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To evaluate the test-retest reproducibility of vibratory perception (VPT) and thermal discrimination (TDT) thresholds on the foot in older adults, we examined 20 50–76-year-old subjects with, and 19 without non-insulin-dependent diabetes mellitus. Adjusted reference values for both thresholds were obtained by assessing the relations with age, body height, and sex among 216 subjects with normal glucose tolerance, of the same age, sampled randomly from a geographically defined general population. The VPT appeared to be more reproducible than the TDT (reliability coefficient 0.89 vs. 0.54). The reproducibility of the VPT was inversely related to age and better for men than for women. Diabetes and glycemic level did not affect the reproducibility of either threshold. Both thresholds were related to age and height. Women had a higher VPT than men. The relations between sex and sensory thresholds at the lower limb, reported in previous studies, were probably confounded by height. © 1994 John Wiley & Sons, Inc.

Key words: vibratory threshold • thermal threshold • reproducibility • reference values • older adults

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SENSORY THRESHOLDS IN OLDER ADULTS: REPRODUCIBILITY AND REFERENCE VALUES

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Polyneuropathy is generally assumed to be a common complication of diabetes mellitus. During recent decades, efforts have been made to develop valid and reproducible means of assessing diabetic polyneuropathy.^{12,15} At present, consensus seems to be emerging with respect to the categories of measures which should ideally be covered in order to fully classify this polymorphic and frequently subclinical entity.²⁹ Quantitative sensory testing is one of those categories, in which vibratory and thermal perception—indexing large and small nerve fiber function, respectively—are among the most frequently tested sensory modalities. However, uncertainty remains, with respect to both the criteria for (ab)normality and the optimal choice of

specific methods within each category of measurement.

Reproducibility is a major consideration when a choice between different tests has to be made. It affects both sensitivity and specificity of the measurement as a diagnostic tool and the statistical power of clinical and epidemiological investigations. To date, there are only limited published data on the reproducibility of sensory threshold tests and the patient characteristics which may affect it. Moreover, the available information is often reported inadequately.

Criteria for (ab)normality should ultimately be based on the relation between test scores, on the one hand, and current or future morbidity and mortality on the other hand. As long as longitudinal studies on these relations are not available, data on the distribution of measurement values in healthy populations must form the main basis for the distinction between normality and abnormality. Previous studies have provided reference values for different measures of sensory neuropathy.^{8,19,37} However, these studies were not based on a sample from a geographically defined general population, and they may well have included subjects with unknown non-insulin-dependent diabetes mellitus and impaired glucose tolerance, condi-

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tions which are both prevalent in older age groups and likely to affect peripheral sensory function.¹⁷ Moreover, in most studies, reference values of sensory thresholds at the lower limb are adjusted for age and sex only, whereas body height might also be an independent influential factor.^{18,32,37}

In this study, we address the issues of both reproducibility and reference values with respect to two commonly used quantitative measures of sensory function, paying special attention to the aspects mentioned above.

SUBJECTS AND METHODS

All study participants were involved in the cohort of the Hoorn Study, an epidemiological study on glucose metabolism in a general Caucasian population. For this study, a random sample of 50–76-year-old subjects was taken from the population register of the town of Hoorn in the Netherlands (56,000 inhabitants). Of the 3553 subjects invited for the study, 2540 (71.5%) participated, of whom 56 were excluded from analysis and further study because they were non-Caucasian. Thus, the final study cohort consisted of 2484 subjects. Information on age, sex, body height, weight, and history of diabetes was obtained by interview for 90% of the nonparticipants.

All members of the cohort not known to have diabetes mellitus underwent a 75 g oral glucose tolerance test (OGTT).³⁶ A random sample, stratified by glucose tolerance, age, and sex, underwent a second OGTT within 3–5 weeks. A subsequent sample was invited to undergo an examination concerning a number of diabetes-related disorders, including polyneuropathy.

This report is based on two subpopulations from the Hoorn Study cohort. First, for the assessment of reproducibility, we aimed at the inclusion of 40 subjects, with an equal distribution over the sexes and with clear contrasts regarding age and glucose tolerance (younger vs. older members of the cohort age group, normal glucose tolerance vs. diabetes mellitus). Thus, 43 consecutive participants falling within one of these eight sex/age/glucose tolerance categories were invited to attend a second neurological examination 2–3 weeks after the first one.

Second, the assessment of reference values involved all subjects invited for the neurological examination who had a normal glucose tolerance on two OGTTs ($n = 277$). Subjects taking drugs or having diseases which are known to interfere with the central or peripheral nerve function were excluded. Consequently, we excluded 19 subjects

with a history of lumbar disc disease, Parkinson's disease, cerebrovascular events, systemic lupus erythematoses, or spinal cord lesion. Also excluded were 8 subjects taking barbiturates, phenytoine, neuroleptic drugs, or benzodiazepines (in the latter two cases, only if the dosage exceeded more than one single dose at night).

The study protocol was approved by the Ethics Committee of the Vrije Universiteit Academic Hospital. Informed consent was given by all participants.

Laboratory Examination. Glycosylated hemoglobin (HbA_{1c}), reflecting the glycemic level during the preceding 6–8 weeks, was determined by ion-exchange high performance liquid chromatography, using the modular diabetes monitoring system (Bio-Rad, Veenendaal, The Netherlands; normal range 4.3–6.1%).

Physical Examination. Knee and ankle reflexes and vibratory sensation at the medial malleoli (128-Hz tuning fork) were classified as present or absent for each participant, by one single observer (P.J.B.).

Sensory Function Tests. The vibratory perception threshold (VPT) was assessed at the dorsum of the right big toe, using a Vibrometer (Somedic, Stockholm, Sweden, type IV) modified by mounting it on an adjustable balance in order to ensure a constant vertical force of 250 g.⁵ Employing the method of limits, the amplitude of the probe, vibrating at 100 Hz, was increased and the subject was asked to indicate the moment when he started to feel the vibration.¹⁹ The VPT was measured in microns vibratory amplitude and was defined as the mean of six of ten measurements, excluding the two highest and the two lowest values. The temperature discrimination threshold (TDT) was assessed by means of a two-alternative forced-choice testing procedure described earlier.⁶ Two thermostimulators were applied, one after another, on the dorsum of the right foot with a constant force of 200 g. The temperature of the first stimulator was equal to the skin temperature of the area tested, which was monitored continuously. The temperature of the second stimulator was set at random either higher or lower than the temperature of the first. Each time the stimulators were applied, the subject was asked whether the second stimulator was warmer or colder than the first one. Initially, the temperature difference was equal to 10°C. Subsequently (representing a correct re-

sponse by X and an incorrect one by O), the difference was halved if the response sequence was XXX or XXOX, and doubled if it was O, XO, or XXOO.³⁵ In this way the magnitude of the temperature difference increased or decreased according to the responses of the subject in question. An increase after a decrease (or vice versa) defined a reversal point. The test was continued until eight reversal points were reached. The TDT was then defined as the mean temperature difference (in °C) at the last six reversal points.

All tests were performed by one of three observers, using the same pair of instruments. A quiet ambience was ensured, with a constant room temperature between 18° and 22°C. All subjects were asked to refrain from smoking and drinking coffee during the 2 h prior to the examination. The tests took place between 8:30 AM and 4:00 PM, at least 1 h after a light meal.

Data Analysis. A logarithmic transformation ($\log_{10}$) was carried out in order to normalize the distribution of thermal and vibratory threshold data. Log-transformed values were used in all analyses.

In the reproducibility study, the mean value and standard deviation of all measurements were calculated for both tests. To quantify reproducibility, the difference between the first and the second measurement was computed for all subjects. It was verified that the mean of the differences did not differ statistically significantly from zero.⁷ Differences were plotted against the means of pairs of repeated measurements to examine whether there was a relation between the difference and the mean threshold level. Next, the standard deviation of the differences, SD_{dif} (equal to $\sqrt{(\sum \text{differences}^2)/n}$), and the reliability coefficient (equal to the correlation coefficient between the first and the second measurements), were calculated as quantitative measures of reproducibility, both with a 95% confidence interval.³⁰ The coefficient of variation was computed as the ratio of the within-subject standard deviation (equal to $SD_{dif}/\sqrt{2}$) to the mean of all measurements.

Regression analyses were performed, with the absolute value of the difference between first and second measurement as the dependent variable, in order to investigate the potential influence of age, sex, and glycemic level on the reproducibility of both thresholds. Finally, the SD_{dif} was computed for relevant subcategories of the study population.

In the reference value study, in order to assess the representativeness of the relevant segment of

the Hoorn Study cohort, the distribution of age, sex, body height, weight, and history of diabetes was compared among participants and nonparticipants without a self-reported history of diabetes. Similarly, a number of parameters were compared between subjects eligible for the reference value study who did, and those who did not participate.

To compute reference values, a regression analysis was carried out with the $\log_{10}$ threshold as the dependent, and age, sex, and height as the independent variables. Thus, for both sensory functions the best fitting regression equation ($\log_{10} \text{threshold} = a + b \cdot \text{age} + c \cdot \text{height} + d \cdot \text{sex}$) was derived, which provides the best estimate of the mean $\log_{10}$ threshold at given values of the independent variables. The upper limits of the ranges including 90%, 95%, and 97.5% of the log-transformed values of the reference population were estimated by adding $t \cdot SD_{res}$ up to the mean threshold calculated from the regression model, where SD_{res} is the residual standard deviation and t is the 90th, 95th, or 97.5th percentile of the appropriate t -distribution, i.e., 1.282, 1.645, and 1.96, respectively.

RESULTS

Reproducibility. All subjects invited agreed to participate. However, 4 of them had to be excluded, as they were unable to come to the study center within 25 days due to temporary illness (Table 1). The time interval between both examinations ranged from 13 to 24 days (mean $\pm$ SD 17.2 $\pm$ 3.3 days). The VPT of all participants could be assessed on both occasions. However, because of a technical problem, the TDT of one 72-year-old male diabetic subject could not be estimated.

Both sensory function tests were feasible in this middle-aged and elderly population. However, the assessment of VPT took much less time than the TDT assessment (5 to 10 min vs. 15 to 25 min) and was experienced as much easier by the study subjects.

Table 1. Characteristics of subjects in reproducibility study.

	Age 51–61 yr		Age 71–76 yr	
	Normal GT	Diabetes mellitus	Normal GT	Diabetes mellitus
<i>n</i>	11	10	8	10
Male/female	5/6	6/4	5/3	4/6
Age (years)*	54.6 (2.9)	57.5 (2.4)	73.5 (1.5)	72.3 (0.8)
Duration				
DM (years)*	—	3.1 (4.6)	—	2.8 (5.9)
HbA _{1c} (%)*	5.2 (0.5)	6.7 (1.4)	5.1 (0.4)	7.3 (3.2)

GT, glucose tolerance; DM, diabetes mellitus; HbA_{1c}, glycosylated hemoglobin.
*Mean (SD).

Table 2. Test-retest reproducibility of vibratory perception and thermal discrimination threshold ($\log_{10}$ transformed).

	Pooled data			Measures of reproducibility		
	<i>n</i>	Mean	SD	SD _{diff} (95% CI)	Reliability coefficient (95% CI)	Coefficient of variation
VPT ($\log_{10} \mu\text{m}$)	39	0.93	0.67	0.32 (0.25–0.40)	0.89 (0.80–0.94)	0.24
TDT ($\log_{10} ^\circ\text{C}$)	38	–0.48	0.50	0.49 (0.39–0.61)	0.54 (0.26–0.73)	0.72

SD_{diff}, standard deviation of differences between first and second measurement.

The mean of the differences between the $\log$ -transformed threshold data obtained at the first and the second measurement was small, and not significantly different from zero for either VPT or TDT ($-0.01 \log \mu\text{m}$, $P > 0.5$ and $0.1 \log ^\circ\text{C}$, $P = 0.2$, respectively), permitting the use of the data to assess reproducibility. Plots did not show a relation between differences and means of pairs of either measurements. Measures of reproducibility for both thresholds are presented in Table 2. Regression analysis showed that age, sex, diabetes (yes/no) and HbA_{1c} had no statistically significant effect on the *absolute* difference between repeated TDT assessments (P -values between 0.2 and 0.9). For the VPT, however, the difference between measurements was influenced by sex (women showing differences which were $0.16 \log \mu\text{m}$ higher than those of men, $P = 0.02$) and showed a tendency to be affected by age (with an increase of $0.007 \log \mu\text{m}/\text{year}$, $P < 0.06$) in a multiple regression analysis. No relation with diabetes and HbA_{1c} was found. In accordance with the result of the regression analysis, the standard deviation of the differences rose from 0.18 in the category of younger men to 0.51 in the older female category (Table 3).

Reference Values. Among the subjects invited for the Hoorn Study who did not report a history of diabetes mellitus, participants were slightly older (1.3 year) and more often female (54% vs. 52%) than nonparticipants. Mean body weight of partic-

ipants measured at the study center was 2.3 kg higher, and mean body height 2.2 cm lower than the corresponding self-reported values of nonparticipants (data not shown).

Of the 250 subjects eligible for the reference value study, 216 (86%) participated (Table 4). Controlling for age and sex, participants on an average had similar systolic and diastolic blood pressures, fasting and postload glucose levels, and waist-hip ratios as nonparticipants (data not shown). Sensory function tests were performed within 12 weeks after the second OGTT in the majority (95%) of cases.

In a multiple regression analysis, both VPT and TDT were significantly related to age ($P < 0.0001$ and $P < 0.01$, respectively) and body height ($P < 0.0001$ and $P < 0.05$). Only VPT showed a relation with sex, women having on average a somewhat higher threshold than men ($P = 0.01$). The magnitude of the sex difference was comparable to a difference of 5 years in age. The best fitting regression equations are presented in Table 5, together with the $t \cdot \text{SD}_{\text{res}}$ values which provide the upper limits of the reference ranges. For example, for a 68-year-old woman, height 173 cm, the upper limit of the 95% reference range of the log vibra-

Table 3. Reproducibility of vibratory perception threshold ($\log_{10}$ transformed) in categories of age and sex.

Sex	Age range	Mean age (SD) (years)	<i>n</i>	SD _{diff}
Men	Lower	56.8 (2.8)	11	0.18
	Higher	73.1 (1.6)	9	0.25
Women	Lower	55.1 (3.1)	10	0.25
	Higher	72.7 (1.0)	9	0.51

SD_{diff}, standard deviation of differences between first and second measurement, in $\log_{10} \mu\text{m}$ vibratory amplitude.

Table 4. Characteristics of subjects in reference value study.

	Age range (years)		
	50–59	60–69	70–76
<i>n</i>	84	79	53
Male/female	53/31	35/44	28/25
Mean age (SD)	55.0 (2.4)	64.9 (3.0)	73.0 (2.0)
Ankle reflexes bilaterally absent (%)	8.4	14.1	18.9
Malleolar vibration sensation bilaterally absent (%)	0	3.9	9.4

Table 5. Log₁₀ sensory threshold as a function of age, height, and sex among healthy subjects aged 50–76 yr (*n* = 216): intercept; regression coefficients (95% CI); standard deviation of residuals (SD_{res}); and upper limits of 90%, 95%, and 97.5% reference ranges.

	a Intercept	b Age (yr)	c Height (cm)	d Sex (M = 0, F = 1)	SD _{res}	<i>t</i> _{0.90} • SD _{res}	<i>t</i> _{0.95} • SD _{res}	<i>t</i> _{0.97} • SD _{res}
VPT (log ₁₀ μm)	−5.69 (−7.27; −4.11)	0.033 (0.027; 0.040)	0.026 (0.018; 0.034)	0.19 (0.04; 0.33)	0.38	0.48	0.62	0.74
TDT (log ₁₀ °C)	−3.08 (−4.50; −1.65)	0.014 (0.006; 0.023)	0.010 (0.003; 0.018)	NS	0.47	0.60	0.77	0.92

M, male; F, female; NS, not significant.

tory threshold, is equal to: $-5.69 + 68 \cdot 0.033 + 173 \cdot 0.026 + 0.19 + 0.62 = 1.862 \log_{10} \mu\text{m}$. Thus, the vibratory perception of this woman is statistically abnormal at the 95% level, when her vibratory threshold at the big toe exceeds 72.8 μm. Leaving aside the effect of sex, Table 6 provides the reference values of the vibratory threshold in microns, adjusted for age and height.

DISCUSSION

This study enables comparison of the reproducibility of two commonly used quantitative sensory assessment methods in older adults. Moreover, it is the first to provide a valid, general population basis for the derivation of adequately adjusted reference values.

Reproducibility. Comparing the reproducibility of different measurement methods poses some difficulties in data analysis and interpretation. A measure which provides a direct, unconditional insight into reproducibility is the standard deviation of the differences between pairs of repeated measurements (SD_{dif}) (or, more generally, the within-subject standard deviation of repeated measurements).⁷ The SD_{dif} can easily be interpreted by realizing that 95% of the second measurements lie in the interval defined by the first measurement $\pm 1.96 \text{ SD}_{\text{dif}}$. The coefficient of variation, as defined here and in other studies, relates the within-subject standard deviation to the mean value of pooled measurements. It provides no other information on reproducibility apart from the SD_{dif}.

Table 6. Vibratory perception threshold (microns): upper limits of ranges including 90%, 95%, and 97.5% of the values of a reference population aged 50–76 yr (*n* = 216), in relation to age and body height.

	Height (cm)								
Age	150	155	160	165	170	175	180	185	190
50 yr									
90%	4.3	5.3	6.5	8.1	10.1	12.5	15.5	19.2	23.8
95%	5.9	7.3	9.0	11.2	13.9	17.2	21.3	26.4	32.7
97.5%	7.7	9.6	11.9	14.7	18.3	22.7	28.1	34.8	43.2
55 yr									
90%	6.2	7.7	9.5	11.8	14.6	18.1	22.5	27.9	34.6
95%	8.5	10.6	13.1	16.2	20.1	25.0	31.0	38.4	47.6
97.5%	11.2	13.9	17.3	21.4	26.6	32.9	40.8	50.6	62.8
60 yr									
90%	9.0	11.2	13.8	17.1	21.3	26.4	32.7	40.5	50.2
95%	12.4	15.4	19.0	23.6	29.3	36.3	45.0	55.8	69.2
97.5%	16.3	20.3	25.1	31.1	38.6	47.9	59.4	73.6	91.3
65 yr									
90%	13.1	16.2	20.1	24.9	30.9	38.3	47.5	58.9	73.0
95%	18.0	22.3	27.7	34.3	42.5	52.7	65.4	81.1	100.5
97.5%	23.7	29.4	36.5	45.3	56.1	69.6	86.3	107.0	132.6
70 yr									
90%	19.0	23.6	29.2	36.2	44.9	55.7	69.0	85.6	106.1
95%	26.2	32.4	40.2	49.9	61.8	76.6	95.0	117.8	146.1
97.5%	34.5	42.8	53.1	65.8	81.6	101.1	125.4	155.5	192.7
75 yr									
90%	27.6	34.2	42.5	52.6	65.3	80.9	100.3	124.4	154.2
95%	38.0	47.1	58.4	72.5	89.8	111.4	138.1	171.2	212.3
97.5%	50.2	62.2	77.1	95.6	118.5	147.0	182.2	225.9	280.1

The obvious drawback of the SD_{dif} as a measure of reproducibility is the impossibility to compare methods with different scales of measurement. Here the reliability coefficient provides a partial solution. Easily computed as the coefficient of correlation between the first and the second measurements, it can be interpreted as the proportion of variance of the measurement that represents true variation in the quantity measured, as distinct from random error.³⁰ Unfortunately, the reliability coefficient can be used for direct comparison of the reproducibility of different methods only when the relevant *interindividual* variability of the quantities measured is the same in the respective study populations. This is a highly questionable assumption in most cases. It is likely to be valid, however, when related entities are measured in one study population, as is the case in our study. Therefore, the difference we found between the reliability coefficients of vibratory and thermal thresholds may be assumed to reflect a true and rather impressive difference in reproducibility between the two sensory function tests. This finding may be explained by inherent characteristics of the two different sensory systems, as it is in accordance with the general picture emerging from other studies comparing various vibratory and thermal threshold tests.^{3,16,22,27} However, other explanations cannot be excluded. First, the lower reliability of TDT may partly be due to the difference in the psychophysical testing procedure, as the thermal forced-choice method requires much more of the subjects' endurance and concentration than the vibratory method of limits. On the other hand, the forced-choice method is generally assumed to provide more reproducible results than the method of limits.^{10,14} Another factor may be the fact that our method measures both warm and cool sensitivity. Since the warming threshold, in general, is higher than the cooling threshold, and since both thresholds may well differ in one individual,^{10,11,31} it seems plausible that the random reversals of the temperature difference in our method will introduce random measurement error, in addition to the error in the separate measurements of cold and warm perception.²⁹ In agreement with this hypothesis, the data of Claus et al. and Dyck et al. suggest that the reliability coefficients of separate warm and cold perception assessments may not be much lower than that of the VPT found in the present study.^{10,13} Further investigations are required to compare the reproducibility of different thermal threshold tests.

As for the vibratory threshold at the big toe, the

measures of reproducibility reported here seem to agree with data obtained in younger populations.^{5,13,22,24,25,27} The absence of a difference in reproducibility between healthy and diabetic subjects is also in accordance with other studies.^{5,22,27} A finding not reported before is the influence of age and sex on the reproducibility of the VPT. Since factors affecting the perception of a stimulus, like fatigue and lack of concentration, might well be age-related, the association with age is not unexpected.¹⁶ We have no explanation for the lower reproducibility of vibratory thresholds for women. Confirmation by other studies has to be awaited.

Reference Values. The present reference value study is the first which is based on a screening with oral glucose tolerance tests in a random sample from a geographically defined general population. It has, therefore, the major advantage of not including subjects with increased sensory thresholds due to unknown glucose intolerance. Thus, our study can be expected to provide more valid data on the relation between age and sensory function than previous studies. Moreover, the data on nonparticipants show that the present population of healthy subjects is likely to be an unbiased reflection of the corresponding segment of the general population. The difference observed between participants and nonparticipants with respect to body weight and height is in accordance with the bias which can be expected, due to the fact that the data on nonparticipants were self-reported.³⁴

The present reference values for VPT can best be compared with those from the study of Goldberg and Lindblom.¹⁹ Studying the effect of age on the tarsal vibratory perception threshold in microns, they found an increase in the (untransformed) vibratory threshold by a factor of 1.82 per decade, whereas we find an increase by a factor of 1.92, without including height in the regression model. As body height is inversely associated with age and positively associated with vibratory threshold, the inclusion of height in the model results in a further increase in the age effect (amounting to a factor of 2.16 per decade).

The effect of age was also clearly demonstrated in a number of previous studies, using an instrument which measures the vibratory threshold in units of applied voltage instead of the actual amplitude of stimulator movement.^{1,3,8,33,37} As argued as early as 1951 by Gregg, and demonstrated empirically by Goldberg and Lindblom, the relation between voltage and amplitude is rather com-

plicated, depending both on the site of the body tested and on individual characteristics of the study subject.^{19,21} Therefore, one cannot meaningfully compare the magnitude of the age-effect between those studies and ours.

Unlike the findings of other studies, our data demonstrate that, controlling for age and height, healthy women have higher average tarsal vibratory thresholds than men. Wiles et al. and Bergenheim et al., the only investigators who also studied the effect of both age, height, and sex in this respect among healthy subjects, did not find a similar independent and statistically significant sex effect.^{4,37} Previous studies which did find a difference between the sexes among healthy subjects, found an effect opposite to that reported in our study.^{20,33} However, this may well be explained by the fact that in those studies the effect of height was not taken into account. In our analysis, the effect of sex was reversed when height was excluded from the regression model, which is understandable considering the fact that on average men are taller than women. With respect to thermal sensitivity, our data confirm the statistically significant increase of threshold level with age in healthy subjects, as was found in most,^{6,9-11,16,22,23,26} but not all, previous studies.^{2,3,25}

This study is the first to provide clear evidence that the relation between body height and sensory function in the foot also applies for thermal sensitivity. Measured on an untransformed scale, the thermal threshold increases by a factor of 1.3 per 10-cm increase in height. The discrepancy between this finding and the results of Jamal et al., who found a similar, but not significant correlation between leg-length and thermal threshold, may be explained by the difference in sample size.²³

To our knowledge, only one study has reported a difference between the sexes with regard to thermal sensitivity, with women showing lower thresholds than men.¹¹ Here, again, the present investigation demonstrates that confounding by body height may play a role, since in our analysis women also have lower thresholds ($P < 0.05$) when height is not taken into consideration. After including height in the regression model, the sex difference disappears completely.

We conclude that reference values for both vibratory and thermal perception in the foot should be adjusted for age and body height. Adjustment for sex seems to be mandatory for vibratory perception only. The reference values provided by the present study represent valid criteria for statistical normality which can be used in clinical practice

and for clinical and epidemiological investigations. However, the interpretation of sensory perception thresholds in terms of their clinical relevance awaits the outcome of large-scale prospective epidemiological studies.²⁸

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