

# Magnetic Resonance Neurography

## Normal Values and Demographic Determinants of Nerve Caliber and T2 Relaxometry in 60 healthy individuals

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### Abstract

**Purpose** To establish normal values and to identify demographic determinants of quantitative biomarkers in magnetic resonance neurography (MRN).

**Methods** In this study 60 healthy individuals (5 men and 5 women of every decade between 20 and 80 years) were examined according to a standardized MRN protocol at 3 T, including multiecho T2 relaxometry. Nerve cross-sectional area (CSA), transverse relaxation time (T2), and proton spin density (PSD) were assessed for the sciatic, tibial, median, ulnar, and radial nerves. Correlation with demographic variables, such as height, weight, body mass index (BMI), and age was expressed by Pearson coefficients and t-tests were used to compare MRN biomarkers between men and women with and without normalization to body weight and BMI by linear regression.

**Results** The average nerve CSA correlated moderately with height ( $r = 0.28$ ,  $p = 0.04$ ), weight ( $r = 0.40$ ,  $p = 0.002$ ), and BMI ( $r = 0.35$ ,  $p = 0.008$ ), but not with age ( $r = 0.23$ ,  $p = 0.09$ ). While T2 did not correlate with demographic parameters, PSD was strongly inversely associated with BMI ( $r = -0.64$ ,  $p < 0.001$ ) and weight ( $r = -0.557$ ,  $p < 0.001$ ). Sex-dependent differences in imaging marker values were

found for CSA but became negligible after normalization to body weight.

**Conclusion** Quantitative biomarkers of MRN co-vary with demographic variables. As particularly important determinants, we identified body weight for nerve CSA and BMI for PSD. The presented normal values and demographic determinants may assist investigations into the potential of MRN biomarkers in further disease-specific studies.

**Keywords** Magnetic resonance imaging · Peripheral nervous system · Reference values · Demography

### Introduction

Peripheral nerve imaging gains importance in inflammatory, degenerative, neoplastic, metabolic, inherited, and traumatic pathologic conditions of the peripheral nervous system [1–6]. Ultrasonography allows rapid, reliable, and relatively inexpensive assessment of nerve morphology and quantification of nerve caliber especially at superficial sites [7], while magnetic resonance neurography (MRN) can be used to visualize nerves at deeper and more proximal locations. Nerve cross-sectional area (CSA) is the most commonly reported morphologic parameter for both sonography and MRN. Besides morphologic parameters, MRN can be used to acquire quantitative biomarkers by application of dedicated MRI techniques, such as multiecho T2 relaxometry [8, 9]. The T2 relaxometry technique yields the quantities transverse relaxation time (T2) and proton spin density (PSD), which provide information regarding nerve tissue composition. In a simplified model, T2 indicates the amount of free water, whereas PSD may reflect the total water content in one voxel, including a fraction that is tightly restricted by macromolecules [8, 10–13].

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While relaxometry has been extensively investigated in the central nervous system [14, 15], only a few studies have applied MR relaxometry in peripheral nerves, addressing pathologies, such as diabetic neuropathy [8, 16], amyloidosis [10], Charcot-Marie-Tooth disease [17], chronic inflammatory demyelinating polyneuropathy (CIDP) [18], and subclinical ulnar neuropathy at the elbow [9].

A profound understanding of quantitative MRN biomarkers is not only necessary for their systematic assessment in peripheral nerve diseases but also for a thorough analysis of additional determinants, such as age, body height, weight, and gender in healthy individuals. Up to now, the report of normal values of MRN biomarkers has been restricted to control groups of localized or systemic neuropathies [17, 19]; however, a systematic assessment of MRN biomarkers in a larger cohort of healthy individuals has not yet been performed, especially with respect to the correlation of these biomarkers to demographic parameters.

The aim of this study was to establish normal values and to identify demographic determinants of quantitative MRN biomarkers, specifically CSA, T2 and PSD.

## Methods

### Subjects

This prospective study was approved by the institutional ethics committee, and written informed consent was obtained from all participants. For the study 60 healthy subjects were recruited by public announcement and examined according to a standardized MRN protocol.

Inclusion criteria were age between 20 and 80 years such that 5 men and 5 women in each decade were included. Exclusion criteria were previous diagnoses of peripheral or central neurological diseases (e.g. carpal tunnel syndrome, disc herniation, inflammatory peripheral neuropathies, stroke) and systemic diseases (e.g. diabetes, rheumatoid arthritis, vasculitis), as well as contraindications for magnetic resonance imaging (MRI). Gender, age, body weight, body height, and body mass index (BMI) were documented as baseline demographic characteristics.

### Magnetic Resonance Neurography

All subjects were examined using a Magnetom TIM-TRIO (Siemens Healthcare, Erlangen, Germany) at 3.0 T by the following protocol: upper and lower extremities were imaged at mid-upper arm level, mid-thigh, and proximal calf (with proximal alignment of the slab with the tibiofemoral joint) as described previously [18] by one slab of both the following sequences:

**Sequence 1** High resolution T2-weighted turbo-spin-echo (TSE) sequence with spectral fat saturation in axial orientation for assessment of cross-sectional area with the parameters repetition time (TR) = 7000 ms, echo time (TE) = 55 ms, 2 excitations, field of view (FOV) 160 × 160 mm<sup>2</sup>, matrix size = 512 × 333, slice thickness = 3.5 mm, interslice gap = 0.35 mm, voxel size = 0.5 × 0.3 × 3.5 mm<sup>3</sup>, 41 slices, acquisition time per slab 3 min 46 s.

**Sequence 2** Multi-spin-echo (MSE) sequence with spectral fat saturation in axial orientation for T2 relaxometry and with the following parameters: TR = 2400 ms, 12 echoes with echo times of 10, 20, ... 120 ms, FOV 160 × 160 mm<sup>2</sup>, matrix size 192 × 169, slice thickness 3.5 mm, no interslice gap, voxel size 0.9 × 0.8 × 3.5 mm<sup>3</sup>, 11 slices, acquisition time per slab 6 min 50 s.

Imaging was restricted to one randomly selected side. Including survey scans and positioning, the examination averaged approximately 45 min. A 15-channel transmit-receive knee-coil (Siemens Healthcare) was used for imaging of the lower extremities in a supine position, while imaging of the upper extremity was conducted by a 16-channel receive-only multipurpose flex coil in the prone position (Variety, Noras MRI Products, H"ochberg, Germany).

### Image Postprocessing

Sequences with insufficient image quality as evaluated by visual rating were excluded from the analysis (26 out of 660 measurements). Segmentation was conducted (by V.S.) using a freehand region of interest (ROI) in the Digital Imaging and Communications in Medicine (DICOM) viewing software OsiriX (Pixmeo Sarl, Bernex, Switzerland). In the lower extremities the tibial and peroneal portion of the sciatic nerve were assessed separately for analysis of nerve CSA, while T2 relaxometry was restricted to the tibial portion of the sciatic nerve.

### Quantification of Nerve Cross-sectional Area

The high-resolution T2-weighted sequence (sequence 1) was used for segmentation of all nerves at representative locations within the slabs (e.g. the sciatic nerve at mid-thigh, the tibial nerve at the proximal third of the calf, and the ulnar, median and radial nerve at mid-upper arm). Care was taken to select a slice with orthogonal or close to orthogonal section of the nerve and measurements from two consecutive slices were averaged for each nerve. The mean CSA was calculated for those subjects with sufficient image quality at all locations as an average of all analyzed nerves ( $n = 55$ ).

## T2 Relaxometry

Nerves were segmented in the MSE sequence at an echo time (TE) of 50 ms at the central 5 slices of the slab. Nerve signal intensity of the MSE sequence for each TE was obtained using the plug-in ROI enhancement in OsiriX and an exponential function was fitted to the even echoes (TE<sub>2</sub>, TE<sub>4</sub>, ... TE<sub>12</sub>) as:

$$S(TE) = PSD \cdot e^{-\frac{TE}{T_2}} + \text{offset}$$

as described previously [18, 20], where S(TE) is defined as the signal at the echo time TE, T<sub>2</sub> as the transverse relaxation time, and PSD a dimensionless measure for PSD that may be additionally modulated by hardware parameters as signal attenuation. The parameter offset accounts for imperfect signal decay. For each nerve, T<sub>2</sub> and PSD were calculated separately for each of the central five slices of the slab and averaged. Mean T<sub>2</sub> and mean PSD were calculated for each subject as an average of all analyzed nerves.

## Statistical Analysis

All values represent mean ± standard deviation (SD) unless otherwise specified. Statistical analysis was conducted using SPSS version 24 (IBM, Armonk, NY) and Prism version 7 (GraphPad Software, La Jolla, CA). A *p*-value ≤ 0.05 was regarded as statistically significant. Student's *t*-tests were applied to compare continuous variables between men and women. Correlation of variables was described using Pearson coefficients.

Men and women in our cohort differed significantly in weight and BMI. To assess for sex-specific differences, additional comparisons with adjusted values were performed. The CSA was adjusted to a predefined weight of 70 kg by simple linear regression, since it most accurately correlated with body weight. Given the strong correlation of PSD and BMI, PSD was adjusted to a BMI of 22 kg/m<sup>2</sup>, also by simple linear regression. Since T<sub>2</sub> did not significantly correlate with any of the demographic parameters, we did not

calculate any adjusted values. Due to the explorative study design, multiple testing was performed and the reported *p*-values can only be interpreted descriptively.

## Results

### Baseline Demographic Characteristics of Subjects

The study cohort consisted of 60 subjects (30 men and 30 women) aged between 23 and 79 years, covering each age decade between 20 and 80 years by 5 men and 5 women. The mean age was 50.1 ± 17.3 years, mean body height 174.2 ± 9.6 cm, mean weight 75.4 ± 16.5 kg, and mean BMI 24.6 ± 3.9 kg/m<sup>2</sup>. Age was not associated with height (*r* = -0.04, *p* = 0.74), weight (*r* = 0.03, *p* = 0.81), or BMI (*r* = 0.1, *p* = 0.46). Men and women differed significantly in height (men 181.2 ± 6.1 cm, women 167.2 ± 6.9 cm, *p* < 0.001), weight (men 86.8 ± 13.6 kg, women 64.1 ± 10.2 kg, *p* < 0.001), and BMI (men 26.4 ± 3.7 kg/m<sup>2</sup>, women 22.9 ± 3.3 kg/m<sup>2</sup>, *p* < 0.001), but not in age (men 50.5 ± 17.4 years, women 49.7 ± 17.5 years, *p* = 0.87).

### Nerve Cross-Sectional Area

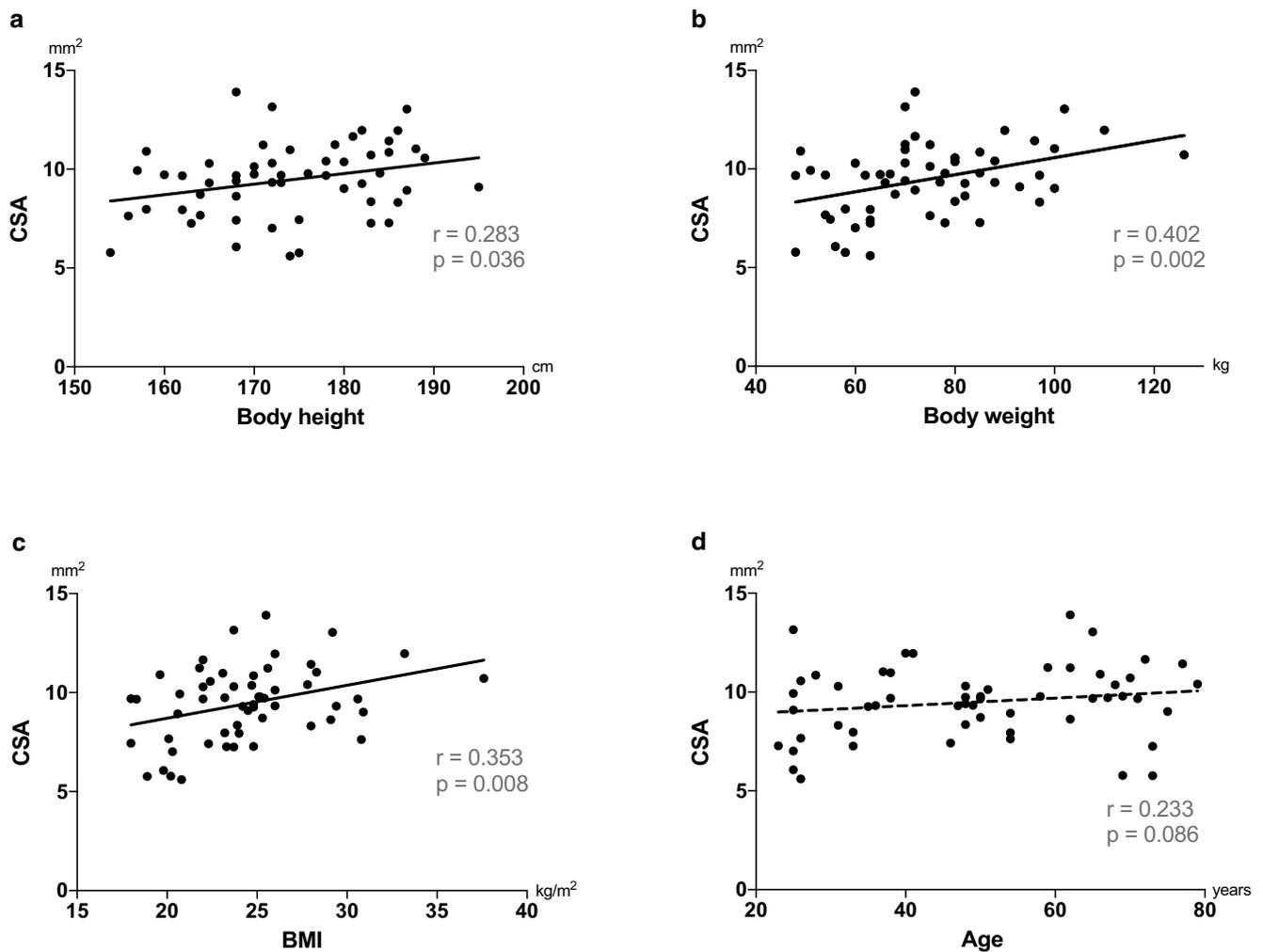
The results of the measurements of nerve CSA for each nerve are presented in Table 1. Additionally, mean values of nerve CSA in different age groups of men and women can be found in Supplementary Table 1.

The mean CSA correlated positively with height (*r* = 0.28, *p* = 0.04), weight (*r* = 0.40, *p* = 0.002), and BMI (*r* = 0.35, *p* = 0.008), while only a non-significant trend to correlate with age was observed (*r* = 0.23, *p* = 0.09) (Fig. 1). In a supplementary single nerve analysis, we found a statistically significant correlation of age and CSA for both the tibial and the peroneal portion of the sciatic nerve at the thigh level (tibial portion: *r* = 0.35, *p* = 0.007, fibular portion: *r* = 0.34, *p* = 0.008) but not for any other nerve.

**Table 1** Nerve cross-sectional area as measured by high-resolution MRN in 60 healthy volunteers

Location	Nerve	Nerve cross-sectional area (CSA) in mm <sup>2</sup>			<i>n</i>
		Mean	SD	Range	
Thigh	Sciatic (tibial)	20.78	5.48	9.84–34.72	60
	Sciatic (fibular)	9.76	3.07	4.92–17.60	60
Lower leg	Tibial	8.05	2.04	4.00–14.80	59
Upper arm	Ulnar	6.03	1.53	2.95–9.81	57
	Median	7.97	1.96	2.86–12.28	57
	Radial	5.06	1.19	2.92–8.10	56
Mean over all nerves		9.45	1.86	5.61–13.90	55

Tibial and fibular portions of the sciatic nerve were measured separately. *n* is the number of subjects included in the analysis after assessment of image quality, *SD* standard deviation



**Fig. 1** Correlation of nerve cross-sectional area (CSA) with demographic variables. **a** Body height, **b** body weight, and **c** body mass index (BMI), correlate positively with mean nerve CSA, averaged over all analyzed locations. **d** Association of age and mean nerve CSA is not significant. *r* Pearson coefficient

## T2 Relaxometry

Table 2 shows nerve-specific values of T2-relaxation time (T2) and PSD. A complementary presentation of relaxometry parameters in different age groups of men and women can be found in Supplementary Tables 2 and 3. Association of mean T2 and PSD with height, weight, BMI, and age was assessed by correlation analyses (Fig. 2). While mean T2 was not associated with any parameter, mean PSD strongly correlated in a negative manner with BMI ( $r = -0.64$ ,  $p < 0.001$ ) and weight ( $r = -0.557$ ,  $p < 0.001$ ), but not with height or age. In a single nerve analysis, we additionally found a significant negative correlation of age and PSD ( $r = -0.50$ ,  $p < 0.001$ ) for the sciatic nerve but not for any of the other analysed locations.

## Sex-Specific Differences of MRN Biomarkers

The mean nerve CSA of male subjects ( $10.03 \pm 1.85$  mm<sup>2</sup>) was significantly larger than the CSA of female subjects ( $8.93 \pm 1.75$  mm<sup>2</sup>,  $p = 0.03$ ; Fig. 3a); however, when CSA values were adjusted to a body weight of 70 kg by simple linear regression, no differences in CSA between the two sexes were observed ( $CSA_{men(70kg)} = 9.31 \pm 1.77$  mm<sup>2</sup> vs.  $CSA_{women(70kg)} = 9.20 \pm 1.67$  mm<sup>2</sup>;  $p = 0.81$ ).

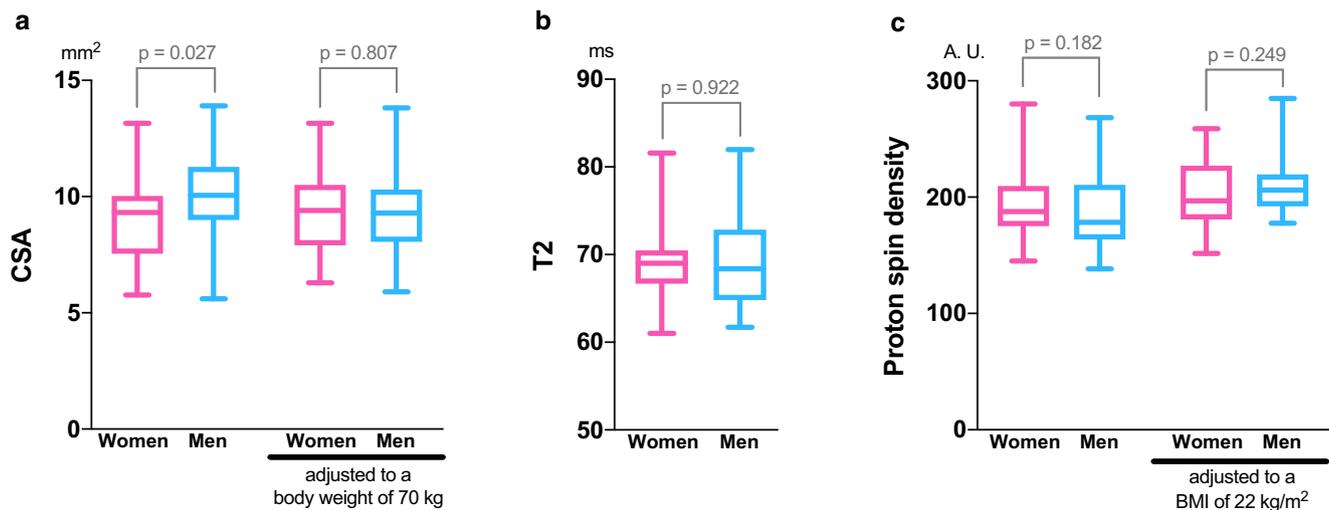
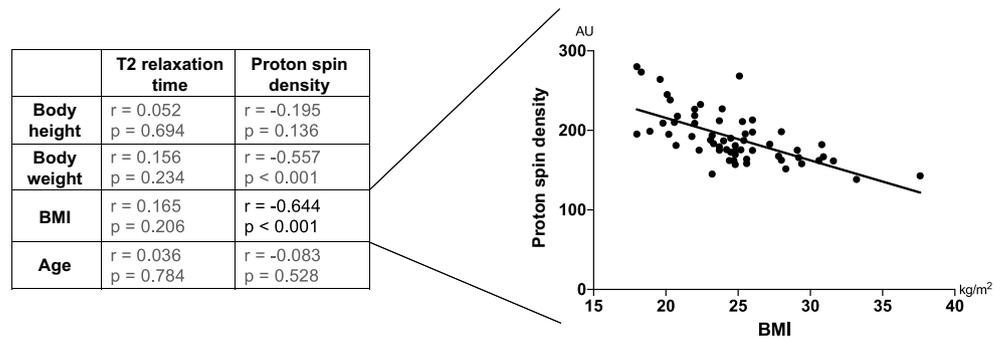
The mean nerve T2 did not differ between the two sexes ( $T2_{men} = 68.9 \pm 4.7$  ms,  $T2_{women} = 68.8 \pm 4.2$  ms,  $p = 0.92$ ; Fig. 3b). Also, mean PSD was not significantly different between men as  $185.4 \pm 29.5$  arbitrary units (AU) and women as  $196.6 \pm 34.4$  AU,  $p = 0.18$ . This non-significant difference in PSD between the two sexes became even smaller after normalization to a BMI of 22 kg/m<sup>2</sup> by simple linear regression ( $PSD_{men(22kg/m^2)} = 208.8 \pm 22.1$  AU vs.  $PSD_{women(22kg/m^2)} = 201.4 \pm 26.9$  AU,  $p = 0.25$ ; Fig. 3c).

**Table 2** Results of multiecho T2-Relaxometry in 60 healthy volunteers

Location	Nerve	Transverse relaxation time T2 in ms			Proton spin density (PSD) in AU			<i>n</i>
		Mean	SD	Range	Mean	SD	Range	
Thigh	Sciatic	70.85	4.91	54.00–79.87	158.68	27.76	103.73–252.34	60
Lower leg	Tibial	63.34	6.54	51.36–82.78	182.91	26.12	99.39–234.63	57
Upper arm	Ulnar	75.30	10.19	48.56–102.11	200.96	72.70	95.77–417.61	57
	Median	69.58	7.00	56.94–56.07	221.03	62.87	109.97–366.94	57
	Radial	65.36	9.16	35.13–85.82	195.06	52.83	86.35–293.54	54
Mean over all nerves		68.83	4.42	61.02–81.98	191.00	32.29	138.31–280.11	60

Analysis of the sciatic nerve was restricted to its tibial portion. *n* is the number of subjects included in the analysis after assessment of image quality; *AU* arbitrary units, *SD* standard deviation

**Fig. 2** Correlation of T2 relaxometry parameters with demographic variables. Mean proton spin density (PSD), averaged over all nerves, correlates most with body mass index (BMI). Mean T2 relaxation time (T2) is not significantly associated with any of the demographic variables. *r* Pearson coefficient, *AU* arbitrary units



**Fig. 3** Sex-specific differences of CSA and T2 relaxometry markers. **a** Mean CSA, averaged over all analyzed nerves, of men was significantly larger than CSA of women. This difference disappeared after adjustment to a predefined body weight of 70 kg by simple linear regression. **b** Mean transverse relaxation time (T2) did not differ significantly between the two sexes. **c** Mean proton spin density (PSD) did not differ significantly between the two sexes, irrespective of normalization to a predefined BMI of 22 kg/m<sup>2</sup> by simple linear regression

## Discussion

In this study we assessed the effect of demographic variables on quantitative biomarkers of MRN. We established normal values for nerve CSA and T2 relaxometry in a cohort of 60 healthy individuals. To our knowledge this is the first study that systematically analyzed multiple quantitative MRN parameters in a larger collective of healthy volunteers

with particular respect to the correlation of these parameters with demographic variables.

Until now, the description of normal values for nerve CSA in larger cohorts has been performed by sonography only. Table 3 shows our results of normal values in relation to those of five different ultrasound studies [21–26]. While the normal values for nerves of the upper arm differ moderately among the ultrasound studies, they are roughly

**Table 3** Normative CSA values in healthy volunteers of this MRI study in relation to the existing sonographic literature

	This study	Cartwright et al. [21]	Cartwright et al. [23]	Cartwright et al. [22]	Kerasnoudis et al. [24]	Seok et al. [25]	Won et al. [26]
Number of subjects	60	60	50	30	75	94	97
Mean age, weight, height	50 years, 76 kg, 174 cm	46 years, 76 kg, 168 cm	45 years, 73 kg, 167 cm	31 years, 71 kg, 166 cm	54 years, 78 kg, 175 cm	45 years, 63 kg, 165 cm	44 years, 63 kg, 163 cm
CSA in mm <sup>2</sup>							
Sciatic	<b>30.5</b> (14.7–46.4) <sup>a</sup>	<b>52.6</b> (24.6–80.6)	n. a.	n. a.	n. a.	<b>45.8</b> (29.0–62.6)	n. a.
Tibial	<b>8.1</b> (4.0–12.1)	<b>25.3</b> (10.7–19.9)	n. a.	n. a.	<b>8.4</b> (3.1–13.8)	<b>10.4</b> (5.0–15.8)	n. a.
Ulnar	<b>6.0</b> (3.0–9.1)	n. a.	n. a.	<b>6.1</b> (4.3–7.9)	<b>6.5</b> (2.9–10.4)	n. a.	<b>5.8</b> (3.8–7.8)
Median	<b>8.0</b> (4.0–11.9)	n. a.	<b>8.9</b> (4.7–13.1)	n. a.	<b>8.4</b> (4.3–12.6)	n. a.	<b>9.4</b> (6.8–12.0)
Radial	<b>5.1</b> (2.7–7.4)	<b>7.9</b> (2.5–13.3)	n. a.	n. a.	<b>3.3</b> (0.2–6.3)	n. a.	<b>4.6</b> (2.8–6.4)

All CSA values are presented as mean with reference interval of mean  $\pm$ 2 standard deviations in brackets. The exact localization of assessment slightly differs between the studies. The sciatic nerve was measured at mid-thigh to lower thigh, the tibial nerve was assessed at popliteal fossa or proximal lower leg. Ulnar, median and radial nerves were assessed at the upper arm or the axilla

<sup>a</sup>In this study, tibial and peroneal portion of the sciatic nerve were assessed separately and added together

comparable to the range of our values. At the lower extremities, however, we measured considerably lower values for CSA of the sciatic nerve compared to Cartwright et al. [21] and Seok et al. [25] and also clearly lower values for the tibial nerve in the lower leg than Cartwright et al. [21], but comparable values to Seok et al. [25] and Kerasnoudis et al. [24]. One explanation for this difference might be that the borders of the sciatic nerve and the tibial nerve were more leniently interpreted in nerve sonography [21] and it might also be more difficult in sonography to obtain a truly axial slice orientation.

Since the tibial and the peroneal portion of the sciatic nerve are clearly discernible on MRN images, we measured both portions separately. The exact localization of the sciatic bifurcation is highly variable [27], and the tibial and peroneal portions of the sciatic nerve are separated by a variable amount of connective tissue, for which the term paraneurial [28] has been proposed. By separately segmenting the tibial and peroneal portion of the sciatic nerve and adding these values, we obtained the full CSA of nervous tissue and impeded the inclusion of paraneurial connective tissue. We cannot exclude that this technique also contributes to the differences of our results and the sonographic measurements [21]. We found that nerve caliber increased with weight, BMI, and height of subjects, and these positive correlations confirmed the findings of multiple ultrasound studies [21, 22, 25, 26]. Kerasnoudis et al. [24] also reported correlations of nerve caliber with weight but only for certain locations and no correlation of nerve size and height at all. In all of these ultrasound studies and in our own work, weight showed the strongest association to nerve size, and since BMI and height both intercorrelate with weight, we suggest that weight should primarily be controlled when assessing nerve size.

The impact of age on nerve size is described heterogeneously in the existing literature. While Cartwright et al. [21] depicted a positive correlation, Won et al. [26] and Seok et al. [25] did not find any significant effect of age on nerve caliber. Kerasnoudis et al. [24] described heterogeneous influences of age that depended on location and were statistically significant only for certain sites. We analyzed the overall effect of age on mean nerve caliber and found no significant correlation but only a statistically non-significant trend that older people tended to have slightly larger nerves. Our findings in synopsis with the existing literature suggest that if age has any consistent effect on nerve caliber in adults at all, it is overall relatively small. The sciatic nerve at the thigh might represent an exception, enlarging moderately with increasing age.

Peripheral nerve T2 relaxometry has been applied in studies of diabetic polyneuropathy [8, 16] and familial amyloid polyneuropathy [10], but an assessment of potential determinants in healthy volunteers has not been performed

so far. We found that the biomarker PSD showed strong correlations to BMI and body weight, whereas T2 did not correlate with any of these variables. Mechanistically, T2 is considered to primarily reflect the amount of free water in one voxel, while PSD indicates the total water content, including the water fraction bound to macromolecules or restricted by myelin [8, 10–13]. Additionally, PSD may be modulated by factors that interfere with the MR signal. We applied spectral fat saturation to the relaxometry sequence, since waiving fat saturation could superimpose perineural fat on the nerve due to chemical shift phenomena and thus impede the selectivity of relaxometry to exclusively nervous tissue. Possible explanations for the decreasing PSD in obese individuals could be a fatty transformation of nerve tissue itself, potentially by a change in the lipid composition of the myelin sheath or the interior connective tissue [29, 30] or an indirect modification of the MR signal by increasing thickness of subcutaneous fat and increasing extremity diameter. Nerve PSD has been proposed as a biomarker of diabetic neuropathy in one study [8]. The inverse correlation of PSD and BMI reported here could provide a possible explanation why another investigation [16] could not confirm an elevation of PSD in diabetic neuropathy. Since study groups in the latter had considerably larger differences in BMI, increasing effects on PSD by neuropathy and decreasing effects by obesity may have cancelled each other out. We recommend that BMI in particular should be controlled when assessing PSD as a quantitative parameter in further studies.

The only age-related effect on relaxometry markers was found in a single nerve analysis for the sciatic nerve at the thigh with a negative association of age and PSD. Since this nerve was also the only one that significantly enlarged with increasing age, we speculate that fatty transformation might cause both caliber enlargement and decrease of PSD.

Another major aim of our study was to determine the influence of sex on MRN biomarkers. Some ultrasound studies [26, 31] reported men to have larger nerves than women, and we can confirm this finding since average nerve CSA in our cohort was significantly smaller in women compared to men; however, since CSA is associated with body weight, this effect can be fully explained by the fact that men in general weigh more than women, which was also a significant observation in our cohort. After adjustment to a predefined body weight of 70 kg, nerve CSA of men and women was virtually equal. These results suggest that selection of sex-matched controls for further studies assessing nerve CSA no longer seems to be necessary but instead, it should be controlled for weight. The MR relaxometry biomarkers T2 and PSD did not differ significantly between men and women.

A limitation of our study is that MRN biomarkers may depend on hardware characteristics of the MR system as well as sequence parameters to various extents. While we

expect CSA as a simple morphologic measure to be robust to sequence parameters, it is prone to accurate segmentation. Of the reported MRN biomarkers, PSD is most difficult to standardize as it directly depends on the measured MR signal. While we excluded participants with any known neurologic or metabolic diseases, an extensive neurologic or electrophysiological examination were beyond the scope of this study; therefore, it should be taken into account that the normal values reported here might include subjects with subclinical neuropathies.

In conclusion, we described normal values of quantitative MRN biomarkers, including CSA and T2 relaxometry. As particularly important determinants, we identified body weight for nerve CSA and BMI for PSD; therefore, we recommend that these variables should be particularly controlled in future studies. After adjustment for body weight, we did not find any effect of gender on nerve CSA. The T2 relaxometry markers did not differ significantly between men and women. The normal values and demographic determinants that we described in a cohort of 60 healthy individuals may assist investigations into the potential of MRN biomarkers in further disease-specific studies.

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### Compliance with ethical guidelines

**Conflict of interests** M. Kronlage, V. Schwehr, D. Schwarz, T. Godel, S. Heiland, M. Bendszus and P. Bäumer declare that they have no competing interests.

**Ethical standards** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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