Cross-sectional area reference values for peripheral nerve ultrasound in adults: A systematic review and meta-analysis—Part II: Lower extremity nerves

Anna Lena Fisse\textsuperscript{1,2} | Aristeidis H. Katsanos\textsuperscript{3} | Ralf Gold\textsuperscript{1,2} | Christos Krogias\textsuperscript{1} | Kalliopi Pitarokoili\textsuperscript{1,2}

\textsuperscript{1}Department of Neurology, St. Josef Hospital, Ruhr University Bochum, Bochum, Germany
\textsuperscript{2}Immunmediated Neuropathies Biobank (INHIBIT), Ruhr University Bochum, Bochum, Germany
\textsuperscript{3}Division of Neurology, McMaster University/Population Health Research Institute, Hamilton, Ontario, Canada

Correspondence
Anna Lena Fisse, Department of Neurology, St. Josef-Hospital, Ruhr University Bochum, Gudrunstrasse 56, 44791 Bochum, Germany.
Email: anna.fisse@rub.de

Abstract

Background and purpose: Measurement of the cross-sectional area (CSA) of peripheral nerves using ultrasound is useful in the evaluation of focal lesions such as entrapment syndromes and inflammatory polyneuropathies. We performed a systematic review and meta-analysis of published CSA reference values for lower extremity nerves.

Methods: We included available-to-date nerve ultrasound studies on healthy adults and provide meta-analysis for CSA of the following nerves: fibular nerve at fibular head, popliteal fossa; tibial nerve at popliteal fossa, malleolus; and sural nerve at the level of the two heads of gastrocnemius muscle. We report regression and correlation analyses for age, gender distribution, height, weight, and geographic continent.

Results: We included 16 studies with 1001 healthy volunteers (mean age = 47.9 years) and 4023 examined nerve sites. Calculated mean pooled CSA of fibular nerve at fibular head was 8.4 mm\textsuperscript{2} (95\% confidence interval [CI] = 6.8–9.9 mm\textsuperscript{2}, \(n = 1166\)), at popliteal fossa was 7.9 mm\textsuperscript{2} (95\% CI = 6.6–9.2 mm\textsuperscript{2}, \(n = 995\)), of tibial nerve at popliteal fossa was 25.9 mm\textsuperscript{2} (95\% CI = 17.5–34.4 mm\textsuperscript{2}, \(n = 771\)), at malleolus was 10.0 mm\textsuperscript{2} (95\% CI = 7.7–12.4 mm\textsuperscript{2}, \(n = 779\)), and of sural nerve was 2.4 mm\textsuperscript{2} (95\% CI = 1.7–3.1 mm\textsuperscript{2}, \(n = 312\)). Substantial heterogeneity across studies (\(I^2 > 50\%\)) was found only for tibial nerve at popliteal fossa. Subgroup analysis revealed a lower CSA of tibial nerve at popliteal fossa and sural nerve in studies conducted in Europe than in North America and New Zealand.

Conclusions: We provide the first meta-analysis on CSA reference values for the lower extremities with no or low heterogeneity of reported CSA values in all nerve sites except tibial nerve at popliteal fossa. Our data facilitate the goal of an international standardized evaluation protocol.

KEYWORDS
fibular nerve, nerve ultrasound, sonography, sural nerve, tibial nerve

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.
© 2021 The Authors. European Journal of Neurology published by John Wiley & Sons Ltd on behalf of European Academy of Neurology
Peripheral nerve sonography has been increasingly used in the past 10 years for measuring the cross-sectional area (CSA) of the peripheral nerves. Lower extremity nerves are frequently examined by ultrasound using detailed examination protocols for diagnosis of inflammatory polyneuropathies [1,2] or in patients with fibular paresis to detect and identify underlying causes of a compression syndrome [3]. Traumatic nerve lesions or nerve tumors are less common issues. Due to increasing use of nerve ultrasound for these clinical issues, several study groups published reference values for CSA measured by tracing nerve boundaries for a number of anatomic sites [4–7]. However, reported reference values show a great variability of measured CSA; for example, for tibial nerve in popliteal fossa, depending on the study, the mean CSA value ranged from 8 to 40 mm² [4,8] Some authors reported effects of age, weight, and gender on CSA [5,9] whereas others could not confirm any association [10]. Therefore, we performed a meta-analysis on CSA reference values of peripheral nerves measured by nerve ultrasound. In this second part of our analysis, we report the results referring to the nerves of the lower extremities.

**METHODS**

This meta-analysis is reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guideline [11]. A systematic literature search of the MEDLINE and Scopus databases was performed by two independent reviewers (A.L.F. and K.P.). The following search terms were used for database search: Nerve AND (sonography OR ultrasound) AND (normal values OR reference values). All studies found by February 2020 were independently reviewed by A.L.F. and K.P. The title and abstract of the studies were screened for whether the studies matched the content of this meta-analysis. Only studies measuring CSA of peripheral nerves with B-mode sonography in healthy adult subjects were included. The following nerves were analyzed: median nerve at wrist, forearm, upper arm; ulnar nerve at Guyon loge, forearm, elbow, upper arm; radial nerve at upper arm; nerve roots C5, C6, C7; vagal nerve at carotid sheath; fibular nerve at fibular head, popliteal fossa; tibial nerve at popliteal fossa, malleolus; and sural nerve at the level of the two heads of gastrocnemius muscle.

Information from the abstract and main text of the identified studies was extracted on characteristics of study participants (including mean age, sex, height, weight, year, and country in which the study was performed), data on methodology (ultrasound device, transducer frequency, measurement sites), and mean CSA of peripheral nerves (including SD).

This procedure was performed separately by two investigators (A.L.F. and K.P.). Disagreements were resolved by discussion between the two review authors and the senior author (C.K.).

The study protocol was not registered in any database.

**Statistical analyses**

Pooled estimates of mean CSA in both the overall and subgroup analyses were calculated with the random effects model (DerSimonian–Laird model). Multivariate meta-regression analyses of CSA measurements with age, height, weight, and gender distribution were also performed under the random-effects model. The equivalent z-test was performed for each pooled estimate, and if \( p < 0.05 \), it was considered statistically significant. We assessed heterogeneity among studies with the Cochran \( Q \) and \( I^2 \) statistics. For geographic subgroup analyses, we used a standard test for heterogeneity across subgroup results to investigate for potential differences between subgroups. All analyses were conducted in Stata MP 16.0 (StataCorp) with the metan and metareg packages. Data are available on request from the authors.

**RESULTS**

**Included studies**

We found 1333 potentially relevant studies, from which 125 eligible studies were retained for full-text evaluation after screening titles and abstracts. Fifty-one studies were excluded after consensus of the two reviewers, most of them due to missing information regarding SD or due to missing data for lower extremity nerves (Table S1). Sixteen studies were included in the review and meta-analysis (Table S2, Figure 1). Seven studies were conducted in Europe, three in North America, three in Asia, two in New Zealand, and one in Africa. The range of frequencies used for ultrasound probe was between 5 and 18 MHz. A total of 4023 measures of lower extremity nerves of cumulatively 1001 healthy people were analyzed. All studies included healthy adults older than 18 years. Mean age was 47.9 years. Mean proportion of female patients was 55%.

**CSA reference values and heterogeneity of reported values**

Calculated mean pooled CSA of fibular nerve at fibula head was 8.4 mm² (95% confidence interval [CI] = 6.8–9.9 mm², \( n = 1166 \)) and at popliteal fossa was 7.9 mm² (95% CI = 6.6–9.2 mm², \( n = 995 \)).

Calculated mean pooled CSA of tibial nerve at popliteal fossa was 25.9 mm² (95% CI = 17.5–34.4 mm², \( n = 771 \)) and at malleolus was 10.0 mm² (95% CI = 7.7–12.4 mm², \( n = 779 \)).

Calculated mean pooled CSA of sural nerve at the level of the gastrocnemius muscle heads was 2.4 mm² (95% CI = 1.7–3.1 mm², \( n = 312 \)).

We found a substantial heterogeneity across studies reporting mean CSA values of tibial nerve at popliteal fossa (\( I^2 = 84.48\% \)) and a low heterogeneity across studies reporting mean CSA values of tibial nerve at malleolus (\( I^2 = 25.72\% \)) and sural nerve (\( I^2 = 28.90\% \)). No heterogeneity was found across studies reporting CSA values for fibular nerve.
These results are shown in Table 1. Figures 2 and 3 show results of the meta-analysis of CSA for tibial nerve of popliteal fossa and sural nerve. Results for fibular nerve and tibial nerve at malleolus are given in Figures S1–S3.

### Correlations of CSA with age, gender distribution, height, weight, and geographic differences

No significant effects of age, height, and weight could be recorded in univariate or multivariate regression analysis. CSA of tibial nerve at popliteal fossa was reported to be higher in studies conducted in North America and New Zealand than in Europe, Asia, and Africa ($p = 0.00$). This was also the case with regard to CSA of sural nerve, which was higher in studies conducted in New Zealand than in European studies ($p = 0.02$). For other nerve sites, geographic continent had no effect on CSA. There were no significant differences of CSA in the analysis of gender proportion.

Results of meta-regression analyses are shown in Table 2 and Figure S4.

### DISCUSSION

Results of a meta-analysis of ultrasound CSA reference values for lower extremity nerves are presented for the first time in this study.
High variability accompanied by a substantial heterogeneity of reported reference values was found in this meta-analysis only for tibial nerve in popliteal fossa. This probably results from tibial nerve being difficult to examine and the nerve boundaries being difficult to define in the depths of the popliteal fossa. Anatomical aspects such as obesity can also influence the reliability of the measurement with nerve ultrasound. Furthermore, it seems that the CSA of the tibial nerve changes significantly between the distal and the proximal section of the popliteal fossa, as our group has described before [12]. Therefore, the definition of the anatomical section of the measurement has to be precise (distal, medial, or proximal part of the popliteal fossa) to decrease heterogeneity in the future.

Low heterogeneity for CSA of tibial nerve at malleolus probably results from the issue that in some individuals, including healthy controls.

### Figure 2
Meta-analysis of cross-sectional area (CSA) of tibial nerve at popliteal fossa in healthy controls. Mean CSA and 95% confidence interval (CI) are shown in millimeters. Studies are sorted by geographic region: 1, Europe; 2, North America; 3, Asia; 5, Africa.

| Study | Effect Size with 95% CI | Weight (%) |
|-------|-------------------------|------------|
| 1     | 8.20 [5.06, 11.34]      | 17.44      |
| 2     | 6.40 [5.26, 11.54]      | 17.44      |
| 3     | 8.60 [5.13, 12.07]      | 14.25      |
| 4     | 6.00 [3.80, 8.20]       | 35.27      |

Test of $\theta$, $Q(3) = 2.65$, $p = 0.45$

### Figure 3
Meta-analysis of cross-sectional area (CSA) of sural nerve at the level of gastrocnemius muscle heads in healthy controls. Mean CSA and 95% confidence interval (CI) are shown in millimeters. Studies are sorted by geographic region: 1, Europe; 4, New Zealand.

| Study | Effect Size with 95% CI | Weight (%) |
|-------|-------------------------|------------|
| 1     | 1.80 [0.62, 2.98]       | 22.01      |
| 2     | 2.69 [1.21, 4.16]       | 16.14      |
| 3     | 1.82 [0.57, 3.07]       | 20.27      |
| 4     | 1.84 [0.61, 3.07]       | 20.69      |

Test of $\theta$, $Q(3) = 1.07$, $p = 0.78$
people, tibial nerve at malleolus is difficult to distinguish due to density of surrounding structures and bone echo, even though it lies quite superficially. Regarding low heterogeneity of CSA of sural nerve, this could be due to the interindividual anatomical differences; the sural nerve forms from the medial cutaneous branch of the tibial nerve and the lateral cutaneous branch of the common fibular nerve. This formation can occur at different levels of the calf. Depending on whether the measurement is taken above or below the formation, a slightly different CSA can result. Fortunately, heterogeneity of CSA for fibular nerve was low, even at the fibular head, where the nerve is often flattened, or the bone can complicate visualization.

Overall, polyneuropathy ultrasound protocols using the anatomical regions described in this meta-analysis have been established in recent years, as can be recognized from the large number of studies investigating these specific nerve sites. We hereby provide meta-analytical data for these regions and therefore recommend using these examination sites, to reach an internationally standardized paraclinical evaluation. Nonetheless, each ultrasound laboratory should compare its own normal values to the results of this meta-analysis and aim to reduce deviations as much as possible.

In this meta-analysis, correlation of CSA of lower extremity nerves with age, height, or weight was not found, suggesting that the influence of age, height, and weight do not need to be considered in everyday clinical practice. However, there were considerable regional differences, with higher CSA reference values for tibial nerve at popliteal fossa and sural nerve in US and New Zealand than in European studies, which could result either from methodological differences in ultrasound examinations between these regions or from actual different population characteristics. However, the latter seems unlikely, as we did not find any association with height, weight, age, or gender distribution in our analysis. Therefore, internationally standardized protocols are necessary to avoid methodological differences. However, the number of available studies per continent was small for the analysis of geographic differences; therefore, results must be interpreted with caution.

One limitation of the meta-analysis is that the associations detected at the population level might not be present at the individual patient level (ecological fallacy). Also, the lack of significant associations could be attributed to vast heterogeneity between studies rather than the lack of the presence of true associations. Beyond this, we could not analyze the influence of ultrasound device or frequency of ultrasound probe on CSA values, as various devices were used, and frequencies were only given as a range, for example 8–15 MHz, in the majority of publications. Moreover, in very few publications, different anatomical regions were examined (e.g., sural nerve at malleolus) that were not included in this analysis. In this second part of our meta-analysis, we report only on results for lower extremity nerves. Results for upper extremity nerves are given in Part I (Fisse et al., under review). For nerves such as brachial plexus and nerve roots, which are also technically difficult to examine, a similar heterogeneity must be expected.

In conclusion, we provide reference values of CSA of lower extremity nerves that are based for the first time on meta-analysis of 4023 examined nerve sites. Heterogeneity of reported studies was substantial only for tibial nerve at popliteal fossa, probably due to anatomical difficulties. All other analyzed nerve sites showed no or low heterogeneity of reported values. Subgroup analysis revealed no influence of age, height, and weight. Our meta-analytical data facilitate the goal of an international standardized evaluation protocol.

**ACKNOWLEDGEMENTS**
Open Access funding enabled and organized by Projekt DEAL.
WOA Institution: Ruhr-Universität Bochum
Blended DEAL: Projekt DEAL

**CONFLICT OF INTEREST**
R.G. has received consultation fees and speaker honoraria from Bayer, Schering, Biogen Idec, Merck Serono, Novartis, Sanofi-Aventis, and Teva. He also acknowledges grant support from Bayer Schering, Biogen Idec, Merck Serono, Sanofi-Aventis, and Teva, none related to this article. K.P. has received travel grants and speakers’ honoraria from Novartis, Biogen Idec, Teva, Bayer, Celgene, CSL Behring, and Grifols, all not related to this article. C.K. has received travel grants and honoraria from Bayer Vital and Daiichi-Sankyo. The other authors declare no financial or other conflicts of interest.

---

**TABLE 2** Results of meta-regression analysis and test of group differences

| Nerve     | Site                      | Meta-regression analysis, mean age, \( p \) | Meta-regression analysis, height, \( p \) | Meta-regression analysis, weight, \( p \) | Meta-regression analysis, male proportion, \( p \) (coefficient) | Test of group differences in geographic region, \( p \) |
|-----------|---------------------------|---------------------------------------------|--------------------------------------------|--------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Fibular nerve | Fibula head | n.s.                                     | n.s.                                       | n.s.                                       | n.s.                                            | n.s.                                             |
|           | Popliteal fossa | n.s.                                     | n.s.                                       | n.s.                                       | n.s.                                            | n.s.                                             |
| Tibial nerve | Popliteal fossa | n.s.                                     | n.s.                                       | n.s.                                       | n.s.                                            | 0.00a                                            |
|           | Malleolus     | n.s.                                     | n.s.                                       | n.s.                                       | n.s.                                            | n.s.                                             |
| Sural nerve | Heads of gastrocnemius muscle | n.s.                                     | n.s.                                       | n.s.                                       | n.s.                                            | 0.02a                                            |

Abbreviation: n.s., not significant.

aStatistically significant.
AUTHOR CONTRIBUTIONS
Anna Lena Fisse: conceptualization (equal), data curation (equal), formal analysis (equal), investigation (equal), methodology (equal), project administration (equal), resources (lead), writing–original draft (lead), writing–review & editing (lead). Aristeidis H. Katsanos: formal analysis (supporting), methodology (supporting), software (supporting), supervision (supporting), validation (supporting), writing–original draft (supporting). Ralf Gold: conceptualization (supporting), funding acquisition (lead), resources (equal), supervision (supporting), writing–original draft (supporting). Christos Krogias: conceptualization (lead), data curation (supporting), formal analysis (lead), methodology (lead), project administration (supporting), software (lead), supervision (equal), validation (equal), visualization (lead), writing–original draft (equal), writing–review & editing (equal). Kalliopi Pitarokoili: conceptualization (lead), methodology (supporting), project administration (supporting), supervision (equal), validation (equal), writing–original draft (equal), writing–review & editing (equal).

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID
Anna Lena Fisse https://orcid.org/0000-0003-0493-8656
Aristeidis H. Katsanos https://orcid.org/0000-0002-6359-0023
Christos Krogias https://orcid.org/0000-0003-2965-4051
Kalliopi Pitarokoili https://orcid.org/0000-0002-2483-4929

REFERENCES
1. Kerasnoudis A, Pitarokoili K, Gold R, Yoon M-S. Bochum ultrasound score allows distinction of chronic inflammatory from multifocal acquired demyelinating polyneuropathies. J Neurol Sci. 2015;348(1-2):211-215. https://doi.org/10.1016/j.jns.2014.12.010
2. Grimm A, Décard BF, Axer H, Fuhr P. The Ultrasound pattern sum score - UPSS. A new method to differentiate acute and sub-acute neuropathies using ultrasound of the peripheral nerves. Clin Neurophysiol. 2015;126(11):2216-2225. https://doi.org/10.1016/j.clinph.2015.01.011
3. Visser LH, Hens V, Soethout M, Deugd-Maria V, Pijnenburg J, Brekelmans GJF. Diagnostic value of high-resolution sonography in common fibular neuropathy at the fibular head. Muscle Nerve. 2013;48(2):171-178. https://doi.org/10.1002/mus.23729
4. Kerasnoudis A, Pitarokoili K, Behrendt V, Gold R, Yoon M-S. Cross sectional area reference values for sonography of peripheral nerves and brachial plexus. Clin Neurophysiol. 2013;124(9):1881-1888. https://doi.org/10.1016/j.clinph.2013.03.007
5. Cartwright MS, Passmore LV, Yoon J, Brown ME, Caress JB, Walker FO. Cross-sectional area reference values for nerve ultrasonography. Muscle Nerve. 2008;37(5):566-571. https://doi.org/10.1002/mus.21009
6. Cartwright MS, Mayans DR, Gillson NA, Griffin LP, Walker FO. Nerve cross-sectional area in extremes of age. Muscle Nerve. 2013;47(6):890-893. https://doi.org/10.1002/mus.23718
7. Bathala L, Kumar P, Kumar K, Shaik AB, Visser LH. Normal values of median nerve cross-sectional area obtained by ultrasound along its course in the arm with electrophysiological correlations, in 100 Asian subjects. Muscle Nerve. 2014;49(2):284-286. https://doi.org/10.1002/mus.23912
8. Mulroy E, Pelosi L, Leadbetter R, et al. Peripheral nerve ultrasound in Friedreich ataxia. Muscle Nerve. 2018;57(5):852-856. https://doi.org/10.1002/mus.26012
9. Tahmaz M, Yoon M, Schellinger PD, Philippis J. Cross-sectional area in median and ulnar nerve ultrasound correlates with hand volume. Muscle Nerve. Published online. 2020;62(1):83–88. https://doi.org/10.1002/mus.26881
10. Grimm A, Winter N, Rattay TW, et al. A look inside the nerve - Morphology of nerve fascicles in healthy controls and patients with polyneuropathy. Clin Neurophysiol. 2017;128(12):2521-2526. https://doi.org/10.1016/j.clinph.2017.08.022
11. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Medicine. 2009;6(7):e1000097. https://doi.org/10.1371/journal.pmed.1000097
12. Kronlage M, Pitarokoili K, Schwarz D, et al. Diffusion tensor imaging in chronic inflammatory demyelinating polyneuropathy: diagnostic accuracy and correlation with electrophysiology. Invest Radiol. 2017;52(11):701-707. https://doi.org/10.1097/rlr.0000000000000394

SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Fisse AL, Katsanos AH, Gold R, Krogias C, Pitarokoili K. Cross-sectional area reference values for peripheral nerve ultrasound in adults: A systematic review and meta-analysis—Part II: Lower extremity nerves. Eur J Neurol. 2021;28:2313–2318. https://doi.org/10.1111/en.14850