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Association of breastfeeding duration with longitudinal changes in vertebral bone marrow, paraspinal muscle composition, and metabolic parameters in premenopausal women over five years

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ABSTRACT

Objective: To investigate the association between breastfeeding duration and longitudinal changes in MRI-based proton-density fat fraction (PDFF) of vertebral bone marrow, paraspinal musculature (PSM), and metabolic parameters in premenopausal women.

Methods: Thirty-seven women (age 36.3 ± 3.8 years) were evaluated with the subgroups of women who breastfed ≤8 months vs. >8 months. All women underwent a 3 T MRI scan, including chemical shift encoding-based water-fat separation, postpartum (11.10 ± 2.38 months) and at 5-year follow-up. Glucose metabolism was analyzed at both visits using the updated Homeostasis Model Assessment (HOMA-2). PDFF values of lumbar and thoracic vertebrae and PSM were assessed, along with the cross-sectional area of PSM. Associations between breastfeeding duration and changes in bone marrow and muscle composition were assessed using multivariable linear regression models adjusted for age and body mass index (BMI).

Results: Women who breastfed >8 months showed a greater decrease in PDFF of the lumbar vertebrae (−9.62 ± 5.42 % vs. −4.69 ± 7.72 %; $p = 0.03$) and autochthonous muscles (AM) (−1.32 ± 2.52 % vs. 0.37 ± 2.48 %; $p = 0.047$) between baseline and 5-year follow-up compared to women who breastfed ≤8 months. Breastfeeding >8 months was significantly associated with greater reductions in both $PDFF_{lumbar}$ ($\beta = -5.34$ %; $p = 0.03$) and $PDFF_{AM}$ ($\beta = -1.84$ %; $p = 0.03$) independent of baseline BMI and age.

Conclusion: Longer breastfeeding duration is associated with a higher decrease of vertebral bone marrow adiposity and fat infiltration of autochthonous muscles over 5 years in premenopausal women, indicating potential benefits for maternal bone and muscle composition.

1. Introduction

Chemical shift encoding-based water-fat MRI (CSE-MRI), determining the proton-density fat fraction (PDFF), is a non-invasive, radiation-free fat quantification method for bone marrow and muscle [1–6]. Bone mineral density (BMD) is inversely correlated with vertebral

Abbreviations: CSE-MRI, Chemical shift encoding-based water-fat MRI; PDFF, Proton density fat fraction; BMD, Bone mineral density; BF, Breastfeeding; GDM, Gestational diabetes; DXA, Dual-energy X-ray absorptiometry; T2D, Type 2 diabetes; PSM, Paraspinal muscles; pGDM, Prior gestational diabetes; pGDM-controls, No prior gestational diabetes; OGTT, Oral glucose tolerance test; HOMA, Homeostasis Model Assessment; HOMA2-IR, HOMA-insulin resistance; HOMA2-S, HOMA-insulin sensitivity; CSA, Cross sectional area; AM, Autochthonous muscles; PM, Psoas muscles; ROI, Region of interest; ROC, Receiver operating characteristic; AUC, Area under the curve; ICC, Intraclass correlation coefficient; RMSCV, Root mean square coefficient of variation.

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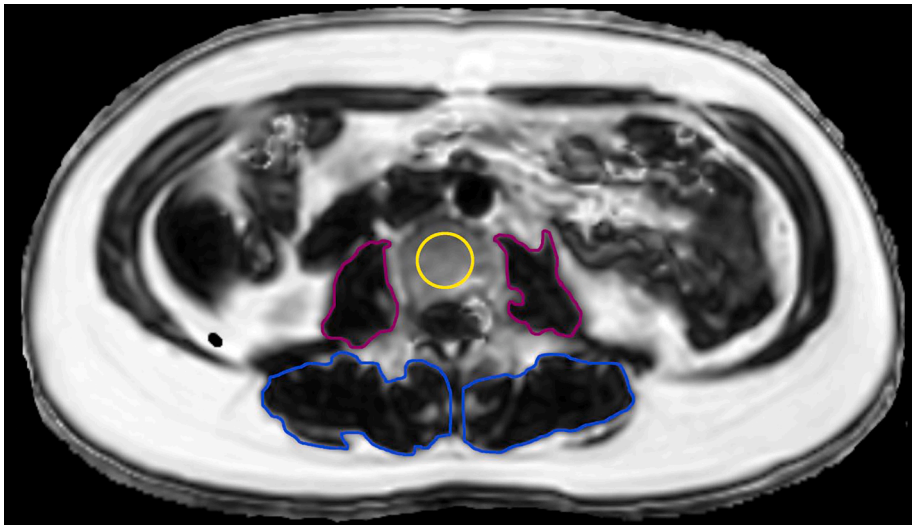

Fig. 1. Example PDFF map at the level of L3: Region of interest (ROI) placement in the center of L3 (yellow), as well as representative segmentations of the autochthonous muscles (AM; blue) and psoas muscles (PM; purple) on both sides.

bone marrow fat [7–9]. Several studies have shown that vertebral bone marrow PDFF is a potential biomarker of impaired bone health, with a significant longitudinal increase in the year prior to a vertebral compression fracture [10–14].

Breastfeeding (BF) has previously been shown to have metabolic benefits for women with prior gestational diabetes (GDM) [15]. Moreover, BF duration showed no association with BMD at one year postpartum, assessed using dual-energy X-ray absorptiometry (DXA) based measurements [15]. However, conflicting data on BF and bone mass suggest a transient loss of bone mass and increased markers of bone turnover during the exclusive BF period due to hormonal changes and the metabolic demands of lactation [16,17]. Furthermore, BF improves postpartum glucose metabolism and reduces the risk of developing type 2 diabetes (T2D) in women with a history of GDM [18]. Nevertheless, to our knowledge, no previous study has assessed the long-term association between BF duration and both musculoskeletal and metabolic health.

GDM, a milder form of prediabetes or hyperglycaemia, poses a risk for developing T2D, although pathologic glucose metabolism typically resolves postpartum [19,20]. A recent study found elevated PDFF in the vertebral bone marrow of premenopausal women with recent GDM within one year post-delivery [21], and the association between vertebral bone marrow PDFF and paraspinal muscle (PSM) PDFF has been demonstrated in the context of osteoporosis [12,22–24]. Therefore, the relationship between CSE-MR imaging, musculoskeletal health and metabolic changes has been investigated previously and remains of great interest for further evaluation.

This study aims to investigate the longitudinal association of BF duration and PDFF of the vertebral bone marrow and the PSM in the thoracic and lumbar region, as well as the glucose metabolism, in premenopausal women.

2. Material and methods

2.1. Patient selection and characteristics

The study was approved by the local institutional review board (Ethics Committee of the Faculty of Medicine, LMU Munich; Ethics proposal number 300-11). All study participants provided written and informed consent prior to their participation in the study. Longitudinal analyses were performed retrospectively within the monocenter observational prospective study [19]. The study included women with a prior history of gestational diabetes (pGDM) and women who had a normoglycemic pregnancy (pGDM-control) between April 2013 and September 2015 with MRI at baseline (6 to 15 months postpartum) and 5-year follow-up. The diagnosis of pGDM was made using a 75 g oral glucose tolerance test (OGTT) after the 23rd week of gestation, following the criteria of the International Association of the Diabetes and Pregnancy Study (IADPSG) [25]. BF was defined as complete/full or partial BF at the time of baseline MRI with a median BF duration of 342 [interquartile range 246–393] days in the BF group with longer BF duration (>8 months) and 205 [119–256] days in the group with shorter BF duration (≤8 months). At the time of the baseline visit and MRI all individuals of non-BF group had stopped breastfeeding. Study participants who underwent MRI at the baseline and 5-year follow-up visits, using the same MRI protocol and MR system, were selected for this study.

Anthropometric, clinical, and clinical chemistry measurements were obtained at baseline and 5-year follow-up as previously described [19,26]. Participants' physical activity was measured by monitoring their step counts with an accelerometer (Aiper Motion 440, v3.2.4.0, Aipermon GmbH) at BL as reported previously [21].

A 5-point 75-g OGTT was performed at baseline and follow-up after at least 10 h of fasting with measurements of plasma glucose and serum insulin. Definitions of the American Diabetes Association were used to distinguish between normal vs. pathologic glucose tolerance [27]. To assess metabolic syndrome, we used the International Diabetes Federation (IDF) Worldwide Definition of Metabolic Syndrome for women [28].

The updated Homeostasis Model Assessment (HOMA2) was calculated from fasting plasma insulin, c-peptide and glucose levels at baseline to estimate the insulin sensitivity (HOMA-S/HOMA2-S) and insulin resistance (HOMA-IR/HOMA2-IR) [29].

2.2. MRI

MRI scans were scheduled after the initial study inclusion and the 5-year follow-up visit. Whole-body MR examinations, including a three-echo 3D gradient-echo sequence, were conducted using a 3-tesla system (Ingenia, Philips Healthcare, Best, The Netherlands) as described previously [21]. The detailed MRI protocol is described in the Supplementary Materials. PDFF maps were generated by evaluating the ratio of the fat signal (F) to the combined fat and water signals (F + W), expressed as a percentage: F/(F + W)*100 %, using the computed water and fat images by the MRI software (Philips Healthcare). Our approach for calculating the fat fraction has been described in previous literature and confirmed to be reproducible [30,31].

Table 1
Descriptive statistics of anamnestic and anthropologic data grouped by breastfeeding (BF) duration at baseline and 5-year follow-up. Normally distributed data are given as mean ± standard deviation and non-normally distributed data as median [interquartile range].

	BF > 8	BF ≤ 8	p-value
Number of patients (n)	19	18	
History of gestational diabetes (n)	10	9	
Age at delivery (years)	34.53 ± 3.39	36.28 ± 4.08	0.16
Time between delivery and baseline MRI (months)	10.73 ± 2.31	11.85 ± 2.43	0.16
Breastfeeding duration (days)	342 [246–393]	205 [119–256]	**< 0.01**
Time between baseline and follow-up examination visit (months)	51.00 [49.00–53.5]	52.5 [50.25–54.00]	0.45
Time between baseline and follow-up MRI (months)	52.00 [49.50–54.50]	52.00 [50–53.75]	0.95
Steps per day at baseline visit	8135 ± 1766	7291 ± 1467	0.15
Age at examination visit (years)			
Baseline	35.42 ± 3.39	37.22 ± 4.17	0.16
Follow-up	39.63 ± 3.22	41.67 ± 4.17	0.10
BMI at examination visit (kg/m^2)			
Baseline	22.69 [21.34–24.94]	22.96 [19.52–26.19]	0.16
Follow-up	23.72 [21.82–26.18]	24.61 [19.93–26.58]	0.99
Time between examination visit and MRI (days)			
Baseline	37 [27–65]	59 [20–91]	0.55
Follow-up	55 [40–73]	52 [29–92]	0.96
Pathologic glucose metabolism (n)			
Baseline	2	7	0.06
Follow-up	7	7	1.00
One or more criteria of metabolic syndrome* met (n)			
Baseline	4	11	**0.02**
Follow-up	7	10	0.33
Overweight (BMI ≥ 25 kg/m^2) (n)			
Baseline	5	8	0.31
Follow-up	6	9	0.32

Abbreviations: BF > 8, women breastfeeding > 8 months; BF ≤ 8, women breastfeeding ≤ 8 months; BMI, body-mass-index.
* Criteria of metabolic syndrome: waist > 88 cm, triclyceride ≥ 150 mg/dl, high-density lipoprotein (HDL) < 50 mg/dl, hypertension (systolic blood pressure ≥ 130 mmHG or diastolic blood pressure ≥ 85 mmHG, fasting blood glucose ≥ 100 mg/dl.

Table 2
Descriptive statistics of MRI data of PDFF and CSA analyses grouped by breastfeeding (BF) duration at baseline and 5-year follow-up. Normally distributed data are given as mean ± standard deviation and non-normally distributed data as median [interquartile range].

	BF > 8	BF ≤ 8	p-value
$PDFF_{lumbar}$ (%)			
Baseline	43.51 ± 11.03	40.78 ± 10.87	0.45
Follow-up	33.89 ± 10.91	36.09 ± 9.86	0.53
$\Delta PDFF_{lumbar}$ (%)			
$\Delta PDFF_{lumbar}$ (%)	−9.62 ± 5.42	−4.69 ± 7.72	**0.03**
Corrected-$\Delta PDFF_{lumbar}$ (%)	–22.61 ± 11.66	−8.95 ± 23.47	**0.04**
$PDFF_{thoracic}$ (%)			
Baseline	37.9 ± 10.78	35.72 ± 9.72	0.52
Follow-up	22.83 [20.36–28.73)]	26.42 ± 7.65	0.66
$\Delta PDFF_{thoracic}$ (%)			
$\Delta PDFF_{thoracic}$ (%)	−11.32 ± 8.65	−9.30 ± 6.25	0.42
Corrected-$\Delta PDFF_{thoracic}$ (%)	−30.40 ± 18.67	−24.83 ± 14.93	0.32
$PDFF_{PM}$ (%)			
Baseline	9.27 ± 1.69	8.72 ± 2.81	0.48
Follow-up	7.50 [6.89–9.28]	8.54 [6.68–10.7]	0.71
$\Delta PDFF_{PM}$ (%)			
$\Delta PDFF_{PM}$ (%)	−1.82 [−2.16 – −0.06]	−0.37 [−1.49–1.2]	**<0.05**
Corrected-$\Delta PDFF_{PM}$ (%)	−15.66 [−24.7 – −0.79]	−3.69 [−15.46–15.20]	0.07
$PDFF_{AM}$ (%)			
Baseline	13.17 [10.98–15.77]	11.71 [9.86–13.71]	0.22
Follow-up	12.19 ± 3.19	12.86 ± 4.31	0.60
$\Delta PDFF_{AM}$ (%)			
$\Delta PDFF_{AM}$ (%)	−1.32 ± 2.52	0.37 ± 2.48	**<0.05**
Corrected-$\Delta PDFF_{AM}$ (%)	−9.03 ± 18.92	6.72 ± 23.77	**0.03**
CSA_{PM} (cm^2)			
Baseline	7.51 ± 1.39	8.13 ± 1.32	0.17
Follow-up	8.06 ± 1.45	8.5 ± 1.64	0.40
ΔCSA_{PM} (%)			
ΔCSA_{PM} (%)	0.55 ± 0.83	0.36 ± 1.21	0.58
CSA_{AM} (cm^2)			
Baseline	14.57 ± 2.51	16.04 ± 2.52	0.08
Follow-up	16.5 ± 3.52	17.03 ± 3.15	0.63
ΔCSA_{AM} (%)			
ΔCSA_{AM} (%)	1.93 ± 1.50	1.00 ± 2.04	0.12

Abbreviations: BF > 8, women breastfeeding > 8 months; BF ≤ 8, women breastfeeding ≤ 8 months; PDFF, proton density fat fraction; AM, autochthonous muscles; PM, Psoas muscles; CSA, Cross-sectional area; Δ describes the increase or decrease from baseline to follow-up. The corrected ΔPDFF is calculates as $(PDFF_{Follow\text{-}up} - PDFF_{Baseline})/PDFF_{Baseline}$.

2.3. Quantitative MRI analysis

All MR images were reviewed for vertebral fractures and bone lesions prior to assessment. However, none of the included study participants demonstrated any morphological osseous pathology or abnormality. Segmentations of the vertebrae and the PSM were performed by a trained researcher (Y.S.) and reviewed by two board-certified radiologists (N.H., A.S.G. with 9 and 12 years of experience in musculoskeletal imaging, respectively) using the PDFF maps (Visage Imaging, Inc., San Diego, CA, United States), as described previously [21]. The region of interest (ROI) was centered on the vertebral bodies from TH9 to TH12 and from L1 to L4, and the mean values and standard deviations were calculated. Starting from the level of L1, the cross-sectional area (CSA) of the PSM, including the autochthonous muscles (AM) and the psoas muscle (PM), was semi-automatically segmented bilaterally across three slices spaced 5 cm apart from the thickest part of the muscle, and the values were averaged. The absolute change (Δ) of PDFF between baseline and 5-year follow-up was calculated as $PDFF_{FU} - PDFF_{BL}$, the corrected ΔPDFF as $(PDFF_{FU} - PDFF_{BL})/PDFF_{BL}$. All measurements were conducted blinded to participants' clinical data and demographics. Fig. 1 displays a representative PDFF map with the assessment of CSA and PDFF ROI measurement.

A random sample of 10 subjects from the baseline and follow-up cohorts was independently re-analyzed 4 weeks later separately by Y. S. and N.H. to assess intra- and inter-reader reproducibility.

2.4. Statistical analysis

Statistical analyses were performed by Y.S. using Rstudio Build 421 "Mountain Hydrangea" (R Foundation for Statistical Computing, Vienna, Austria). Statistical tests were two-sided, $\alpha = 0.05$. Normally distributed variables were reported as mean ± standard deviation, non-normally distributed variables as median (interquartile range). Pearson's correlation was used for normally distributed variables and Spearman's rank correlation for non-normally distributed variables. For group comparison, two-sample *t*-test or Wilcoxon rank-sum test/Mann-Whitney *U* test, and Welch's *t*-test and Mood's median test were used. Fisher's exact test was used for categorical variables for groups of less than 5 women; otherwise, Chi-squared test was used. Multivariable linear regression models were used to assess the influence of age, BMI, and BF duration (BF > 8 vs. BF ≤ 8 months, or in days) on the changes in PDFF of the lumbar spine, thoracic spine, or PSM. Multivariable logistic regression models were performed to evaluate the impact of age, BMI,

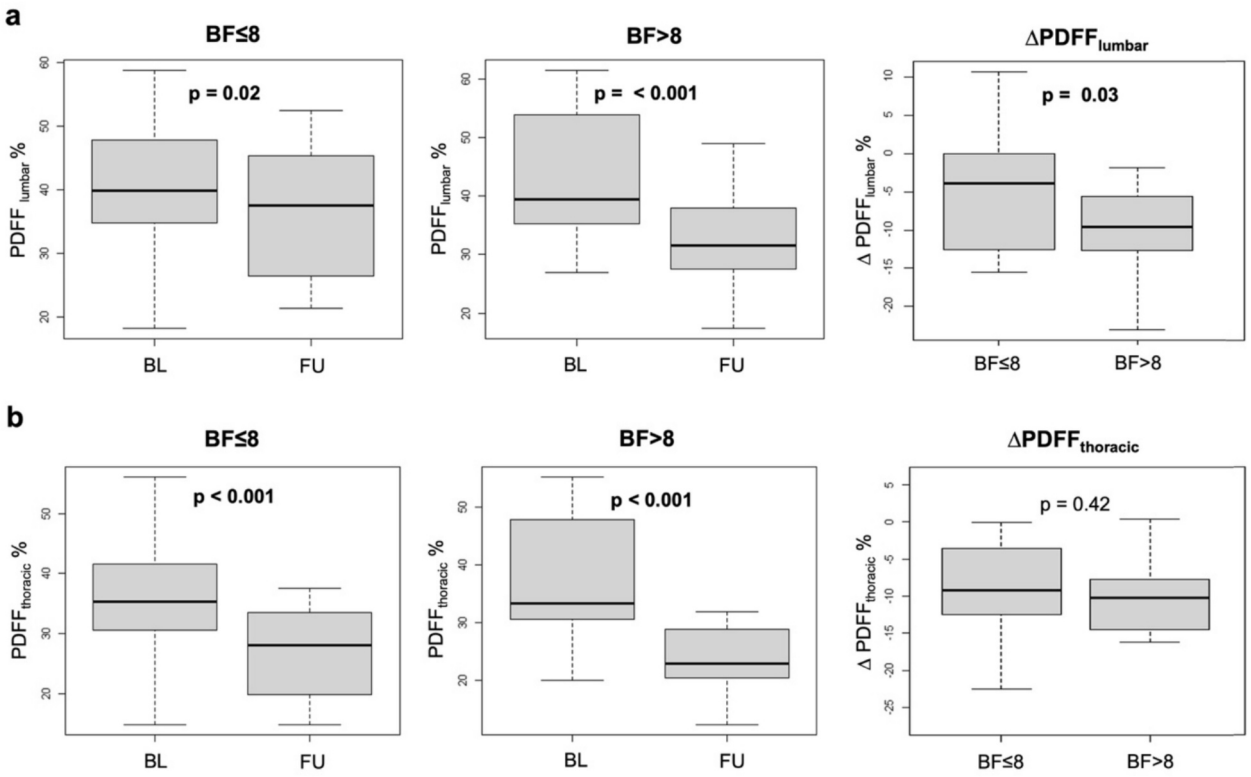

Fig. 2. Horizontally arranged within-group comparisons at baseline (BL) and 5-year follow-up (FU) for women breastfeeding ≤8 months (BF ≤ 8) and those breastfeeding >8 months (BF > 8), along with longitudinal group comparisons between BL and FU for changes in mean proton density fat fraction (ΔPDFF). This includes (a) the lumbar vertebral bone marrow (levels L1 to L4) ($PDFF_{lumbar}$) and (b) the thoracic vertebral bone marrow (levels T9 to T12) ($PDFF_{thoracic}$).

and changes of PDFF of the lumbar, thoracic spine or PSM on group classification based on breastfeeding duration (BF > 8 vs. BF ≤ 8 months). Receiver operating characteristic (ROC) analyses assessed the PDFF cut-off values for differentiating between women who breastfed ≤6 months (BF ≤ 8) and >8 months (BF > 8). The cut-off value with the highest Youden index was selected as the optimum cut-off value. Due to the small number of women with and without prior GDM an exploratory sub-analysis was performed for the assessment of associations between prior GDM and BF duration. The area under the curve (AUC) was reported with a 95 % confidence interval. Inter- and intra-reader reproducibility for PDFF values were assessed using intraclass correlation coefficient (ICC) and root mean square coefficient of variation (RMSCV).

3. Results

3.1. Patient characteristics

Patient characteristics grouped by BF duration are listed in Table 1. Thirty-seven, premenopausal women were included (19 with long duration BF, BF > 8 months, and 18 with short duration BF, BF ≤ 8 months). Significantly more women in the short duration BF group met criteria for metabolic syndrome ($p = 0.02$).

Patient characteristics and results of the exploratory analysis of women with (pGDM) and without GDM (pGDM-control) are listed in Supplementary Tables 1–5.

3.2. Quantitative MR imaging analysis

Descriptive statistics of MRI data of PDFF and CSA analyses grouped by BF duration at baseline and 5-year follow-up are listed in Table 2.

The bone marrow adiposity of the lumbar spine ($PDFF_{lumbar}$) decreased significantly more in the long duration BF group over 5 years ($p = 0.03$; Fig. 2 and Fig. 5). The association remained significant after

Table 3
Linear regression models for the association of change in PDFF and CSA between baseline and 5-year follow-up with breastfeeding duration (>8 months vs. ≤8 months).

	Adjusted multivariable model		Unadjusted multivariable model	
Dependent variable	ß coefficient [95 % CI of ß]	p-value	ß coefficient [95 % CI of ß]	p-value
$\Delta PDFF_{lumbar}$ (%)	−5.34[−9.99, −0.68]	**0.03**	−4.93 [−9.36 – −0.50]	**0.03**
$\Delta PDFF_{thoracic}$ (%)	−2.52 [−7.92–2.87]	0.35	−2.02 [−7.09–3.04]	0.42
$\Delta PDFF_{AM}$ (%)	−1.84[−3.53, −1.5]	**0.03**	−1.69 [−3.36 – −0.02]	**< 0.05**
$\Delta PDFF_{PM}$ (%)	−1.21 [−2.48–0.07]	0.06	−0.98 [−2.19–0.24]	0.11
ΔCSA_{AM} (cm^2)	0.64 [−0.58–1.86]	0.29	0.93 [−0.26–2.12]	0.12
ΔCSA_{PM} (cm^2)	0.24 [−0.47–0.96]	0.49	0.19 [−0.5–0.88]	0.58
Corrected-$\Delta PDFF_{lumbar}$ (%)	−14.38 [−26.77 – −1.99]	**0.02**	−13.66 [−25.92 – −1.39]	**0.03**
Corrected-$\Delta PDFF_{thoracic}$ (%)	−7.19 [−19.18–4.81]	0.23	−5.58 [−16.9–5.75]	0.32
Corrected-$\Delta PDFF_{AM}$ (%)	−17.01 [−31.48 – −2.54]	**0.02**	−15.75 [−30.04 – −1.45]	**0.03**
Corrected-$\Delta PDFF_{PM}$ (%)	−15.26 [−30.81–0.28]	0.05	−13.09 [−27.82–1.65]	0.08

*Adjusted for age and body mass index at baseline visit.
Abbreviations: PDFF, proton-density fat fraction; AM, autochthonous muscles; PM, Psoas muscles; CSA, Cross-sectional area; Δ describes the increase or decrease from baseline to follow-up. The corrected ΔPDFF is calculates as ($PDFF_{Follow\text{-}up}$ − $PDFF_{Baseline}$)/$PDFF_{Baseline}$. CI, Confidence interval.

Table 4
Linear regression models for the association of change in PDFF and CSA between baseline and 5-year follow-up with breastfeeding duration in days.

	Adjusted multivariable model*		Unadjusted multivariable model	
Dependent variable	ß coefficient [95 % CI of ß]	p-value	ß coefficient [95 % CI of ß]	p-value
$\Delta PDFF_{lumbar}$ (%)	−0.015 [−0.028–0.001]	**0.04**	−0.014 [−0.028–0.001]	**0.03**
$\Delta PDFF_{thoracic}$ (%)	−0.013 [−0.028–0.002]	0.08	−0.013 [−0.028–0.001]	0.07
$\Delta PDFF_{AM}$ (%)	−0.004 [−0.009–0.001]	0.13	−0.004 [−0.001–0.001]	0.13
$\Delta PDFF_{PM}$ (%)	−0,001 [−0.005–0.003]	0.61	−0.001 [−0.004–0.002]	0.56
ΔCSA_{AM} (cm^2)	0.002 [−0.002–0.005]	0.33	0.001 [−0.002–0.005]	0.43
ΔCSA_{PM} (cm^2)	−0.0003 [−0.0024–0.0018]	0.76	−0.0003 [−0.0023–0.0018]	0.78
Corrected-$\Delta PDFF_{lumbar}$ (%)	−0.03 [−0.07–0.01]	0.11	−0.03 [−0.07–0.01]	0.13
Corrected-$\Delta PDFF_{thoracic}$ (%)	−0.029 [−0.063–0.004]	0.09	−0.030 [−0.063–0.003]	0.07
Corrected-$\Delta PDFF_{AM}$ (%)	−0.03 [−0.07–0.02]	0.20	−0.03 [−0.07–0.02]	0.21
Corrected-$\Delta PDFF_{PM}$ (%)	−0.01 [−0.06–0.04]	0.63	−0.01 [−0.06–0.03]	0.60

*Adjusted for age and body mass index at baseline visit.
Abbreviations: PDFF, proton-density fat fraction; AM, autochthonous muscles; PM, Psoas muscles; CSA, Cross-sectional area; Δ describes the increase or decrease from baseline to follow-up. The corrected ΔPDFF is calculates as ($PDFF_{Follow\text{-}up}$ − $PDFF_{Baseline}$)/$PDFF_{Baseline}$; OR, Odds ratio; CI, Confidence interval.

Table 5
Logistic regression models for the association of breastfeeding duration (>8 months vs. ≤8 months) with the change in PDFF and CSA between baseline and 5-year follow-up.

	Adjusted multivariable model*		Unadjusted multivariable model	
Independent variable	Odds ratio (OR) [95 % CI of OR]	p-value	Odds ratio (OR) [95 % CI of OR]	p-value
Greater decrease in $\Delta PDFF_{lumbar}$ (%)	1.12 [1.02; 1.32]	**0.04**	1.13 [1.01–1.28]	**0.04**
Greater decrease in $\Delta PDFF_{AM}$ (%)	1.39 [1.04; 1.95]	**0.04**	1.32 [1.01–1.79]	0.05
Greater decrease in $\Delta PDFF_{PM}$ (%)	1.47 [1.00–2.33]	0.07	1.36 [0.94–2.06]	0.12
Greater decrease in $\Delta PDFF_{thoracic}$ (%)	1.05 [0.96–1.16]	0.34	1.04 [0.95–1.14]	0.41
Greater increase in ΔCSA_{AM} (cm^2)	1.28 [0.84–2.06]	0.26	1.37 [0.94–2.17]	0.13
Greater increase in ΔCSA_{PM} (cm^2)	1.29 [0.64–2.76]	0.47	1.21 [0.63–2.43]	0.58
Greater decrease in corrected-$\Delta PDFF_{lumbar}$ (%)	1.06 [1.01–1.12]	**0.04**	1.05 [1.01–1.11]	**<0.05**
Greater decrease in corrected-$\Delta PDFF_{thoracic}$ (%)	1.03 [0.99–1.07]	0.22	1.02 [0.98–1.06]	0.32
Greater decrease in corrected-$\Delta PDFF_{AM}$ (%)	1.04 [1.01–1.09]	**0.03**	1.036 [1.003–1.077]	**0.04**
Greater decrease in corrected-$\Delta PDFF_{PM}$ (%)	1.03 [1.00–1.07]	0.06	1.03 [1.00–1.07]	0.09

*Adjusted for age and body mass index at baseline visit.
Abbreviations: PDFF, proton-density fat fraction; AM, autochthonous muscles; PM, Psoas muscles; CSA, Cross-sectional area; Δ describes the increase or decrease from baseline to follow-up. The corrected ΔPDFF is calculates as ($PDFF_{Follow\text{-}up}$ − $PDFF_{Baseline}$)/$PDFF_{Baseline}$; OR, Odds ratio; CI, Confidence interval.

adjusting for BMI and age at baseline (β = −5.34 %; 95 % CI [−9.99; −0.68]; $p = 0.03$; Table 3). Additionally, longer BF duration in days was significantly associated with a greater decrease of $PDFF_{lumbar}$ (β = −0.02 %; 95 % CI [−0.028–0.001]; $p = 0.04$; Table 4). In the multivariable logistic regression model, adjusted for age and BMI at baseline, longer BF duration (>8 months) also increased the odds of a greater $PDFF_{lumbar}$ reduction (OR = 1.12; 95 % CI [1.02–1.32]; $p = 0.04$; Table 5).

Muscle fat infiltration of the PM ($PDFF_{PM}$) and AM ($PDFF_{AM}$) decreased significantly within the long duration BF group from baseline to 5-year FU ($p \leq 0.04$) (Fig. 3). The long duration BF group showed a significant greater reduction of the AM muscle fat infiltration after adjusting the analysis for BMI and age at baseline (β = −1.84 %; 95 % CI [−3.53; −0.15]; $p = 0.03$; Table 4). Moreover, women who breastfed >8 months had significantly higher odds of experiencing a greater decrease of AM fatty muscle infiltration (OR = 1.39; 95 % CI [1.04–1.95]; $p = 0.04$; Table 5).

ROC analyses showed that the longitudinal changes in $PDFF_{lumbar}$ and $PDFF_{AM}$ could differentiate between women with longer and shorter breastfeeding duration, with AUCs of 0.68 and 0.67, respectively. The optimal cut-offs were −3.28 % for $PDFF_{lumbar}$ and −2.22 % for $PDFF_{AM}$ (Fig. 4).

A strong negative correlation was observed for the corrected mean change of $PDFF_{PM}$ and the BF duration (r = −0.52, $p = 0.02$).

The CSA of the PSM (AM and PM) increased significantly among the long duration BF group between baseline and 5-year follow-up ($p_{PSM} < 0.01$).

3.3. Insulin sensitivity and resistance

Insulin resistance (HOMA2-IR) was significantly lower ($p = 0.02$), and insulin sensitivity (HOMA2-S) significantly higher at baseline ($p = 0.01$) in the long duration BF group compared to the short duration BF group (Fig. 6). No significant correlations were found between PDFF of the vertebrae and the PSM and CSA of the PSM both at baseline and 5-year follow up and HOMA2-IR and HOMA2-S ($p > 0.05$). In the subgroup analysis the same results for the insulin indices were observed within the GDM group between the long and short duration BF individuals ($p_{HOMA2\text{-}S} = 0.01$, $p_{HOMA2\text{-}IR} \leq 0.01$, Supplementary Table 4).

3.4. Inter- and intrareader agreement

Inter-reader agreement for mean PDFF of Th9–L4 and the PSM was excellent (ICC, 0.97 [95 % CI, 0.96–0.99] and 0.98 [95 % CI, 0.96–0.99]). Inter-reader reproducibility was excellent with RMSCV < 1.0 % (0.96 % and 0.98 %, respectively). Intra-reader agreement was also excellent (ICC, 0.98 [95 % CI, 0.97–0.99]), as was intra-reader reproducibility, with RMSCV < 1.0 % (0.92 % and 0.94 %).

4. Discussion

In our study of premenopausal women, the long duration BF group (BF > 8 months) demonstrated a greater decrease in bone marrow PDFF of the lumbar spine and AM PDFF between BL and 5-year follow-up, compared to the short duration BF group (BF ≤ 8 months), suggesting a reduction in bone marrow adiposity and fatty muscle infiltration. Moreover, we found significant associations between BF duration and longitudinal changes of PDFF of the lumbar spine and AM. Within the long duration BF group, significant decreases in PDFF values of the PSM (PM and AM) were observed, alongside a significant increase in CSA, suggesting reduced fatty muscle infiltration and atrophy. Furthermore, the long duration BF group showed significantly better insulin resistance and insulin sensitivity indices and less individuals met one or more criteria for metabolic syndrome at BL compared to the short duration BF

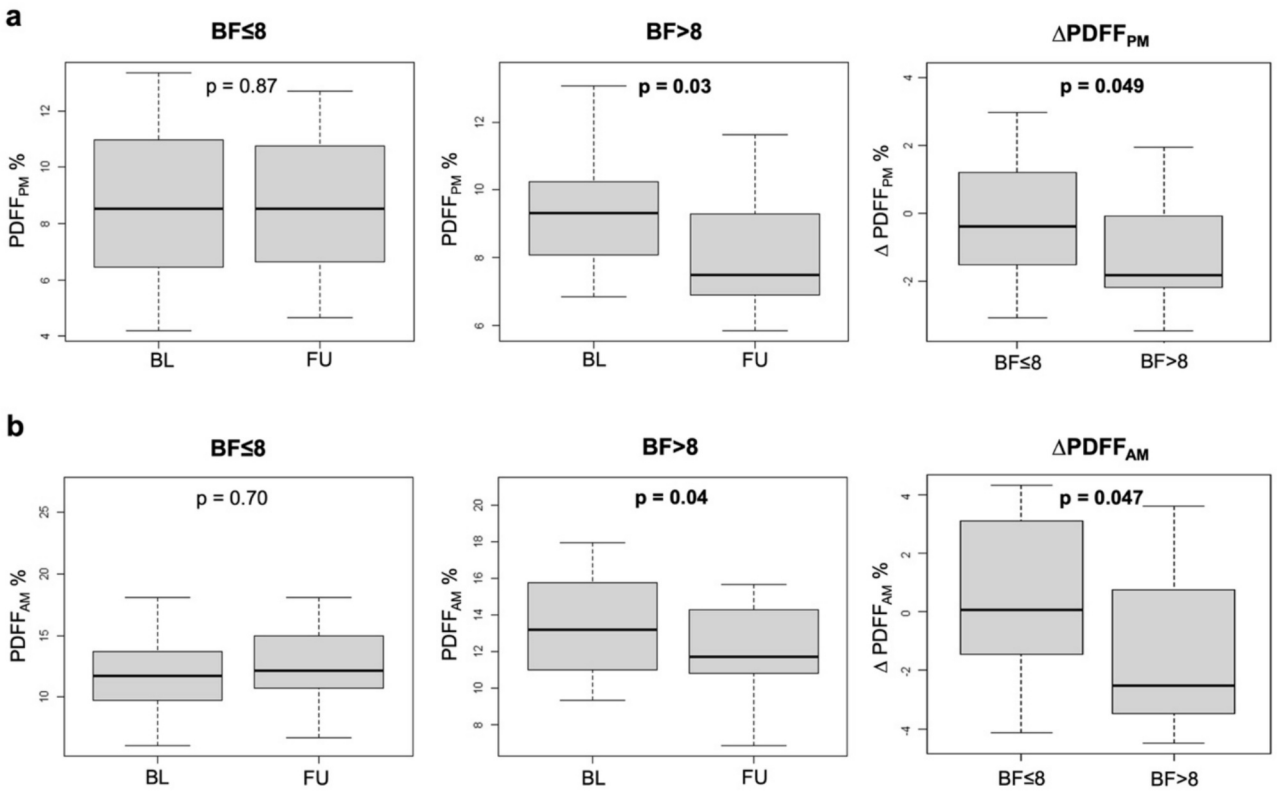

Fig. 3. Horizontally arranged within-group comparisons at baseline (BL) and five-year follow-up (FU) for women breastfeeding ≤8 months (BF ≤ 8) and women breastfeeding >8 months (BF > 8), along with longitudinal group comparisons between BL and FU for changes in mean proton density fat fraction (ΔPDFF). This includes (a) the bilateral psoas muscles ($PDFF_{PM}$) and (b) the bilateral autochthonous muscles ($PDFF_{AM}$).

group, indicating an improved glucose metabolism.

BF is associated with transient bone loss driven by increased calcium demands and hormonal changes, particularly hypoestrogenemia due to prolactin induced suppression of the hypothalamic-pituitary-ovarian axis [32]. Elevated parathyroid hormone related protein (PTH-rP) levels and reduced efficiency of calcium absorption further promote bone resorption [33]. While DXA studies reveal mixed findings about the extend and persistence of lactation-related bone loss, a recent *meta*-analysis suggests that BMD reduction is temporary, with a strong tendency to recover, depending on the return of menstruation and weaning [17]. However, methodological heterogeneity including variable follow up intervals, measurement techniques, and skeletal sites among the analyzed studies remain a critical limitation. HR-pQCT studies further indicate that cortical bone is more affected than trabecular bone, with increased cortical porosity and reduced cortical thickness [34,35]. Regarding the long-term effects of BF the majority of data suggest that skeletal strength is restored after lactation, and BF may even be protective against future fractures [36].

Against this background, vertebral bone marrow PDFF has recently demonstrated to visualize changes of bone marrow composition in certain patients and therefore may reflect bone quality and consequently osteoporosis risk [7–9]. To our knowledge, this is the first study to examine its association with BF. At baseline MRI (11.9 months postpartum), vertebral bone marrow adiposity did not differ significantly between the long and short BF groups. Given that complete BMD recovery is typically expected approximately 12 months after weaning [16,17], incomplete bone marrow recovery may explain the findings in the short BF group, who ceased BF approximately 5 months before. By the 5-year follow-up, the lactation-induced bone marrow loss appears restored in both groups. Notably, the significantly greater "relative" decrease (corrected ΔPDFF) in lumbar vertebral bone marrow adiposity and AM fatty infiltration in the long BF group may suggest that BF > 8 months facilitates bone marrow and muscle recovery, rather than being due to higher baseline PDFF values in the longer BF group. Importantly, compared with the recent *meta*-analysis by Grizzo et al. on BF and BMD [17], the follow-up period in our study was considerably longer (5 years vs. 15.4 months postpartum), thereby providing novel insights in long-term recovery patterns. Nevertheless, future studies incorporating DXA or QCT are needed to validate vertebral PDFF as a biomarker for bone strength in premenopausal women after pregnancy. The beneficial association of longer BF with decreased fatty infiltration of the AM in premenopausal women complements findings in elderly postmenopausal women, where prolonged BF has been linked to less sarcopenia in the appendicular skeletal muscle mass, measured by DXA [37]. This highlights that BF duration may influence not only skeletal recovery but also maternal muscle quality, which is of potential long-term metabolic relevance.

Besides the effect of longer BF on vertebral bone marrow and musculature, the longer BF individuals simultaneously showed significantly lower insulin resistance and higher insulin sensitivity and met significantly less likely one or more criteria of metabolic syndrome at baseline. This supports previous findings that BF improves postpartum glucose metabolism in women after normoglycemic pregnancy [38,39] Diabetes and osteoporosis share progression pathways, with vertebral bone marrow predominantly composed of insulin-responsive adipocytes [40]. Patients with T2D show an increased fracture risk, yet paradoxically demonstrate a normal or even increased BMD, leading to an underestimation of bone fragility [41]. Glucose homeostasis affects bone marrow fat phenotypes, as demonstrated by a negative association between the amount of marrow fat and BMD in postmenopausal women with T2D [42–45]. Moreover, elevated bone marrow PDFF is associated with insulin resistance in postmenopausal women with T2D [45] and elevated HbA1c in obese individuals [46]. Diabetes presents heterogeneously, which may explain contradictory results in studies showing

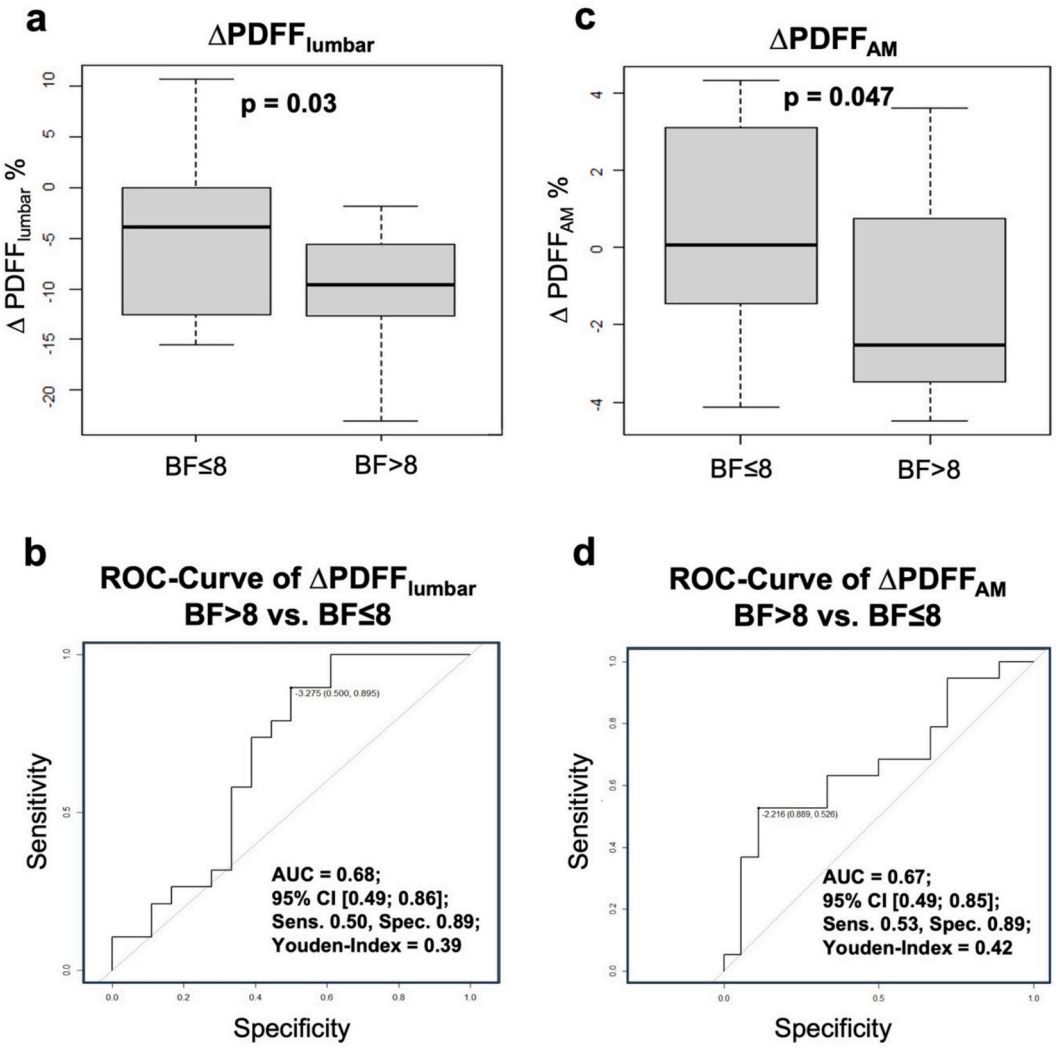

Fig. 4. Box-plot diagrams illustrating the change in mean proton density fat fraction of the (a) lumbar vertebral bone marrow (levels L1 to L4) ($\Delta PDFF_{lumber}$) and (c) bilateral autochthonous muscles ($\Delta PDFF_{AM}$) in women breastfeeding >8 months (BF > 8) compared to women breastfeeding ≤8 months (BF ≤ 8) between baseline and 5-year follow-up. Receiver operating characteristic (ROC) curves for (b) ($\Delta PDFF_{lumber}$) and (d) ($\Delta PDFF_{AM}$) to differentiate between the BF > 8 and BF ≤ 8 groups. Confidence interval (CI), area under the curve (AUC).

higher marrow fat content in T2D patients compared to healthy individuals [45,47], or no significant difference [43,48,49].

In the exploratory sub-cohort analysis among women with prior GDM, the longer BF women showed significantly better insulin sensitivity and resistance indices, fewer cases of pathologic glucose metabolism, and fulfilled one or more criteria of metabolic syndrome. This beneficial association between longer BF duration and improved postpartum glycemic status in GDM women aligns with previous studies [18,50–57]. Regarding the PDFF values of the spine and the PSM, similar changes were observed between long duration and short duration BF women within the GDM group as in the overall comparison between the two groups, however, these changes did not reach statistical significance. Yet, these results need to be treated cautiously, since the analyses were purely experimental based on small sample sizes within the sub-cohorts.

4.1. Limitations

The study has several important limitations. First, the sample size of our study was relatively small because only MRI study participants using the identical protocol and scanner system were selected to minimize potential measurement bias from varying methods. Second, missing pre-pregnancy data (anthropometrics, clinical parameters, and PDFF), unavailable postpartum weight trajectories, and unmeasured confounders such as dietary habits and the return of menses, limit the interpretation of PDFF changes. Third, missing BMD data (DXA or QCT) preclude validation of vertebral bone marrow PDFF in postpartum women. As DXA cannot distinguish cortical from trabecular bone, and PDFF captures marrow fat only within trabecular bone, our results may reflect changes in fat metabolism rather than true alterations in bone strength. Fourth, the analysis did not differentiate between exclusive and partial BF due to the absence of detailed records, which is relevant because exclusive BF has been linked to greater short-term bone loss [58]. Moreover, the analysis did not account for parity, which may affect maternal bone metabolism. Fifth, MRI measurements were not scheduled relative to breastfeeding cessation or return of menses, potentially confounding outcome interpretation. Finally, the small sample size of the sub-cohort analysis of women with history of GDM prevented adjustment for relevant covariates; these findings should therefore be interpreted with caution.

5. Conclusion

These findings may indicate a potential association of longer BF

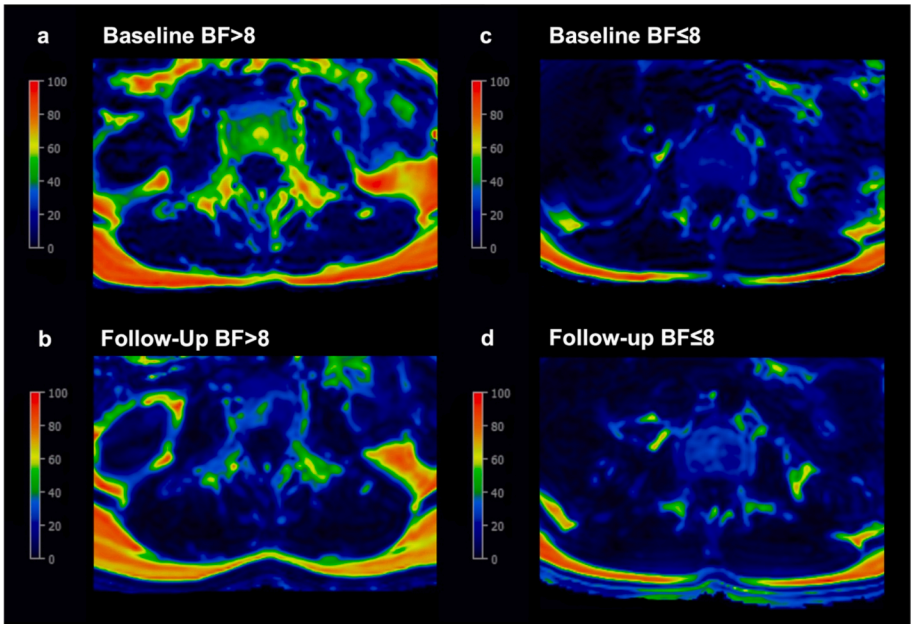

Fig. 5. Example color-coded proton-density fat-fraction (PDFF) map at the level of L2: (a) Woman who breastfed >8 months (BF > 8), BMI 20.97 kg/m^2, mean PDFF of the lumbar spine 43.04 %, the psoas 8.09 %, and autochthonous muscle 11.03 %. The same woman is shown in (b) at 5-year follow-up with a mean PDFF of 30.23 % in the lumbar spine, 6.20 % in the psoas, and 7.31 % in the autochthonous muscle. (c) Woman who breastfed ≤8 months (BF ≤ 8) with a BMI of 19.15 kg/m^2 and a mean PDFF of the lumbar spine of 46.63 %, the psoas of 6.51 %, and autochthonous muscle of 8.17 %. (d) At 5-year follow-up, her mean PDFF in the lumbar spine, psoas, and autochthonous muscle was 44.39 %, 4.67 %, and 6.72 %, respectively.

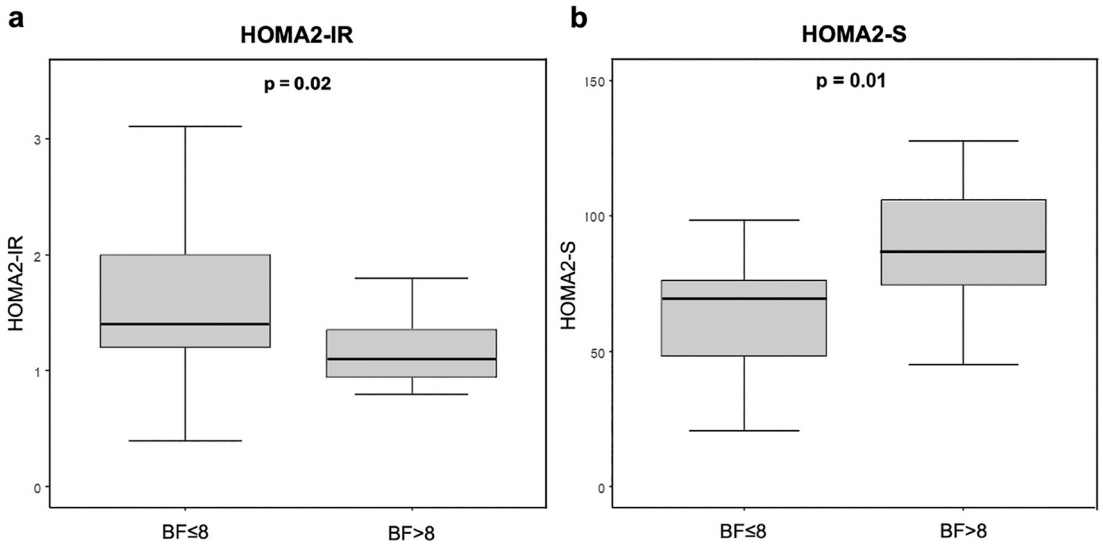

Fig. 6. Box-plot diagrams showing the difference between HOMA2-IR and HOMA2-S at baseline in women breastfeeding >8 months (BF > 8) compared to women breastfeeding ≤8 months (BF ≤ 8). HOMA2-S, Homeostasis Model Assessment 2 – insulin sensitivity; HOMA2-IR, Homeostasis Model Assessment 2 – insulin resistance.

duration (>8 months) and favourable bone and muscle composition, as well as aspects of maternal metabolic health, compared to shorter BF duration (≤8 months), although causality cannot be established. Further research with larger cohorts is warranted to confirm and explore these associations in greater detail and to investigate the underlying mechanisms.

CRediT authorship contribution statement

N. Hesse: Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Y. Stohldreier:** Writing – review & editing, Investigation, Formal analysis, Data curation. **S. Schlaeger:** Software, Formal analysis. **S. Theuerl:** Software, Data curation. **O. Dietrich:** Writing – review & editing, Software, Formal analysis. **H. Hermann:** Formal analysis. **I. Kaiser:** Data curation. **J. Seissler:** Writing – review & editing, Supervision, Resources, Project administration. **E. Pappa:** Data curation. **U. Ferrari:** Writing – review & editing, Supervision, Project administration, Conceptualization. **A.S. Gersing:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Conceptualization.

Declaration of competing interest

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejrad.2025.112514.

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