportion with historic albuminuria. Conversely, women had higher levels of total- and LDL cholesterol and a higher frequency of family history of CVD.

Female sex, higher age and the presence of albuminuria have been associated with lower MFR in individuals with type 2 diabetes, consistent with our findings [19, 37]. Despite the observed difference in MFR between sexes, our study does however not indicate sex-specific associations to known cardiovascular risk factors Since women have a lower MFR regardless of other risk factors, the presence of additional risk factors is likely to further reduce their MFR, bringing them closer to the cut-off value (< 2) compared to men at the same age.

However, it is important to note that none of the risk factors assessed in this study had large effect sizes or explained a substantial proportion of the variation in MBF and MFR.

The relatively low prevalence of MFR < 2 (21.9%) in our cohort compared to other studies including people with diabetes, may in part be explained by key differences in selection of the participants. A study from Patel et al., where all participants were referred for cardiac PET/CT—potentially reflecting a higher pre-test likelihood of disease demonstrated a prevalence of MFR < 2 of 63% [11]. In our study participants were enrolled without referral filtering, thereby capturing a broader and possibly less advanced disease spectrum. Although Patel et al. report on some medications such as statins, beta-blockers, aspirin, and insulin, information on the prescription of newer glucose-lowering agents with cardioprotective effects (e.g., SGLT2 inhibitors and GLP-1 receptor agonists) were not provided. The prescription of these agents was relatively high (45.8% and 50.8%, respectively) in our cohort, which may have contributed to the low prevalence of MFR < 2. The higher MBF values reported in our participants compared to previous studies likely reflects methodological differences, including the use of a 1-compartment kinetic model [14] rather than net retention modeling, and adenosine as the vasodilator, which produces stronger hyperaemia than regadenoson or dipyridamole [16].

Strengths and limitations

A key strength of the study is the large sample size, which, to our knowledge, makes it the largest study to date evaluating MFR in individuals with type 2 diabetes who are asymptomatic and without known CVD. MFR was assessed using cardiac PET, which is considered the gold standard for non-invasive measurement of MFR [38]. Additionally, the multicenter design, including participants from both primary and tertiary care settings enhances the generalizability of the findings.

However, several limitations must be acknowledged. The cross-sectional study design prevents conclusions about causality. The overrepresentation of men (70.5%) is an important limitation that may introduce bias and reduced the statistical power to detect sex-specific interactions. Furthermore, the lack of data on menopause status is a limitation, as hormonal changes could influence MFR, as already discussed. Likewise, the lack of information on autoimmune diseases, which have been associated with higher rest MBF and lower MFR is a limitation [39, 40]. Most participants were of Caucasian ethnicity, which may limit the generalizability of the results to other populations.

As the participants were selected to asymptomatic and without known CVD, our findings might be biased. This is because men, who often present with classical CVD symptoms, are typically diagnosed earlier and thus excluded from our study.

Furthermore, we did not assess serum caffeine levels, splenic switch-off, or heart-rate changes to confirm vasodilator response, so we cannot exclude that some participants achieved insufficient vasodilator response. Perfusion tracers such as ^{13}N-NH_3, ^{15}O-water, or ^{18}F-Flurpiridaz—owing to their nearly linear extraction fractions—may provide a more accurate assessment of microcirculatory disturbances compared to ^{82}Rb. While this remains a theoretical consideration, it's important to emphasize that the quantitative evaluation of myocardial perfusion using PET is influenced by numerous factors, with tracer extraction being only one of them. Moreover, there is a notable lack of comprehensive studies directly comparing the performance of different perfusion tracers, both in general and specifically within people with diabetes.

Finally, we examined potential sex-dependent associations for eight cardiovascular risk factors without adjusting for multiplicity and report one statistically significant association. This association has, however, been reported previously [16]. Non-linear associations between cardiovascular outcomes and risk factors, such as BMI, have been reported. However, we did not assess non-linearity in this study, as it was not the primary focus. Future studies could explore this further.

Conclusion

In individuals with type 2 diabetes but without known CVD, women exhibited lower MFR but higher MBF at both rest and stress compared to men. These findings confirm and extend previous research highlighting sex-related differences in MBF dynamics in a high-risk population with type 2 diabetes. We found no significant sex-dependent associations between traditional cardiovascular risk factors and MBF or MFR. However, our results suggest that older age may be associated with a slower decline in MFR in women, consistent with recent findings in people without diabetes [16]. These findings suggest that considering sex differences may be important in the assessment of the myocardial circulation.

The prospective part of this study will provide valuable insights into the role of MFR and MBF as risk factors for CVD and mortality in both sexes and explore if thresholds should be stratified by sex.

Abbreviations

BMI	Body mass index
CACS	Coronary artery calcium score
CAD	Coronary artery disease
CVD	Cardiovascular disease
CI	Confidence interval
eGFR	Estimated glomerular filtration rate
GLP-1 RA	Glucagon-like peptide-1 receptor agonists
GLS	Global longitudinal strain
HbA1c	Glycated hemoglobin
Hs-CRP	High sensitivity C-reactive protein
IQR	Interquartile range

LDL	Low-density lipoprotein
LVEF	Left ventricular ejection fraction
MBF	Myocardial blood flow
MFR	Myocardial flow reserve
NT-proBNP	N-terminal pro-brain natriuretic peptide
82-Rb PET/CT	82-Rubidium positron emission tomography/computed tomography
ProANP	Pro-atrial natriuretic peptide
RAAS	Renin-angiotensin-aldosterone system
SD	Standard deviation
SDCC	Steno Diabetes Center Copenhagen
SGLT2-i	Sodium-glucose cotransporter-2 inhibitors
UACR	Urine albumin creatinine ratio

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-025-02717-5.

Additional file 1.

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Author contributions

ACSM, IKBR, RSR, EHZ, MBB, PH, LH, AK, PR and TWH contributed to the study design and data interpretation. ACSM, IKBR, VSW, PH, ULK, ML, AKE, TBS, MCHL and RSR, acquired data. ACSM, IKBR and VSW recruited participants. ACSM and MBB performed statistical analysis. ACSM drafted the manuscript. The final manuscript was critically read, revised, and approved by all authors. TWH is the guarantor of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Avilability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki. All participants provided written consent, and the protocol was approved by the Danish National Committee on Health Research Ethics (H-19063311).

Consent for publication

Not applicable.

Competing interests

PR has received speaking fees and/or consultancy to Steno Diabetes Center Copenhagen from Eli Lilly, Novo Nordisk, Sanofi Aventis, Vifor, Boehringer Ingelheim, Astellas, Gilead, Bayer, AstraZeneca, Mundipharma, and MSD. PR has received research grants from Novo Nordisk AstraZeneca. PR, TWH and RSR had shares in Novo Nordisk. AK and RSR has received consultancy fees from Novo Nordisk. EHZ is a full-time employee in Novo Nordisk and has shares in Novo Nordisk. IKR is a full-time employee at Novo Nordisk. ML: has received speaker and consultancy fees from AstraZeneca, Bayer, Boeringer Ingelheim, Novo Nordisk, GlaxoSmithKline, and is an investigator in clinical studies sponsored by Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Janssen, MSD and Novo Nordisk. JPG has served as consultant for Novo Nordisk on measurement of bioactive peptides. TBS has received research grants from Pfizer, Sanofi Pasteur, GSK, Novo Nordisk, AstraZeneca, Boston Scientific and GE Healthcare, consulting fees from Novo Nordisk, IQVIA, Parexel, Amgen, CSL Seqirus, GSK and Sanofi Pasteur, and lecture fees from Bayer, Novartis, Sanofi Pasteur, GE healthcare and GSK. The other authors declare that there is no duality of interest associated with this manuscript.

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