Comparability of size measurements of the pancreas in magnetic resonance imaging and transabdominal ultrasound

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Abstract
Introduction: Transabdominal ultrasound (US) and magnetic resonance imaging (MRI) are commonly used for the examination of the pancreas in clinical routine. We therefore were interested in the concordance of these two imaging methods for the size measurement of the pancreas and how age, gender, and body mass index (BMI) affect the organ size.

Methods: A total of 342 participants from the Study of Health in Pomerania underwent whole-body MRI and transabdominal US on the same day, and the diameter of the pancreatic head, body, and tail were measured. The agreement between US and MRI measurements was assessed by Bland and Altman plots. Intraclass correlation coefficients were used to compare observers. A multivariable regression model was applied using the independent variables age, gender, and body mass index.

Results: Compared to MRI, abdominal US returned smaller values for each segment of the pancreas, with a high level of inconsistency between these two methods. The mean difference was 0.39, 0.18, and 0.54 cm for the head, body, and tail, respectively. A high interobserver variability was detected for US. Multivariable analysis showed that pancreatic size in all three segments increased with BMI in both genders whereas pancreatic head and tail size decreased with age, an effect more marked in women.

Conclusions: Agreement of pancreatic size measurements is poor between US and MRI. These limitations should be considered when evaluating morphologic features for pathologic conditions or setting limits of normal size. Adjustments for BMI, gender, and age may also be warranted.

1 | INTRODUCTION

In clinical routine, the morphology of abdominal organs and their pathologic findings is often assessed by different imaging methods to yield maximal information. Morphological assessments of the pancreas are relevant...
in the diagnosis of acute and chronic pancreatitis (Banks et al., 2013; Hoffmeister et al., 2015; Lerch et al., 1989) including autoimmune pancreatitis (Pickartz, Mayerle, & Lerch, 2007) or neoplasms of the organ (Hohl et al., 2004; Seufferlein et al., 2013) and for diagnostic workup of type 2 diabetes (Al-Mrabeh, Hollingsworth, Steven, & Taylor, 2016; Bilgin et al., 2009; Macauley, Percival, Thelwall, Hollingsworth, & Taylor, 2015). Moreover, a combination of different imaging methods is often used in clinical practice before establishing a diagnosis. In addition, measurements of organ size may vary due to factors either related to the pancreas itself such as its irregular shape and variable fat content (Gress et al., 1994; Syed et al., 2012), organ size may vary due to factors either related to the pancreas itself such as its irregular shape and variable fat content (Gress et al., 1994; Syed et al., 2012), body weight (Cuntz, Frank, Lehnter, & Fichter, 2000; Niederau et al., 1983) and gender (Niederau et al., 1983) as well as other sources of measurement bias such as operator effects, differences in posture, diurnal changes, measurement protocol, and machine type (De Molto et al., 2013; Dimcevski, Erchinger, Havre, & Gilja, 2013; Sienz, Ignee, & Dietrich, 2011).

Abdominal ultrasound (US) is an almost ubiquitously available and noninvasive method for investigation of abdominal organs like the pancreas. Therefore, it is often used as the first imaging method even when the patient has to undergo further imaging examinations. However, US is a highly operator-dependent technique, and imaging quality can be limited for example due to intestinal gas or marked obesity (Brown, Sirlin, Hoyt, & Casola, 2003). Other noninvasive imaging techniques for evaluation of the pancreas include computed tomography (CT) and magnetic resonance imaging (MRI). They produce cross-sectional images usually in a transversal orientation. Although operator effects have been demonstrated for these techniques as well, they are less pronounced than in US, so that MRI measurements are often considered to be more reliable (Ryan, Semelka, Molina, Yonkers, & Vaidean, 2010; van Vliet et al., 2008). Compared to CT, MRI provides better soft tissue contrast and in combination with magnetic resonance cholangiopancreatography (MRCP) it can be used for evaluating of the pancreatic duct (Bulow et al., 2014; Mensel et al., 2014). Validity of different imaging modalities has been assessed for cystic (Lee et al., 2015; Maimone et al., 2010) and solid lesions (Tummal, Junaidi, & Agarwal, 2011; Vukobrat-Bijedic et al., 2014) of the pancreas but there is still a lack of studies comparing the morphology and size of the anatomic segments of the pancreas, particularly for US. Due to advances in US technology and improved imaging quality this technique becomes more relevant for diagnostic and therapeutic strategies (Engjom et al., 2017; Lerch et al., 1992; Poza-Cordon & Ripolles-Gonzalez, 2014; Sun et al., 2017). Therefore, a comparison with high resolution imaging methods such as CT or MRI with US is justified.

We have used the Study of Health in Pomerania (SHIP), a population-based study, launched in 1997 in the region of West Pomerania in Northeast Germany, that follows two main objectives: first, it assesses prevalence and distribution of common risk factors and a broad range of subclinical disorders and clinical diseases and second, it analyzes their underlying associations (Ludemann et al., 2000). SHIP collects clinical and anthropometric data and is therefore suitable for analyses in the general population.

Our study has two objectives, that is, (a) to investigate the agreement between the two measuring methods for pancreatic size (US and MRI) and (b) to assess the effect of age, gender and body mass index (BMI) on pancreatic size measured by MRI. A better understanding of confounding factors and sources of bias will assist the interpretation of pancreatic size measurements in clinical settings.

## 2 Methods

### 2.1 Study population

Participants were recruited from the SHIP-2 project, a second examination follow-up of the first SHIP cohort that was conducted between 2008 and 2012 (Volzke et al., 2011). In total 2,333 participants were recruited for SHIP-2, of which 1,182 (50.7%) were examined by MRI and 744 (31.9%) by US. None of the participants had any known previous pancreatic disorders and probands with a history of pancreatitis, anatomical variants such as pancreas divisum or pancreatic tumors were excluded. We only included subjects investigated by both MRI and US on the same day. After approval by the local institutional review board (SHIP/2013/35/D), the retrospective analysis of data was initiated. Written informed consent was obtained from each individual. The final dataset included 342 individuals who underwent both MRI and US on the same day, 12 of which were excluded due to complete air superposition of the pancreas. In 25 individuals, the pancreas was only partly visible: in 2 and 21 individuals the pancreatic head and tail, respectively, were not visible and in 2 individuals both the pancreatic head and tail were not visible. In addition, one outlier was excluded due to implausible values for the body and the tail ultimately ending up to 326 trans-abdominal US measurements for the head, 329 for the body and 306 for the tail. Mean age was 56.8 years (±12.5 years), and 45.2% of participants were males. Mean BMI was 27.6 kg/m$^2$ indicating overweight (25–30 kg/m$^2$) according to international classification (Table 1). The process of selection of individuals for the study was summarized by a flow chart (Supporting Information Figure S1).

### 2.2 Transabdominal US

Measurements were carried out by 12 physicians, who were experienced examiners for ultrasonography and had undergone a training instruction to standardize the examination procedure for SHIP. This included an experience of at least US 2,500 examinations of the abdomen. US examination was performed using an ALOKA ProSound SSD-5000 SV ultrasound machine (Hitachi Medical Systems, Wiesbaden, Germany). Participants were examined in supine position after an overnight fasting period. The pancreas was accessed by subcostal view, the pancreatic head and body were measured in ventral-dorsal direction and the tail was measured perpendicular to the main axis of the organ (Supporting Information Figure S2A-C). Data were recorded electronically via a computer-based data entry mask. A cohort of 50 subjects was examined by two US examiners who separately measured all three anatomic segments of the pancreas to calculate inter-observer variability for this method.
TABLE 1  Characterization of the study population

| Variable              | n   | Mean  | SD    | Median | Interquartile range | Range |
|-----------------------|-----|-------|-------|--------|---------------------|-------|
| Age (years)           | 330 | 56.8  | 12.5  | 57     | 47–66               | 31–88 |
| Body weight (kg)      | 330 | 79.5  | 14.8  | 78.1   | 68.2–89.8           | 47.7–118.7 |
| Height (cm)           | 330 | 169.5 | 9.4   | 169    | 163–177            | 145–192 |
| BMI (kg/m²)           | 330 | 27.6  | 4.1   | 27.2   | 24.8–30.3           | 17.3–39.6 |
| No. of measurements per US examiner | 330 | nd*  | nd*   | 27     | 9.5–35.75          | 3–78  |

Note: Mean, SD, median, interquartile range, and range of the variables describing the study population (age, body height, body weight, and body mass index (BMI)). Pancreatic size of 330 participants was measured by ultrasound (US) and magnetic resonance imaging (MRI) in a population-based study (SHIP-2 cohort) in Mecklenburg–Pomerania between July 2, 2008 and June 19, 2012.

*nd, not normally distributed.

TABLE 2  Measurements of the pancreas by US and MRI

| Modality and anatomic part | n   | Mean  | SD    | Median | Interquartile range | Range |
|----------------------------|-----|-------|-------|--------|---------------------|-------|
| Size measured by US (cm)   |     |       |       |        |                     |       |
| Head                       | 326 | 2.46  | 0.63  | 2.5    | 2.04–2.80           | 0.80–5.10 |
| Body                       | 329 | 1.27  | 0.46  | 1.2    | 0.95–1.51           | 0.30–3.20 |
| Tail                       | 306 | 1.62  | 0.60  | 1.5    | 1.20–2.00           | 0.40–3.60 |
| Size measured by MRI (cm)  |     |       |       |        |                     |       |
| Head                       | 330 | 2.85  | 0.57  | 2.8    | 2.46–3.16           | 1.55–5.29 |
| Body                       | 330 | 1.45  | 0.43  | 1.5    | 1.15–1.64           | 0.66–3.28 |
| Tail                       | 330 | 2.17  | 0.48  | 2.1    | 1.83–2.50           | 0.96–3.55 |

Note: Mean, SD, median, interquartile range, and range of the pancreatic size for the parts head, body, and tail.

2.3  MRI data acquisition

Whole-body MRI was performed using a MAGNETOM Avanto 1.5 Tesla imaging unit (Siemens Healthcare GmbH, Erlangen, Germany). The study sequences covered all upper abdominal organs including the pancreas (Hegenscheid et al., 2009). Pancreatic size was measured using an axial fat saturated T1-weighted flash 2D sequence acquired with 6.0 mm slice thickness and the following imaging parameters: repetition time TR: 251 ms; echo time TE: 4.13 ms; flip angle FA: 70°; pixel size 2.3 × 1.6 mm, gap size of 1.2 mm; bandwidth 140 Hz/Px; scan time 1:16 min. The 2D data set was acquired in the axial plane. Locations of measurements are shown in Supporting Information Figure S2D–F.

Measurement was performed by a medical student (D.D.) under supervision of an experienced observer in MR imaging of abdominal organs (M.L.K). Interobserver variability was computed in a random subsample of 17.5% individuals (60/342) by a second experienced radiologist (R.B.). MR images were analyzed using IMPAX viewer (version 6; Agfa healthcare, Mortsel, Belgium).

2.4  Statistical analysis

Statistical analysis was performed using Stata 14.0 (StataCorp, College Station, TX). For MRI and transabdominal US, interobserver variability was assessed by means of intraclass correlation coefficients (ICCs) using the icc command. Mean bias was calculated as the mean difference between two observers. Agreement was classified as excellent (>0.80), good (0.61–0.80), moderate (0.41–0.60), fair (0.20–0.40), and poor (<0.20). A stratified analysis was carried out to assess whether ICC values varied with BMI. For that purpose, participants were categorized as nonoverweight (<25 kg/m²), overweight (25 and <30 kg/m²) and obese (>30 kg/m²).

Scatterplots stratified by part of the pancreas (head, body, tail) were produced to visualize the association between US and MRI. Boxplots were created to investigate the distribution of US measurements per examiner. Bland and Altman plots were used to assess agreement between US and MRI measurements (Bland & Altman, 1986; Giavarina, 2015), whereby the mean of the two measurements (US and MRI) was plotted versus the difference. No adjustment was made for confounding variables gender, age, and BMI as both measurements were taken on the same subject (matched analysis).

The mixed command was used to adjust for the random effect of US examiner using a random-intercept model. Variance introduced by the examiner (refffects option of the pred command) was derived from this model and subtracted from the US measurements to remove the examiner effect. These adjusted US measurements were used to compute Bland–Altman plots again to assess the change compared to the estimates obtained for unadjusted measurements. The intraclass correlation coefficient (ICC) was derived from the model using the estat icc command and interpreted according to the same criteria as outlined above.

Linear regression (regress command) was used to predict MRI based pancreatic size of head, body and tail depending on the variables BMI, age and gender. Interactions were tested for all significant variables of the main effect model. A significance threshold of 0.05 was applied. Margins plots were used to visually display the three possible two-way interactions between BMI, age and gender for each of pancreatic head, body and tail with fixed values of the third variable not included in the interaction (BMI and age: median; gender: males) (marginsplot command). Model fit was assessed by visual inspection of residuals.
3 | RESULTS

3.1 | Interobserver variability for MRI and transabdominal US

The interobserver variability of MRI data in transverse orientation was moderate for pancreatic head (ICC = 0.55 [0.34–0.70]) with a mean bias of 5.00 ± 4.19 mm, good for pancreatic body (ICC = 0.82 [0.72–0.89]) with a mean bias of −1.14 ± 2.80 mm, and poor for the pancreatic tail (ICC = 0.40 [0.17–0.59]) with a mean bias of 3.11 ± 4.58 mm. The interobserver variability of US was high for pancreatic head (ICC = 0.77 [0.62–0.86]) with a mean bias of 0.94 ± 4.39 mm, moderate for pancreatic body (ICC = 0.67 [0.49–0.80] with a mean bias of 0.50 ± 2.69 mm) and tail (ICC = 0.67 [0.48–0.80] with a mean bias of −0.13 ± 3.23 mm). These results indicate the both imaging methods are associated with a considerable interobserver variability.

FIGURE 1  Bland–Altman plots showing the absolute difference in pancreatic size measurements against average values (cm) between magnetic resonance imaging (MRI) and ultrasonography (US) for the head (n = 326; top left), body (n = 329; top right) and tail (n = 307; bottom). The solid and dashed lines represent the mean difference and its 95% confidence intervals, respectively.

FIGURE 2  Box plots showing the median and dispersion of pancreatic size (y-axis; cm) measured by 12 examiners (x-axis) by means of ultrasonography (US) for the head (n = 326; top left), body (n = 329; top right) and tail (n = 307; bottom).
3.2 Concordance of MRI and US

Pancreatic size in each anatomical section was smaller when measured by US than by MRI (Table 2). The mean difference between MRI and US measurements was 0.39 cm for the head, 0.18 cm for the body, and 0.54 cm for the tail, which corresponds to a relative difference of 14.4–43.3% (Figure 1). The discrepancy was highest for the tail and lowest for the body. The wide 95% confidence intervals (CIs) further indicate a high level of inconsistency. Furthermore, Bland and Altman plots indicated certain trends in the data: First, the pancreatic head tended to show smaller measurements in US compared to MRI for smaller means of these two measurements. Second, for the body and tail, dispersion of the differences tended to be stronger for larger mean values of the two measurements.

**FIGURE 3** Bland–Altman plots showing the absolute difference in pancreatic size measurements against average values (cm) between magnetic resonance imaging (MRI) and residuals of ultrasonography (US) after removing the random effect of examiner for the head (n = 326; top left), body (n = 329; top right) and tail (n = 307; bottom). The solid and dashed lines represent the mean difference and its 95% confidence intervals, respectively.

US measurements were adjusted for the effect of examiner, given that considerable variability was observed between examiners in the boxplots (Figure 2). The multilevel model estimated the intraclass coefficient (ICC) for US examiner as 0.25 (95% CI: 0.11–0.47), 0.15 (95% CI: 0.05–0.36) and 0.30 (95% CI: 0.13–0.54) for head, body and tail, respectively, indicating poor to fair agreement between examiners. No consistent trend was observed when calculating ICC stratified by BMI category. For the size of the pancreatic head and body, agreement was actually lower for nonobese individuals than for obese (head and body) and overweight individuals (head). For tail measurements, no difference was observed for the different BMI categories (Supporting Information Table S1).

After adjusting for the US examiner effect, the mean difference between MRI and US measurements decreased to 0.31 (11.8% of...
MRI), 0.12 (9.3%), and 0.45 cm (24.4%) for the head, body, and tail, respectively (Figure 3). The trends observed for Bland and Altman plots for the raw values diminished considerably using the adjusted values.

### 3.3 Dependence on age, gender, and BMI

Using MRI as a basis, we observed for all three pancreatic segments that pancreatic size increases with BMI, decreases with age, and is smaller in females than males. The main effect model resulted in R-squared values of 18.3% for the pancreatic head, 35.4% for the body, and 11.4% for the tail.

For the pancreatic head, size slightly increased with higher BMI but was not significantly different among different age groups of the study population (Figure 4a) or between males and females (Figure 4b). Size decreased with age in females but not in males (\( p = .03 \), Figure 4c). In contrast, a stronger increase of pancreatic body size with BMI was observed in males than in females, which was highly significant (\( p = .007 \)) leading to lines drifting apart with higher BMI. An interaction of pancreatic body and BMI for different age groups or gender was not significant (Figure 5a,b). Pancreatic body size slightly decreased with higher age, but did not significantly differ between both genders (Figure 5c). For the pancreatic tail, there was an increase of size with higher BMI, but no significant interactions were observed among different age groups (Figure 6a) or males and females (Figure 6b). Pancreatic
4 | DISCUSSION

Transabdominal US is an important diagnostic tool for a variety of gastroenterological disorders since it is usually used as the first diagnostic examination. It is ubiquitously available and easy to handle despite its dependence on the examiner’s experience. In addition, quality of imaging in US has dramatically improved so that one can assume that this imaging method will gain more importance for diagnosis and interventional procedures in the future. Not all patients with pancreatic disorders automatically receive cross-sectional-imaging such as MRI, which usually is reserved for more complex questions. For example, patients with mild acute pancreatitis or for diagnostic workup for diabetes mellitus normally undergo US. That is why decision-making process of clinicians is often based on US as an only imaging modality.

Therefore, we were interested in the accuracy of US measurements compared to a method with an acknowledged high imaging quality of the pancreas which is MRI (Bulow et al., 2014; Kuhn et al., 2015). By using the population-based SHIP, we recruited a large number of healthy individuals who were examined by both methods on the same day (Volzke et al., 2011).

There was a discrepancy between measurements by MRI and transabdominal US. Generally, US measured smaller sizes for each segment of the pancreas when compared to MRI. Differences ranged between 14.4 and 43.3% depending on the part of the organ and was greatest for the tail. Our study further demonstrated, that in 7% of the volunteers the pancreatic tail was not visible by US. To the best of our knowledge there are no comparative studies investigating the normal pancreas by both MRI and US. Organ size was assessed in previous studies using transabdominal US alone to define reference values for this technique (Sienz et al., 2011). In case of MRI, morphometry of the pancreas is usually performed by calculation of the pancreatic volume (Macauley et al., 2015; Virostko, Hilmes, Eitel, Moore, & Powers, 2016) and only one MRI study directly measured pancreatic anterior–posterior diameters (Sato et al., 2012). Second, our data showed a great variability of size measurements in US. One reason is that 12 different sonographers investigated the pancreas and we found a strong interobserver variability with only fair to poor agreement although all our imagers were trained for gastrointestinal US. In a study focusing on the quality of ultrasonography of adnexal masses performed by radiologists, comparably poor findings were obtained in spite of differences of their US experience and numbers of examinations. However, examiners who underwent sub specialization in female reproductive tract performed better (Levine et al., 2008). Unfortunately, studies on the quality of US performance for organs of the upper abdomen including the pancreas are lacking so that further investigations will be helpful.

The visual plane of the pancreas on ultrasonography may also impact measurements. Some authors have used other approaches such as a sagittal (Niederau et al., 1983) or cranio-caudal view (Pochhammer, Szekessy, Frentzel-Beyme, & Hollstein, 1984) or even an inclined position originating from a transversal view (Kolmannskog, Vatn, Swensen, Aakhus, & Gjone, 1983) instead of anterior–posterior measurements. These inconsistencies of capturing US images bear measurement variations as well, making comparisons of studies more complicated and should be kept in mind by the clinicians when drawing conclusions based on imaging results. Although the size of a healthy pancreas is mostly irrelevant in daily clinical routine, the discrepancies between US and MRI should not be disregarded, especially in the case of potentially pathological pancreatic lesions.

Our results further indicate that the size of the pancreas is dependent on anthropometric data, age, and gender of individuals. There are conflicting data regarding dependence of organ size on age (Sienz et al., 2011). No relevant alteration of size was observed in individuals with a healthy pancreas or with diabetes mellitus (Silva et al., 1993; Vossen, 1986), but the echogenicity of the parenchyma was found to increase with age (Zimmermann, Frank, Weiss-Simon, Burkhard, & Seidel, 1981). Others reported an increase (Niederau et al., 1983) or a decrease of organ size (Ker, Tabata, Sheen, Jan, & Chen, 1984) with age. Measurements were mostly performed using sagittal diameter. Our data indicate a decrease of organ size with increasing age, which is dependent on the gender of the volunteer. In females, the size of the pancreatic head and tail decreased more prominently with age compared to males. These data indicate that age effects are more pronounced in the pancreatic head and tail than in the pancreatic body.

In addition, there was an increase of pancreatic body size along with increasing BMI, which was more prominent in males than in females. Our observations are in line with other studies that also reported a positive correlation between pancreatic size and BMI (Niederau et al., 1983). Irrespective of the organ segment, men showed larger sizes than women being comparable to observations from Niederau and co-workers (Niederau et al., 1983) while others have found a smaller pancreatic head in men (Silva et al., 1993). Possibly, the larger pancreas size in obese individuals results from fatty infiltration of the pancreas, analogous to development of fatty liver, caused by a progressive beta-cell dysfunction in the endocrine pancreas (Misra et al., 2015). Moreover, a positive correlation of pancreatic fat content with BMI has been described in the SHIP-TREND cohort, which was recruited between 2008 and 2015 in the same region like our study (Kuhn et al., 2015).

Since the three investigated predictors alone explained up to 34% of the variation in pancreatic size, it is hypothesized that reference values taking these individual factors into account may be useful in a clinical setting to assess pancreatic pathology. Apart from laboratory parameters that help for the selection of individuals and estimation of the number of study participants in clinical studies (Farkas et al., 2019) variations of anatomic sizes of the pancreas should also be considered. Therefore, pretrained investigators for US or cross-sectional imaging such as MRI or CT should be available.

There are limitations to our study. First, 12 examiners investigated the pancreas by US whereas only a single investigator read all MR images. Although all involved examiners had experience in abdominal US and went thorough standardization training the levels of professionalism differed in that group as not all ultrasonographers...
were accredited investigators by the German Society for Ultrasound in Medicine (DEGUM) (Heese & Gorg, 2006). Potential variations in the expertise of examiners may explain the variance. However, this circumstance reflects real clinical situations where different examiners, sometimes with different levels of experience, perform US of the abdomen in the clinical setting. In addition, interobserver variations in reading of MR images occur despite following a standardized protocol as we have noticed in a subgroup of individuals that were examined by a second radiologist. These depended on the anatomic segment of the pancreas and were highest when measuring the pancreatic tail. Technical limitations in MRI as slice thickness and gap size might explain these variabilities leading to changes of organ sizes when examining another transversal image layer.

Second, it can be argued that measurements of the organ size have been done here in asymptomatic individuals and that no size comparison of pathologic findings was included. However, the study was designed as a methodological approach for comparison of both techniques in a population-based setting. It provided results from a large-scale data set of individuals including information on various predictor variables such as age, gender and BMI. Even if the differences of sizes between US and MRI appear to be too small to be relevant for clinical issues, our study serves as a basis for further studies investigating pathologic conditions such as solid or cystic lesions. For instance when assessing tumors size (besides its relation to other anatomic structures), even small variances of measurements can become clinically relevant and potentially imply therapeutic consequences. Indeed, in the context of the growing importance of imaging modalities this comparative study indicates that diagnostics based on US measurements should be followed by a confirmatory diagnostic procedure due to the risk of measurement bias.

5 | CONCLUSIONS

We conclude that measurements of the pancreas size performed by US need to be interpreted with caution as they differ to MRI, a cross-sectional imaging method, which is considered to be more objective. Second, there is a substantial variation of measurement results among ultrasonographers limiting the comparability of organ size evaluations. Sources of individual variability due age, gender, and BMI should be considered when evaluating morphologic features to diagnose pathologic conditions.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

A.A.A., B.S., H.V., and M.M.L. designed the study. Ultrasound measurements were carried out and analyzed by A.A.A., D.D., T.P., C.B., P.M., and P.S. MRI measurements were carried out and analyzed by D.D., M.L.K., R.B., and J.K. B.S. and T.I. performed statistical analysis. A.A.A. and B.S. wrote the manuscript. All authors read and approved the final manuscript.

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section at the end of this article.