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Normal Values of Sudomotor Function Assessed by Electrochemical Skin Conductance in the African Population --Manuscript Draft--

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Corresponding Author:	Banfantini Pikabe LARE Université de Limoges LIMOGES, Nouvelle-Aquitaine FRANCE
First Author:	Banfantini Pikabe LARE
Order of Authors:	Banfantini Pikabe LARE Banfantini Piakbe Pikabe Lare, MSc Jérémy Jost, Pharm D, PhD Kossivi Apetse, MD Laurence Salle, MD Pierre Marie Preux, MD, PhD Agnon Balogou, MD, PhD Julien Magne, PhD
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Abstract:	<p>ABSTRACT:</p> <p>Background: Dysfunction of small nerve fibers remains a major public health problem. Subjects suspected of having small nerve fiber damage need to undergo reliable tests to confirm the diagnosis. Sudomotor function test is a reliable non-invasive exploration for detecting peripheral neuropathies. Nevertheless, the normal reference values derived from the sudomotor function test are not known in the African population. The objective of this study is therefore to describe the normal values of Electrochemical Skin Conductance (ESC) measured by the Sudomotor function test in healthy African subjects.</p> <p>Materials and methods: Between December 1st, 2021 and May 31,2022, 475 healthy subjects (median age: 42[31-53] years, 46% of men) had a measurement of ESC, using sudomotor function test in the hands and feet. Investigators proposed the examination and received participants' consent, demographic, anthropometric, biological and clinical data were obtained before the test.</p> <p>Results: ESC were statistically higher in men compared to women (right hand ESC:70 [60-78] vs. 63 [53-72], left hand ESC: 72 [61-80] vs. 68 [57-75], right foot ESC: 77 [82-99] vs. 72 [64-79], ESC left foot : 76 [68-82] vs. 72 [62-78] respectively. ESC were significantly inversely correlated with age (right hand ESC: $r=-0.12$, $p=0.006$; left hand ESC: $r=-0.11$, $p=0.01$; right foot ESC: $r=-0.37$, $p<0.0001$; ESC left foot : $r=-0.38$, $p<0.0001$). Of not, ESC feet's were significantly inversely correlated with body mass index (right foot $r=-0.22$, $p<0.0001$; left foot $r=-0.21$, $p<0.0001$).</p> <p>Conclusion: This study reports normal reference values for ESCs according to age and gender in healthy African population. Progressive decrease in ESC with aging is confirmed by our data. The value of ESC seems lower in African population than in others reported ethnicity. This finding needs to be further explored in additional studies.</p>
Suggested Reviewers:	Dieu Donné gnonlonfoun dieudonne.gnonlonfoun@gmail.com Exepert in the field of peripheral neuropathy.
	Aaron I Vinik vinikai@evms.edu Expert in the field of ESC.
	thierry Adoukouou adoukonouthierry@yahoo.fr Expert in the field of peripheral neuropathy

Normal Values of Sudomotor Function Assessed by Electrochemical Skin Conductance in the African Population

Banfantini Pikabe Lare¹, MSc, Jérémy Jost, Pharm D, PhD², Kossivi Apetse, MD³, Laurence Salle, MD⁴, Pierre Marie Preux, MD, PhD⁵ Agnon Balogou, MD, PhD⁶, Julien Magne, PhD^{7*}

1: Inserm U1094, IRD U270, Univ. Limoges, CHU Limoges, EpiMaCT - Epidemiology of chronic diseases in tropical zone, Institute of Epidemiology and Tropical Neurology, OmegaHealth, Limoges, France. Electronic address: Banfantini_pikabe.lare@unilim.fr

2: INSERM, Univ. Limoges, CHU Limoges, UMR_S 1094, EpiMaCT - Epidemiology of chronic diseases in tropical zone, Institute of Epidemiology and Tropical Neurology, Limoges, France; CHU Limoges, Department of Pharmacy, F-87000 Limoges, France. Electronic address: jeremy.jost@unilim.fr.

3: Nervous System University Research Team (NEURO), University of Lomé; Neurology department CHU Campus of Lomé, Togo. Electronic address: kapetse@hotmail.com

4: INSERM, Univ. Limoges, CHU Limoges, UMR_S 1094, EpiMaCT - Epidemiology of chronic diseases in tropical zone, Institute of Epidemiology and Tropical Neurology, Limoges, France, CHU Limoges, department of Endocrinology, 87000 Limoges, France. Electronic address: laurence.salle@unilim.fr

5: Inserm U1094, IRD U270, Univ. Limoges, CHU Limoges, EpiMaCT - Epidemiology of chronic diseases in tropical zone, Institute of Epidemiology and Tropical Neurology, OmegaHealth, Limoges, France. Electronic address: pierre-marie.preux@unilim.fr

6: Nervous System University Research Team (NEURO), University of Lomé; Neurology department CHU Campus of Lomé, Togo. Electronic address Electronic address:

abalogou@yahoo.fr

7: Inserm U1094, IRD U270, Univ. Limoges, CHU Limoges, EpiMaCT - Epidemiology of chronic diseases in tropical zone, Institute of Epidemiology and Tropical Neurology, OmegaHealth, Limoges, France; CHU Limoges, Department of Cardiology, Dupuytren 2 University Hospital, 16, Rue B. Descottes, 87042, Limoges, France. Electronic address: Julien.magne@unilim.fr.

Corresponding authors:

*Inserm U1094, IRD U270, Univ. Limoges, CHU Limoges, EpiMaCT - Epidemiology of chronic diseases in tropical zone, Institute of Epidemiology and Tropical Neurology, OmegaHealth, Limoges, France; CHU Limoges.

E-mail address: Julien.magne@unilim.fr (J. Magne).

Keywords: *Sudomotor function testing, Sudoscan, Electrochemical Skin Conductance, Normal value*

ABSTRACT:

Background: Dysfunction of small nerve fibers remains a major public health problem. Subjects suspected of having small nerve fiber damage need to undergo reliable tests to confirm the diagnosis. Sudomotor function test is a reliable non-invasive exploration for detecting peripheral neuropathies. Nevertheless, the normal reference values derived from the sudomotor function test are not known in the African population. The objective of this study is therefore to describe the normal values of Electrochemical Skin Conductance (ESC) measured by the Sudomotor function test in healthy African subjects.

Materials and methods: Between December 1st, 2021 and May 31,2022, 475 healthy subjects (median age: 42[31-53] years, 46% of men) had a measurement of ESC, using sudomotor function test in the hands and feet. Investigators proposed the examination and received participants' consent, demographic, anthropometric, biological and clinical data were obtained before the test.

Results: ESC were statistically higher in men compared to women (right hand ESC:70 [60-78] vs. 63 [53-72], left hand ESC: 72 [61-80] vs. 68 [57-75], right foot ESC: 77 [82-99] vs. 72 [64-79], ESC left foot : 76 [68-82] vs. 72 [62-78] respectively. ESC were significantly inversely correlated with age (right hand ESC: $r=-0.12$, $p=0.006$; left hand ESC: $r=-0.11$, $p=0.01$; right foot ESC: $r=-0.37$, $p<0.0001$; ESC left foot : $r=-0.38$, $p<0.0001$). Of note, ESC feet's were significantly inversely correlated with body mass index (right foot $r=-0.22$, $p<0.0001$; left foot $r=-0.21$, $p<0.0001$).

Conclusion: This study reports normal reference values for ESCs according to age and gender in healthy African population. Progressive decrease in ESC with aging is confirmed by our data. The value of ESC seems lower in African population than in others reported ethnicity. This finding needs to be further explored in additional studies.

1. Introduction

Polyneuropathy is a group of disorders that share length-dependent peripheral nerve damage, resulting in predominantly distal sensory loss, pain and, when severe, weakness leading to gait instability, risk of falling and, in some cases, foot ulceration and amputation¹. Autonomic nerve fibers are affected in most generalized peripheral neuropathies. Sweat glands innervated by thin unmyelinated sympathetic C fibers could be easily affected in the early stage of these polyneuropathies that occurs in many neurological, genetic and metabolic diseases including diabetes². There are various tests to evaluate this sweat function, including the quantitative sweat axonal reflex test (QSART), the thermoregulatory sweat test, the sympathetic skin response or skin biopsy. However, these tests are still underused due to their required specialization, the very long time required to perform them and their invasive nature³. Hence, the use of Sudomotor function testing appears to be a helpful and suitable test to improve diagnosis of peripheral neuropathies. The sudomotor function test is a patented device designed to perform a quantitative assessment of sweat gland function based on the electrochemical reaction between sweat ions, measured by electrochemical skin conductance (ESC)⁴. In addition, this test is a non-invasive, simple and rapid device. It is made up of two sets of stainless-steel electrodes on which the subject must place the palms of the hands and the soles of the feet, regions where the density of the sweat glands is greater⁵. Sweat function is affected at an early stage of distal small fiber neuropathy and its assessment seems to be an interesting tool to evaluate neuropathy. Because of the increasing prevalence of diabetes in low- and middle-income countries, screening for polyneuropathy at an early stage seems crucial to limit morbidity and mortality related to diabetic foot wounds. Indeed, diabetes remains the most recurrent cause, accounting for 50% of cases. Peripheral neuropathy affects more than half of all diabetics and is a major cause of morbidity and reduced quality of life due to pain, gait instability and

associated depression⁶. The second most common cause, accounting for about 40% of cases, is idiopathic or cryptogenic polyneuropathy, which is associated with an increased risk of prediabetes and metabolic syndrome⁶. To date, normal reference values of ESC-derived sudomotor function testing in the African population have not been reported. The objectives of this study were (1) to report normal baseline values of ESC measured by sudomotor function testing in the healthy African population and (2) to explore the relationship between ESC and age, sex, and body mass index (BMI).

2. Materials and Methods

1. Study population

The study was prospectively conducted at the University Hospital Center Campus de Lomé in Togo between December 1, 2021 and May 31, 2022. The ethics committee of the Ministry of Health of Togo approved the study (Notice Number 005/2022/CBRS of February 24, 2022). The participants in the study were healthy subjects without any disease related to neuropathy such as metabolic and cardiovascular diseases, renal insufficiency, stroke assessed by physical examination and direct interview with the patient. The patients recruited were persons accompanying hospitalized patients, visitors of the hospital or students aged 18 years and older. Non-inclusion criteria included hospitalized patients, diabetic subjects, subjects with peripheral neuropathies (numbness, tingling, burning, pain, muscle weakness, muscle cramps, dizziness), and patients who did not wish to participate in the study. Subjects were not taking any medications; they had no history of use of potential neurotoxic drugs and no neurological signs or symptoms.

The research was conducted by five investigators divided into different tasks: one investigator was in charge of performing all the sudomotor function testing (BPL) examination (using single device), and others investigators were in charge of proposing the examination to the participants while explaining

the purpose of the research, obtaining participants consent form and collecting anthropometric. The investigators proposed the examination and received consent from the participants.

2. Baseline characteristics

Medical history, demographic and anthropometric data, (weight, height, blood pressure) were collected. Blood glucose was measured with a glucometer. A fasting capillary blood glucose test was performed on site. The fasting blood glucose levels of all participants were normal, below the threshold of 1.26 g/mL.

3. Sudomotor function measurements and test

The sudomotor function measurements and quantification of ESC were performed using Sudomotor function test. This is an innovative, simple and non-invasive device for assessing sudomotor function based on reverse iontophoresis and chronoamperometry⁷.

Each participant was asked to place the parts where the density of the sweat glands was consequent, the palms of the hands and the soles of the feet on stainless steel electrodes connected to a computer for the recording of the ESC and the analysis of their data for a maximum duration of 2 minutes. Data were collected and stored using password secured data collection tools Kobo collect, a software program that allows both the collection and storage of search data. We first extracted the collected data via the Kobo-collect software, which automatically generates the data on an Excel sheet, and then proceeded to process the data. The database was stored and secured on University of Limoges servers.

4. Statistical analyses

Sample size estimation

Based on the study of Vinik et al., performed in 2016⁸ sample size was calculated assuming a mean ESC of $56.7 \pm 17 \mu\text{S}$ for hands and $66.7 \pm 14.3 \mu\text{S}$ for feet. Using an accuracy of 5% of the 95% of

confidence interval, a total of 356 subjects should be included. In order to take into account, the risks of sample fluctuation, missing data and to increase the power of subgroups analysis (according age class and gender), we decided to increase this number by 1 third resulting in 475 subjects. The normality of the distribution of each quantitative variable was estimated using Shapiro-wilk test. Thus, continuous quantitative variables, with skewed distribution, were reported with as median and interquartile [IQR] and the qualitative variables as number and percentage.

Descriptive analysis was used to report ESC measurement values between groups (sex and age classes). The correlation were estimated using Spearman's test. A multiple linear regression analysis was used to determine the association between demographic and anthropometric parameters (age, sex, weight, height, waist circumference, body mass index, systolic and diastolic blood pressure, heart rate) and ESC. $P < 0.05$ was considered statistically significant. All statistical analyses were performed with R software version 4.1.1 (2021-08-10).

3. Results

The demographics characteristics of the overall study population are summarized in Table 1 and stratified by sex. Of the 475 subjects who participated in the study, 220 (46%) were male. The median age of the population was 42[31-53] years. The observed baseline ESC values are summarized in Figure1. ESC levels were significantly higher in men than in women (Figure 2). Grouping together hand and foot (left vs. right). There is a symmetry between the right and the left measurement respectively 70.5 [61-76] and 71.5[62-77] ($p=0.09$).

The ESC measurement according to age classes are reported in Table 2 and the Table 3 summarizes ESC values according to gender and age groups. Age was inversely correlated with the ESC and progressively decrease among age classes.

There was no significant correlation between BMI and both left-and right-hand ESC, whereas there was significant correlation between BMI and both left and right foot (Figure 3, hands $r=-0.07$, $p=0.12$; $r=-0.06$, $p=0.19$; feet $r=-0.21$, $p<0.001$; $r=-0.23$, $p<0.001$, respectively). Using multiple linear regression including systolic and diastolic blood pressure and BMI, only age and gender were independently associated with right hand ECS (age: $\beta=-0.16\pm0.05$, $p<0.001$; male gender: $\beta=-6.86\pm1.35$, $p<0.001$), left hand ESC (age: $\beta=-0.16\pm0.05$, $p<0.001$; male gender: $\beta=-4.63\pm1.34$, $p<0.001$), right foot ESC (age: $\beta=-0.32\pm0.04$, $p<0.001$; male gender $\beta=-2.96\pm1.2$, $p=0.014$) and left hand ESC (age: $\beta=-0.38\pm0.05$, $p<0.001$; male gender $\beta=-3.48\pm1.3$, $p=0.007$). Of note, BMI was not significantly associated with ESC after adjustment for age and sex.

4. Discussion

The present study provides normal reference values for ESC in a healthy African population. This is the first study, to the best of our knowledge of normal ESC values in this population. The measurements of these values are robust because they are performed with a single device. The baseline values observed by ESC measurements in healthy subjects remain higher than those observed by Vinik et al. in the African American population (ESC hands: $57[25-80]$ μS vs. $68[57-75]$ μS and ESC feet: $70[40-84]$ μS vs. $74[64-80]$ μS ⁸). In addition, the values found by Vinik et al. in the European population are significantly higher than our results respectively: ESC hands $72 [47-87]$ μS vs. $68[57-75]$ μS and ESC feet $83.5[69.0-89]$ μS vs $74[64-80]$ μS . Similar disparities has been found between other ethnicity Indeed, using skin biopsy intra-epidermal nerve fiber density (IENFD) test⁹, Lui Y. et al., find that Chinese healthy subjects had lower values than the Finnish population (62.87 ± 15.25 fibers/ mm^2 vs. 114.617 ± 32.322 fibers/ mm^2)¹⁰. Nevertheless, our values were in line with that found by Shivaprasad et al., performed in 2018 in an Indian healthy population (hands and feet 68.9 ± 13.1 and 71 ± 12.9 μS , respectively)¹¹. These values are still lower than those observed by Vinik et

al. in the white population. In sum, these reference data found in African, African-American, Chinese and Indian populations remain lower than those observed in Caucasian populations. According to Shivaprasad et al. these variations in baseline measurements by ethnicity may be explained by differences in secretory capacity, ion transport, or small nerve fiber properties that could contribute to these small variations¹². However, the exact reasons for these ethnic differences in ESC variation remain to be clarified.

Our result confirms a difference in ESC values between men and women, men had higher ESC values than women. Gender effects were detected both neuropathologically and neurophysiologically, particularly in sweat production and sudomotor function¹². This seems a coherent argument, as neuropathological and neurophysiological deficiencies in sudomotor function could affect ESC values. Several authors in research focused on prevalence of peripheral neuropathies in China, Albania and Canada have reported a higher prevalence in women¹³⁻¹⁷. In addition, ESC values of hands and feet decreased with age in our study. Extensive research on the structure and innervation of glandular tissue confirmed that there is an age-related decline in sudomotor nerve density and sudomotor function¹⁸. This phenomenon could be explained by changes in the effector organs accompanying senile skin atrophy and by a certain degree of lack of physical activity associated with a more sedentary lifestyle of the elderly, which could explain this decrease in sudomotor function in this age group. In summary, alterations in peripheral autonomic nervous system function involving sympathetic C-fibers are the first features of a peripheral neuropathy; sweat glands are innervated by these small, unmyelinated sympathetic nerve fibers, and loss of sudomotor function is one of the initial neurophysiological abnormalities detectable in peripheral neuropathy¹⁹. This means that the neuropathy observed in these subjects could be related to obesity. In this regard, our results could

confirm these hypotheses since only the ESC of the feet and not those of the hands were correlated with BMI.

Foot ESC in our study were inversely correlated with BMI. Although derived from a small number of patients, it appears that patients with higher BMI ($>35\text{kg/m}^2$) have lower foot ESC. In this study the majority of subjects were young. Another argument to support this hypothesis concerns a study that observed that all obese diabetic patients who underwent bariatric surgery had a significant improvement in foot ESC from $57\mu\text{S}$ to $70\mu\text{S}$ ⁵.

Our study has some limitations. Initially, the healthy subjects who participated in the study did not undergo any clinical neurological examination by a neurologist. There was no gold standard for the assessment of autonomic neuropathy, but the study population was carefully selected. In addition, an estimate of the sample size was made, includes mainly patients from an urban area which may limit the extrapolation of our results. Nevertheless, it should be noted that this study is the first, to the best of our knowledge, performed in an African population and through which normal values for sudomotor function testing was stated.

5. Conclusion

This study, based on an African population, has allowed us to establish the normal reference values of sudomotor function test derived ESC, which is essential for the management of peripheral neuropathy issues. Progressive decrease in ESC with aging is confirmed by our data. The value of ESC seems lower in African population than in others reported ethnicity. Our results may serve as a reference value for the screening, diagnosis and follow-up of peripheral neuropathy, especially in diabetic patients in the African population.

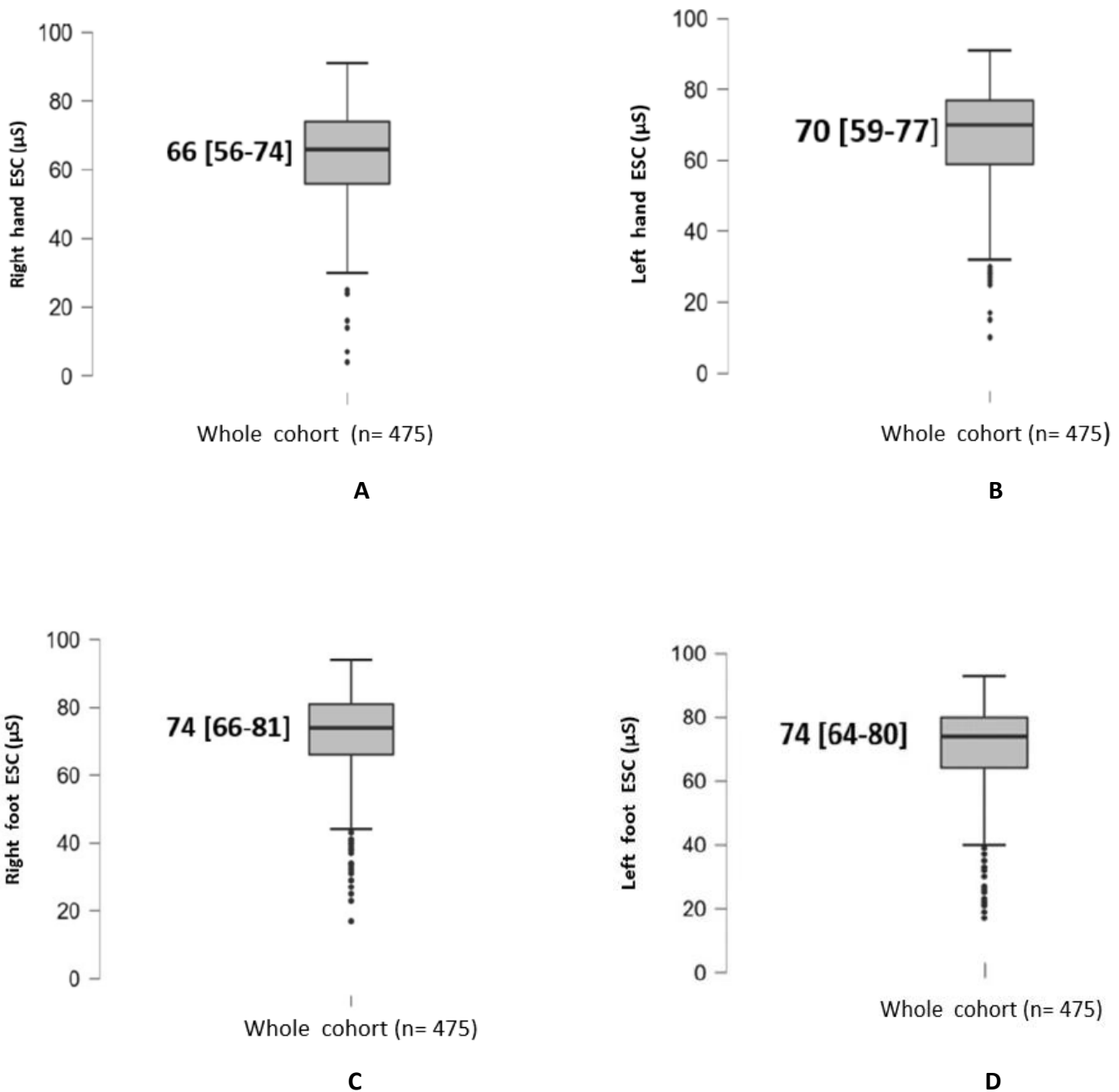
Conflict of interest

None for all authors

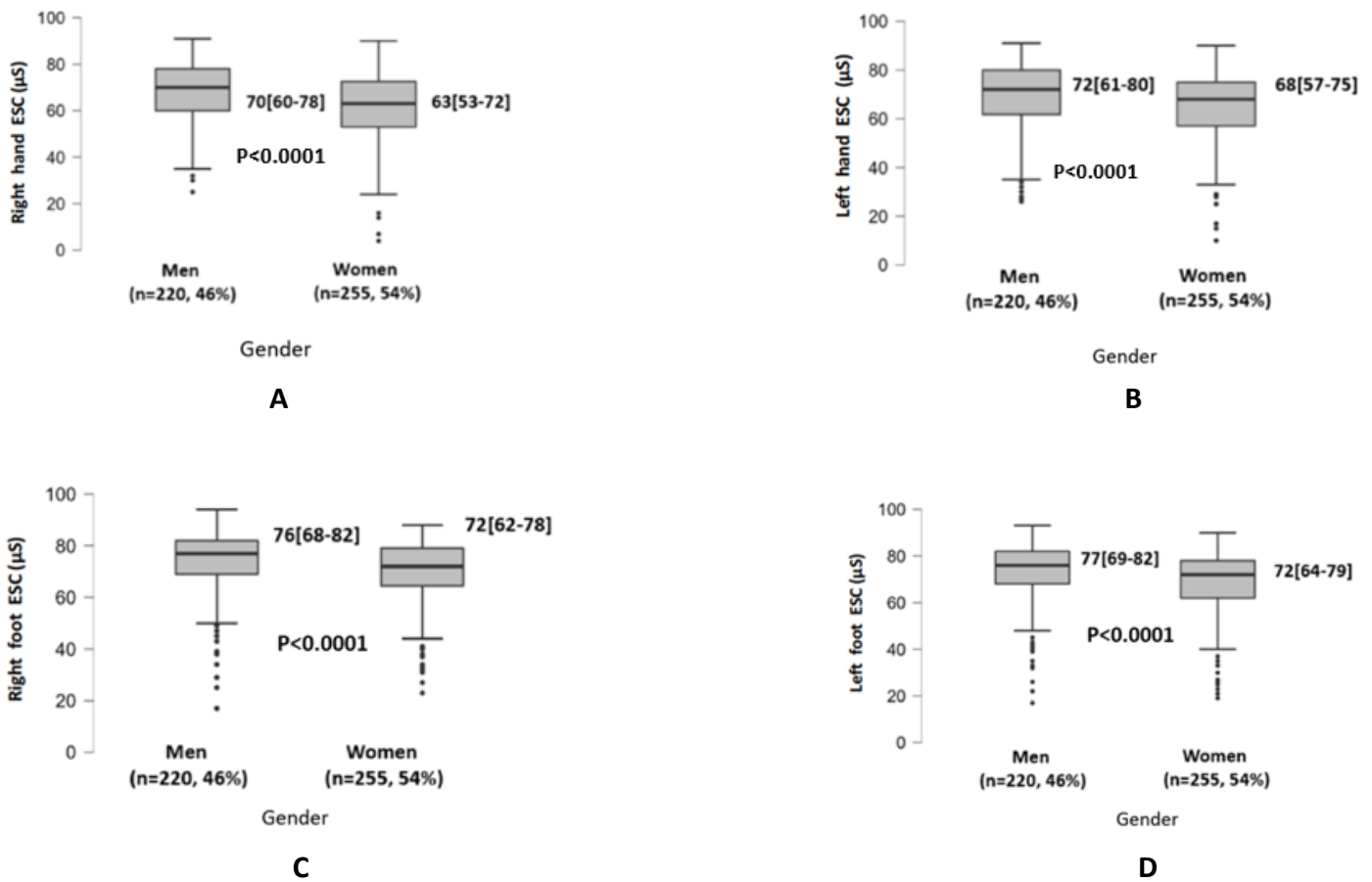
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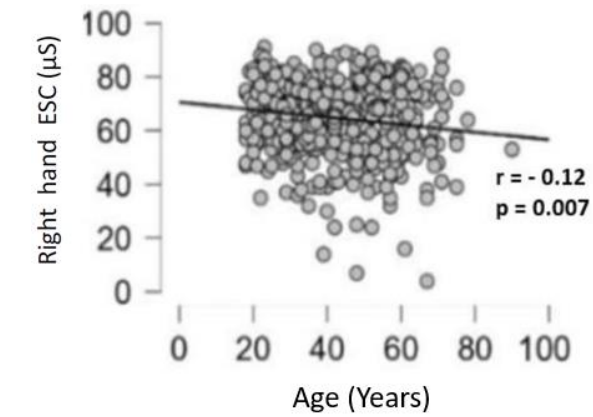
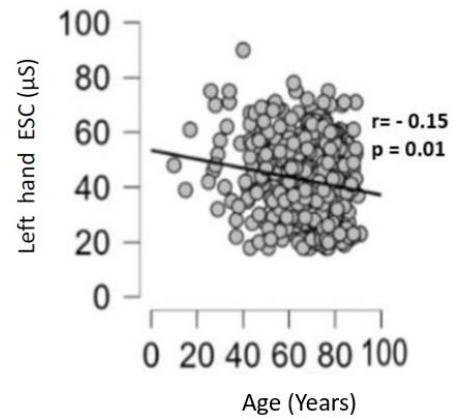
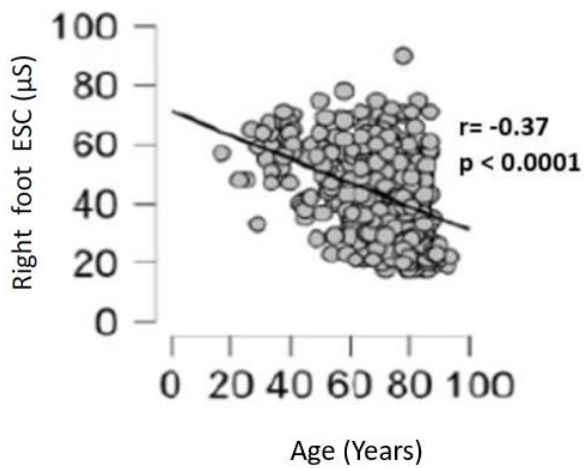
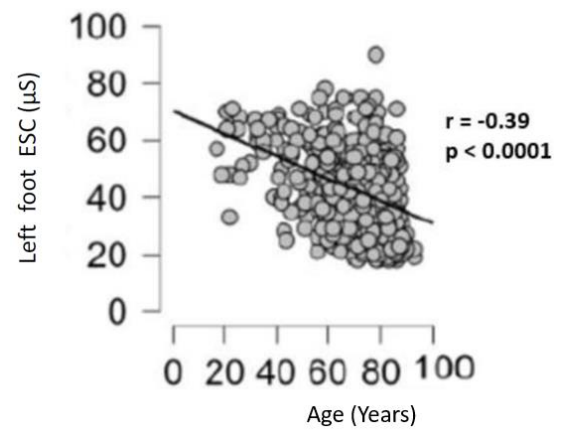
Figure 1: Distribution of electrochemical skin conductances (ESC)

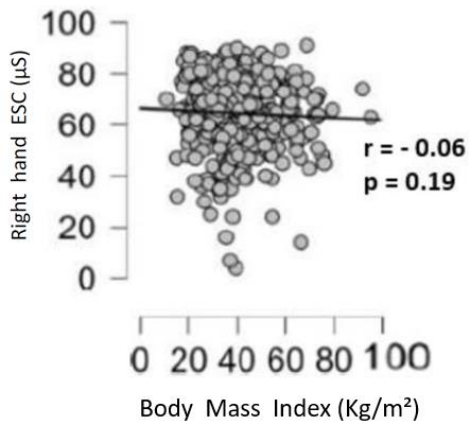
Right hand ESC indicates electrochemical skin conductance right hand; Left hand ESC indicates electrochemical skin conductance left hand; Right foot ESC indicates electrochemical skin conductance right foot; Left foot ESC indicates electrochemical skin conductance left foot

Figure 2: Distribution of electrochemical skin conductances (ESC) according to gender

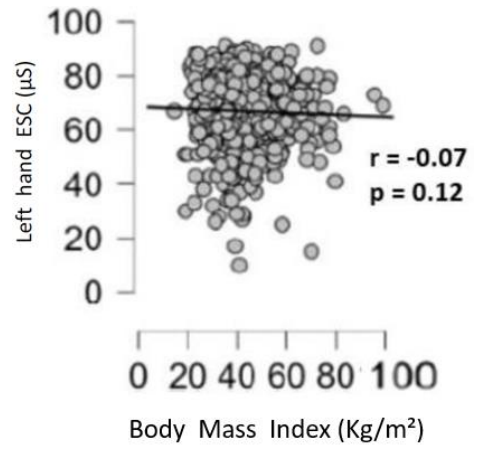
Right hand ESC indicates electrochemical skin conductance right hand; Left hand ESC indicates electrochemical skin conductance left hand; Right foot ESC indicates electrochemical skin conductance right foot; Left foot ESC indicates electrochemical skin conductance left foot

Figure3: Correlation between electrochemical skin conductance (ESC) and age, BMI, the whole cohort (panel A, B, C, D, E, F, G, H)

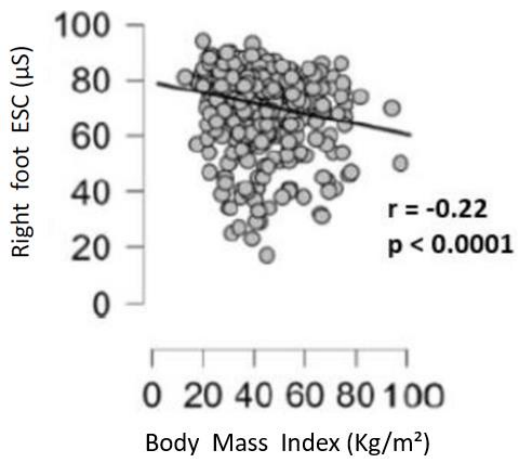
**A****B****C****D**



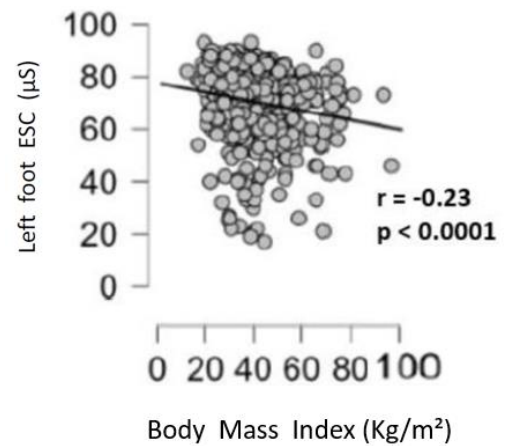
E



F



G



H

Right hand ESC indicates electrochemical skin conductance right hand; Left hand ESC indicates electrochemical skin conductance left hand; Right foot ESC indicates electrochemical skin conductance right foot; Left foot ESC indicates electrochemical skin conductance left foot; BMI indicates body mass index

Table 1: Characteristics of the population and sudomotor function according to sex

Variables	Total (n=475)	Men (n=220 ; 46%)	Women (n=255 ; 54%)
Age, years	42 [31-53]	40 [29-53]	43 [32-53]
BMI, Kg/m²	25 [22-29]	24 [21.3-27]	27 [24-31]
Weight, Kg	71 [61-81]	70 [61-81]	73 [60-81]
Height, cm	166 [160-172]	172 [168-176]	162 [159-166]
Waist size, cm	71 [61-86]	70 [60-86]	71 [65-85]
Heart rate, bpm	67 [62-70]	66 [61-69]	68 [63-71]
Diastolic BP, mmHg	80 [70-80]	80 [70-80]	80 [70-80]
Systolic BP, mmHg	120 [120-130]	120 [120-130]	120 [120-130]

BMI indicates body mass index; BP indicates blood pressure

Table 2: Characteristics of the population and sudomotor function according to age groups

	18 – 30 (n=114; 24%)	31 – 40 (n=108; 23%)	41 – 50 (n=105; 22%)	51 -60 (n=95; 20%)	61 -70 (n=41; 9%)	≥71 (n=12; 2.5%)
ESC_RH, μS	69 [60-76]	66 [56-74]	65 [56-73]	68 [52-75]	63 [54-73] ^a	64 [54-73] ^b
ESC_LH, μS	73 [64-77]	69 [60-77]	68 [57-75]	71 [57-79]	69 [53-73]	62 [38-75]
ESC_RF, μS	80 [74-85]	75 [67-80]	74 [66-79]	72 [61-76]	64 [41-73]	71 [62-78]
ESC_LF, μS	78 [73-84]	74 [66-79]	73 [68-79]	71 [57-77]	59 [41-76]	69 [58-75]

ESC_RH indicates electrochemical skin conductance right hand; ESC_LH indicates electrochemical skin conductance left hand; ESC_RF indicates electrochemical skin conductance right foot; ESC_LF indicates electrochemical skin conductance left foot

Symbol: ^a indicates significant difference with 18 -30 years group; ^b indicates significant difference with 18-30 years group

Table 3: Electrochemical skin conductance (ESC) according to sex and age groups

Age range (years-old)	N (%)	Sex, (N/%)	ESC_RH μS(median)	ESC_RF μS(median)	ESC_LH μS(median)	ESC_LF μS(median)
18-30	114(24%)	Men (59;52%)	73 [65-81]	82 [77-86]	75 [68-81]	82 [77-87]
		Women (55;48%)	65 [56-72]	78 [69-82]	68 [58-74]	77 [70-82]
31-40	108(22.74%)	Men (53;49%)	70 [61-77]	77 [72-82]	70 [62-78]	76 [73-82]
		Women (55;51%)	62 [56-73]	73 [66-78]	67 [56-75]	71 [62-77]
41-50	105(22.11%)	Men (46;44%)	69 [63-78]	77 [69-81]	73 [61-78]	76 [69-80]
		Women (59;56%)	63 [52-71]	72 [64-77]	64 [56-73]	72 [65-78]
51-60	95(20%)	Men (41;43%)	68 [56-77] ^a	70 [61-75]	70 [56-80]	70 [56-74]
		Women (54;57%)	67 [51-71]	72 [62-77]	71 [59-79]	72 [61-72]
61-70	41(8.63%)	Men (14;34%)	64 [56-73] ^b	68 [58-76]	70 [53-72]	67 [56-76]
		Women (27;66%)	59 [50-71]	58 [40-72]	68 [55-73]	53 [35-69]
≥71	12(2.53%)	Men (7;58%)	64 [54-79] ^c	78 [63-80]	62 [37-80]	66 [61-78]
		Women (5;42%)	65 [56-72]	69 [64-74]	63 [54-68]	72 [49-74]

ESC_RH indicates electrochemical skin conductance right hand; ESC_LH indicates electrochemical skin conductance left hand; ESC_RF indicates electrochemical skin conductance right foot; ESC_LF indicates electrochemical skin conductance left foot

Symbol: ^a indicates significant difference with 18 -30 years group; ^b indicates significant difference with 18-30 years group; ^c indicates significant difference with 18 -30 years group