

## RESEARCH ARTICLE

## Sex-based differences and aging in tactile function loss in persons with type 2 diabetes

Stacey L. Gorniak<sup>1\*</sup>, Nereyda Ochoa<sup>1</sup>, Lauren I. Gulley Cox<sup>1</sup>, Aisha Khan<sup>1</sup>, Sahifah Ansari<sup>1</sup>, Beatriz Thames<sup>1</sup>, Haley Ray<sup>1</sup>, Yoshimi F. Lu<sup>1</sup>, Hidetaka Hibino<sup>1</sup>, Nikita Watson<sup>1</sup>, Patrick M. Dougherty<sup>2</sup>

**1** Department of Health and Human Performance, University of Houston, Houston, TX, United States of America, **2** Department of Pain Medicine Research, University of Texas M.D. Anderson Cancer Center, Houston, TX, United States of America

\* [sgorniak@uh.edu](mailto:sgorniak@uh.edu)



## Abstract

## Background

Recent evidence of significant sex-based differences in the presentation of Type 2 Diabetes Mellitus (DM) and its complications has been found in humans, which may contribute to sex-based differences in reduced functionality and quality of life. Some functionality, such as tactile function of the hands, has significant direct impact on quality of life. The purpose of the current study was to explore the impact of DM and sex on tactile function, with consideration of variability in health state measures.

## Research design and methods

A case-control single time point observational study from 2012–2020 in an ethnically diverse population-based community setting. The sample consists of 132 adult individuals: 70 independent community dwelling persons with DM (PwDM) and 62 age- and sex-matched controls (42 males and 90 females in total). The Semmes-Weinstein monofilament test was used to evaluate tactile sensation of the hands.

## Results

Tactile sensation thresholds were adversely impacted by sex, age, degree of handedness, high A<sub>1c</sub>, diagnosis of DM, and neuropathy. Overall, strongly right-handed older adult males with poorly controlled DM and neuropathy possessed the poorest tactile discrimination thresholds. When self-identified minority status was included in a secondary analysis, DM diagnosis was no longer significant; negative impacts of age, neuropathy, degree of handedness, and high A<sub>1c</sub> remained significant.

## Conclusions

The data indicate significant impacts of male sex, age, degree of handedness, self-identified minority status, and metabolic health on the development of poor tactile sensation. This

## OPEN ACCESS

**Citation:** Gorniak SL, Ochoa N, Cox LIG, Khan A, Ansari S, Thames B, et al. (2020) Sex-based differences and aging in tactile function loss in persons with type 2 diabetes. PLoS ONE 15(11): e0242199. <https://doi.org/10.1371/journal.pone.0242199>

**Editor:** Manal S. Fawzy, Suez Canal University Faculty of Medicine, EGYPT

**Received:** June 11, 2020

**Accepted:** October 29, 2020

**Published:** November 12, 2020

**Copyright:** © 2020 Gorniak et al. This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

**Data Availability Statement:** Data Sharing Repository Name: Zenodo (<https://zenodo.org/>) File location: <https://doi.org/10.5281/zenodo.4067003>. What data outputs will the research generate? Protected Health Information Medical Records Information Menopausal Health History Information (if applicable) Adiposity Data (egs. BMI.) Health State Biomarker Data (eg. A1c, blood pressure values) Sensory Function data As public sharing of protected health information such as date of birth, date of diagnosis, dates of treatment and other medical history information pertinent to

each participant may violate HIPAA and the Texas Medical Privacy Act, these data will not be shared to protect patient identity.

**Funding:** This work was supported by American Heart Association Grant (16BGIA27250047) and University of Houston HEALTH Research Institute Basic Biomedical Research Funds to SLG; NIH CA200263 and the H.E.B. Professorship in Cancer Research (PMD). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

**Competing interests:** The authors have declared that no competing interests exist.

combination of modifiable and non-modifiable factors are important considerations in the monitoring and treatment of DM complications.

## Introduction

Over 30 million individuals in the United States (9.4%) are currently living with Type 2 Diabetes Mellitus (DM) [1]. Persons with DM (PwDM) experience declines in hand and finger sensorimotor function as compared to healthy individuals [2–5]; however, self-awareness of these changes is low [2, 5]. Reduced functional hand use has been associated with a loss of independent living and reduced quality of life [6]. Tactile sensitivity loss due to peripheral neuropathy (PN) has been implicated as the primary cause of both sensory and motor deficits in the hands and feet of PwDM [7–10]; however, our recent work has demonstrated that motor changes in PwDM occur independent of such tactile impairment, and appear to be unrelated to disease duration and severity [2–5, 11]. Our data indicate other physiological factors such as vascular dysfunction and functional cortical changes as the underlying mechanism for sensorimotor changes in PwDM [2–5, 11–14]. Due to the confluence of multiple systemic changes in the bodies of PwDM, the contribution of multiple systems—including sex hormone changes and impaired global hemodynamic function—to sensorimotor dysfunction prior to PN diagnosis in PwDM is fully plausible.

Recently, our group found no differences in tactile function of postmenopausal female PwDM as compared to age- and sex-matched controls during the assessment of upper extremity muscle hemodynamics [13]. This finding was intriguing as abnormal hemodynamic function of upper extremity muscle was found in PwDM and supports vascular dysfunction as a potential source of global sensorimotor changes in PwDM [10, 15], particularly in females as females have a higher overall risk of cardiovascular complications with age; however, the lack of between group tactile function differences challenged this point of view. Recent evidence suggests differential presentation of DM and its complications between the sexes—particularly with increased age [1, 16, 17]—potentially due to the anti-inflammatory, cardio-protective, and neuro-protective properties of testosterone [18]. Given that the dataset included only females, it is possible that sex hormones play a significant role in the maintenance or degradation of tactile function in conjunction with DM and aging.

In support of potential sex-based differences in sensory function and aging, some sensory differences have been found to exist between males and females (e.g., proprioception) [19, 20]. Additionally, it has been reported that females exhibit generation of more spinal excitatory potentials as compared to males [20]. It is not clear if these sex-based differences in sensory function persist, are exacerbated by, are or mitigated by the development and progression of DM.

In particular, older adult females are more negatively impacted by risks and complications associated with DM; which are linked to metabolic and sex-hormone changes during the transition from perimenopause to menopause [21]. As testosterone levels begin to decrease prior to perimenopause, the risk for development of cardiovascular disease (CVD), DM, increased adiposity, and systemic inflammation is enhanced. It is speculated that reduced testosterone and its anti-inflammatory effects in combination with the absence of neuroprotective estrogen in postmenopausal females negatively impact hemodynamic response, leading to worsened overall health outcomes for older adult females [22]. However, it is also known that PN occurs more frequently and earlier in males than in females [23–26]. Although the rate of progression to PN is comparable between sexes, significant sex-based differences in response to DM

prevention interventions exists and resultant persistent sex-differences in DM comorbidities abound [27].

In order to explore the potential interaction of DM and sex specifically on tactile function, we have compiled tactile function assessment and health state information data for all studies performed in our laboratory from 2012 through 2020. The purpose of this compilation was to examine the data for impacts of sex, aging, PN, and measures of metabolic health (e.g., glycated hemoglobin,  $A_{1c}$ ) on tactile function. *A priori*, based on reports of increased risk of cardiovascular complications in female PwDM in the evidence base, we hypothesized that females would have worsened tactile function measures as compared to males, with negative impacts of increased age, PN diagnosis, and worsened metabolic health all contributing beyond sex-related impacts. Such findings would reinforce the evidence of sex-based differences in DM presentation in humans, which may directly contribute to sex-based differences in reduced functionality and quality of life with DM [28].

## Methods

### Participants

One hundred and thirty-two (132) adult individuals took part in this case-control single time point observational study from 2012–2020 in Houston, TX, USA. This sample consists of 70 independent community dwelling PwDM and 62 age- and sex-matched independent community dwelling controls (42 males and 90 females in total). A total of 27 cases of PN within the sample were found (20.7%). A total of 61 participants (46.2%) self-identified as either black/ African American or Hispanic/Latino (henceforth referred to as minority persons). Average characteristics for study participants can be found in Table 1. Handedness was assessed by the Edinburgh Inventory [29], ranging from a laterality quotient (LQ) of  $-100$  (strong left-handedness) to  $+100$  (strong right-handedness). All study participants were right-handed based on an LQ of  $> +40$  [29]. Study participants were excluded if they reported a history of neurological and/or musculoskeletal disorders such as: Parkinson disease, Huntington's disease, polio, multiple sclerosis, stroke, traumatic brain injury, carpal tunnel syndrome, rheumatoid arthritis, Monoclonal Gammopathy of Undetermined Significance (MGUS), Paraproteinemic Demyelinating Neuropathy (PDN), Myasthenia Gravis, amputation, or other known hereditary or

**Table 1. Demographic description for study participants.**

	PwDM		Controls	
	M	F	M	F
N	22	48	20	42
Age (years)	64.6 ± 9.0	63.0 ± 6.3	62.9 ± 6.8	63.5 ± 7.1
BMI (kg/m <sup>2</sup> )	31.0 ± 6.7	30.7 ± 7.0	27.1 ± 3.3	27.9 ± 7.1
A <sub>1c</sub> (%)	7.8 ± 1.6	6.5 ± 1.5	5.3 ± 0.2	5.4 ± 0.4
A <sub>1c</sub> (mmol/mol)	62 ± 17	48 ± 16	34 ± 3	36 ± 4
LQ	95 ± 10	97 ± 7	94 ± 8	97 ± 8
SYS (mmHg)	146 ± 17	140 ± 23	137 ± 12	140 ± 21
DIA (mmHg)	83 ± 13	82 ± 14	81 ± 10	83 ± 14
# cases PN	7 (5.4%)	17 (13.1%)	0 (0%)	3 (2.3%)
# self-identify as minority	9 (6.9%)	34 (25.8%)	1 (0.1%)	17 (13.1%)

Values are mean ± SD or count (% of entire sample). Entire sample is 132 participants. A<sub>1c</sub> = glycated hemoglobin, BMI = body mass index, DIA = diastole, F = female, LQ = laterality quotient, M = male, PN = peripheral neuropathy, PwDM = person with Type 2 Diabetes, SYS = systole.

<https://doi.org/10.1371/journal.pone.0242199.t001>

compression neuropathies. In accordance with the Declaration of Helsinki, participants provided written informed consent according to the regulations established by the Institutional Review Board at the University of Houston. The University of Houston Institutional Review Board approved all study procedures.

### Health status information

Glycated hemoglobin ( $A_{1c}$ ) values were assessed for all study participants on site.  $A_{1c}$  values were assessed using a commercially available point of care evaluation kit ( $A_{1c}$  Now+, PTS Diagnostics, Indianapolis, IN, USA). Blood pressure was measured for 113 of the study participants using a commercially available device (Omron Intellisense 10 series Blood Pressure Monitor, Model BP785, Bannockburn, IL, USA); blood pressure was not measured in our first study of the series in 2012. The presence of peripheral neuropathy (PN status) was determined by abnormalities on either clinical examination or EMG/NCV testing (per physician).

### Sensory evaluations

The Semmes-Weinstein monofilament test was used to evaluate tactile sensation of the hands. Monofilament testing sites included the following sites (and respective nerves): tip of the thumb/digit 1 (median nerve), the tip of digit 5 (ulnar nerve), and dorsal aspect of the thumb (radial nerve). During the test, participants kept their eyes closed and verbally indicated if and where they perceived monofilament touch. The monofilament size was increased in an ascending manner from the smallest monofilament unit until the subject was able to detect its touch a minimum of 2 times at the same location.

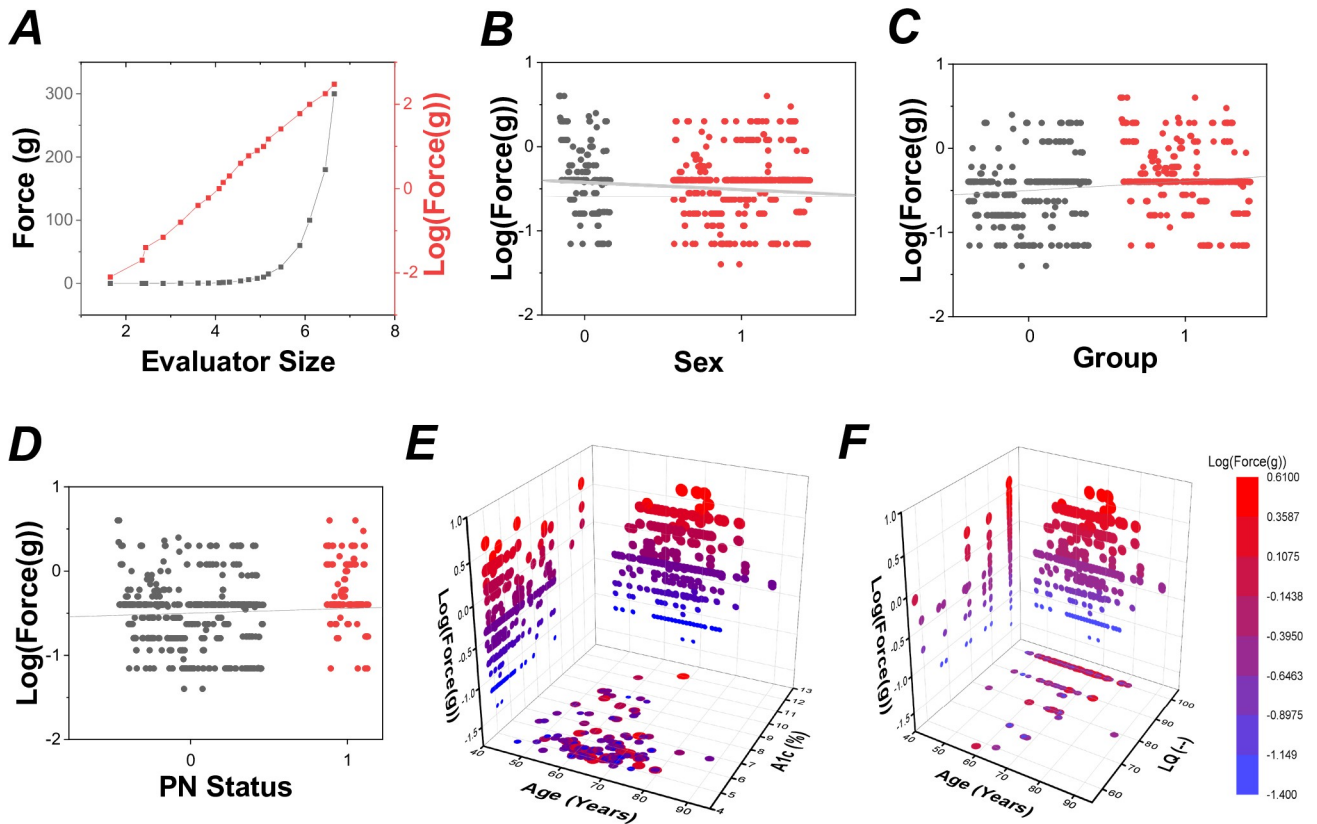
### Statistical analyses

Data were compared between groups using mixed model regressions and subsequent analyses of covariance (ANCOVAs) via SPSS 25 (IBM Corporation, Armonk, NY, USA) and Minitab 17 (Minitab LLC, State College, PA, USA). Monofilament data were log transformed ( $\text{Log}_{10}(\text{Force(g)})$ ) due to non-linearity, illustrated in Fig 1A. Between-subject categorical factors for  $\text{Log}_{10}(\text{Force(g)})$  measures were *Group* (two levels: PwDM and age- and sex-matched controls) and *Sex* (two levels: male and female). Evaluation of monofilament testing site (e.g., median, radial, and ulnar nerves) as well as hand (right versus left) did not produce significant results in our analyses; thus, data are averaged across testing site and hand in the reported results. Evaluation of health state covariates was done to control for health state variability, both within and across the two sample groups. Health state covariates initially considered were: age,  $A_{1c}$ , systole, diastole, disease duration (Duration), body mass index (BMI), PN status (via indicator variable), laterality quotient (LQ), and self-identification of belonging to a minority group (black/African American or Hispanic/Latino, via indicator variable). Covariates were selected via Automatic Linear Modeling (ALM) using forward stepwise selection functions in SPSS. In the event of significant covariates determined via ALM in SPSS and mixed regression/ANCOVA in Minitab, follow-up correlation analyses were performed between the health state covariate and tactile sensory function in Minitab.

## Results

### Tactile evaluation

Significant differences in tactile detection thresholds were found between categorical values in *Group* ( $F_{1,616} = 7.42, p < 0.01$ ), *Sex* ( $F_{1,616} = 12.20, p < 0.001$ ), and positive *PN status* ( $F_{1,616} = 20.31, p < 0.001$ ); such that PwDM, males, and those with a history of PN had worsened



**Fig 1. Monofilament data.** A: Relationship between monofilament size and associated force sensitivity thresholds (in g). Monofilament data were log transformed ( $\text{Log}_{10}(\text{Force(g)})$ ) due to non-linearity inherent to measurement scale. B: Relationship between tactile threshold and Sex; 0 = male, 1 = female. The shaded gray region denotes the 95% confidence interval about the mean value. C: Relationship between tactile threshold and Group; 0 = control, 1 = PwDM. The shaded gray region denotes the 95% confidence interval about the mean value. D: Relationship between tactile threshold and PN status; 0 = no history, 1 = history of PN. The shaded gray region denotes the 95% confidence interval about the mean value. E: Relationship among tactile threshold, chronological age, and glycated hemoglobin ( $A_{1c}$ ). The projection of the 3D data set is shown for each plane of interest. F: Relationship among tactile threshold, chronological age, and laterality quotient (LQ). The projection of the 3D data set is shown for each plane of interest.

<https://doi.org/10.1371/journal.pone.0242199.g001>

detection thresholds, as shown in Fig 1B–1D. A Group  $\times$  Sex interaction was not found. Tactile detection thresholds were further exacerbated by: increased Age ( $F_{1,616} = 7.23, p < 0.01$ ), larger LQ values ( $F_{1,616} = 10.69, p < 0.001$ ), and higher  $A_{1c}$  ( $F_{1,616} = 8.85, p < 0.005$ ). A significant influence of Duration ( $F_{1,616} = 4.75, p < 0.05$ ) was also found. A Group  $\times$  Sex interaction was not found. Fig 1E and 1F illustrate these relationships. Coefficients of the full regression equation for  $\text{Log}_{10}(\text{Force(g)})$  can be found in Table 2.

As incidence of DM is higher in minority persons, we explored the impact of self-declared minority status on  $\text{Log}_{10}(\text{Force(g)})$ , using the same statistical approach. When Minority status ( $F_{1,615} = 11.63, p < 0.001$ ) was included in the model, the Group effect was no longer significant and thus omitted from the secondary regression model. Significant deleterious impacts of male Sex ( $F_{1,615} = 20.15, p < 0.001$ ), positive PN status ( $F_{1,615} = 25.51, p < 0.001$ ), increased Age ( $F_{1,615} = 9.19, p < 0.001$ ), larger LQ values ( $F_{1,615} = 9.95, p < 0.005$ ), and higher  $A_{1c}$  ( $F_{1,615} = 7.19, p < 0.01$ ) persisted in the secondary model. The influence of Duration ( $F_{1,615} = 3.87, p = 0.05$ ) was also found to be at significance. A Group  $\times$  Sex interaction was not found. Coefficients of the secondary regression equation for  $\text{Log}_{10}(\text{Force(g)})$  can be found in Table 2.

Simple bivariate correlation values of  $\text{Log}_{10}(\text{Force(g)})$  and variables of interest can be found in Table 3.

Table 2. Original and secondary regression equation details for  $\text{Log}_{10}(\text{Force(g)})$ .

Factor	Coefficient	t-value	p-value	Coding Notes
<b>Original Regression Model</b>				
Age (years)	0.00585	2.69	< 0.01	N/A
A <sub>1c</sub> (%)	0.0507	2.97	< 0.005	N/A
Duration (months)	-0.000718	-2.18	< 0.05	N/A
Group	0.1031	2.72	< 0.01	0 = Control 1 = PwDM
LQ	0.0064	3.27	< 0.001	> +40 (right-handed)
PN status	0.1765	4.51	< 0.001	0 = No history of PN 1 = PN diagnosis
Sex	-0.1203	-3.49	< 0.001	0 = Male 1 = Female
Regression constant	-1.726	-6.68	< 0.001	N/A
<b>Secondary Regression Model</b>				
Age (years)	0.00657	3.03	< 0.005	N/A
A <sub>1c</sub> (%)	0.0455	2.68	< 0.01	N/A
Duration (months)	-0.000644	-1.97	0.05	N/A
LQ	0.00613	3.15	< 0.005	> +40 (right-handed)
Minority status	0.1181	3.41	< 0.001	0 = Does not identify as minority person 1 = Does identify as minority person
PN status	0.1989	5.05	< 0.001	0 = No history of PN 1 = PN diagnosis
Sex	-0.1635	-4.49	< 0.001	0 = Male 1 = Female
Regression constant	-1.719	-6.70	< 0.001	N/A

A<sub>1c</sub> = glycated hemoglobin, LQ = laterality quotient, N/A = not applicable, PN = peripheral neuropathy, PwDM = person with Type 2 Diabetes.

<https://doi.org/10.1371/journal.pone.0242199.t002>

Assessment of data from only PwDM indicated significant differences in tactile detection thresholds in persons with positive *PN status* ( $F_{1,261} = 15.12$ ,  $p < 0.001$ ), but not *Sex*. Tactile detection thresholds were further exacerbated by high *Diastole* values ( $F_{1,261} = 19.20$ ,  $p < 0.001$ ). Coefficients of the PwDM specific regression equation for  $\text{Log}_{10}(\text{Force(g)})$  can be found in Table 4. Posthoc inclusion of *Diastole* in the primary and secondary models for the entire data set as a single factor and as an interactive factor did not produce significant results.

Table 3. Bivariate regression values for  $\text{Log}_{10}(\text{Force(g)})$  and variables of interest across the full data set.

Factor	r	p-value
Age (years)	0.075	0.056
A <sub>1c</sub> (%)	0.221	< 0.001
Duration (months)	0.094	< 0.05
Minority status	0.117	< 0.005
Group	0.225	< 0.001
LQ	0.125	< 0.005
PN status	0.233	< 0.001
Sex	-0.144	< 0.001

A<sub>1c</sub> = glycated hemoglobin, LQ = laterality quotient, PN = peripheral neuropathy.

<https://doi.org/10.1371/journal.pone.0242199.t003>

## Discussion

The purpose of the current study was to explore the potential influence of DM and sex on tactile function, with consideration of variability in health state measures (e.g., PN diagnosis and  $A_{1c}$ ) in the statistical models. This study is a step towards better understanding sex-based differences in DM complications with aging. *A priori*, based on increased risk of cardiovascular complications in female PwDM in the evidence base, we hypothesized that females will have worsened tactile function measures as compared to males, with negative impacts of increased age, PN diagnosis, and worsened metabolic health all contributing beyond sex-related impacts. Our data indicate an opposite finding to our hypothesis with respect to sex-based differences in tactile function, yet provide evidence of significant impacts due to age, degree of handedness (via laterality quotient), self-identified minority status, and metabolic health. In the following paragraphs, we discuss sex-based differences in tactile function with respect to the evidence base, potential non-modifiable bases for these differences, and implications for both clinicians and patients.

### Influence of sex on sensory function and cortical structure/function

Contrary to our hypothesis, the data indicate general worsened tactile function in adult males as compared to adult females, independent of chronological age. Tactile sensation thresholds were additionally adversely impacted by chronological age and diagnosis of DM and PN, such that older adult males with DM and PN possessed the poorest tactile discrimination thresholds. This is consistent with reports of higher sensory sensitivity in healthy adult females without DM [30, 31] as well as reports of more frequent and earlier presentation of PN in males with DM [23–26]. While the presence of DM and PN were the most significant factors for reduce tactile function in PwDM, sex-based differences existed when the entire sample was considered, suggesting baseline sex-differences in tactile function. The root of these sex-based differences may stem from several sources. While testosterone may generally be considered anti-inflammatory, cardio-protective, and neuro-protective [18], these effects may not directly impact on peripheral nerve function. Instead, estrogen, estrogen signaling, and other androgens may play a larger role in the maintenance of peripheral nerves [32, 33]. Thus, it is possible that hormone therapy could be a potential pathway to preserving peripheral nerve function in males of advanced age prior to development of DM.

Additionally, evidence exists for sexual dimorphism and asymmetry of the cortex [33], indicating a confluence of central and peripheral impacts on tactile function. This sexual dimorphism presents as less cortical asymmetry (i.e., less lateralization) in both structure and function in females [30, 33, 34]. This presentation has been found to vary with handedness [30, 33, 34], consistent with our results. Within this specific area of research, it is not clear as to which of the sex hormones are specifically responsible for the dimorphism; as the complex interaction and impact of testosterone, androgens, and other confounding physiological factors have shown inconsistent trends [33].

Further support for sex-based differences in neurological function via the cortex arises from more mechanistic investigations of cortical dimorphism. Specifically, males are found to have a larger number of cortical neurons; however, these cortical neurons are generally smaller in size as compared to females [35]. It is possible that with aging, these smaller neurons may be at higher risk for degradation in males, given the recent report of persistent metabolic youth in the aging female brain as compared to males [36]. This chronological metabolic difference may also explain the earlier presentation and presence of neurological symptoms (e.g., PN) in males with DM [23–25, 37].

Table 4. PwDM specific regression equation details for  $\text{Log}_{10}(\text{Force}(\text{g}))$ .

Factor	Coefficient	t-value	p-value	Coding Notes
<i>PwDM Regression Model</i>				
Diastole (mmHg)	0.00679	4.38	< 0.001	N/A
PN status	0.1817	3.89	< 0.001	0 = No history of PN 1 = PN diagnosis
Regression constant	-1.059	-8.27	< 0.001	N/A

PN = peripheral neuropathy.

<https://doi.org/10.1371/journal.pone.0242199.t004>

### (Non-)modifiable factors to tactile function and implications for clinicians and patients

The findings of the present study provide insight into a combination of modifiable and non-modifiable factors for clinicians to consider when treating complications of DM. The data reinforce the known importance of several factors associated with DM prevention such as controlling  $A_{1c}$  (glycated hemoglobin) and development of DM. Consistent with current clinical practice, prevention of DM, control of blood pressure, and control of long-term blood sugar across the lifespan are thus emphasized as the most modifiable factors leading to DM complications, including development of diabetic PN. These factors are so significant that they overtook other factors (including sex) contributing to tactile sensation loss in persons diagnosed with DM in the current study. It is essential to control these modifiable factors to prevent irreversible sensory loss in PwDM. Continued monitoring for DM while pursuing preventive measures for DM development by both the patient and clinician are strongly encouraged [38]. The preventive and treatment implications for patients are significant, as patients need to be aware of their control over the development of DM, its myriad complications, and the severity of potential long-term irreversible outcomes of DM. Reinforcement of this concept is critical to preserving long term peripheral nerve function.

The data also indicate a number of non-modifiable factors—such as chronological age, sex, and minority status—as significant in the development of tactile function loss as a DM complication. Despite the non-modifiable nature of these factors, they should be considered as risk factors in monitoring for DM and its complications [38]. Given the increased incidence of DM in minority populations, the development of significant tactile function loss in minority persons in the current sample reinforces the current clinical practice of additional medical monitoring for DM and its complications in persons who self-identify as a minority person.

Last, factors such as degree of handedness/laterality and sex-hormones also played a role in the current findings. There is significant interplay between these two factors, such that handedness/laterality is connected to sexual dimorphism [39, 40]. There is some evidence that handedness may be modifiable in the prenatal and early postnatal timeframes [40]; however, this is not a practical modifiable factor for clinicians treating older adults with DM. While there is some evidence of handedness being linked to cultural hand use and learning, the physiological roots of handedness/laterality typically minimize these social impacts [39]. Note that the study sample did not contain participants who were stroke survivors or persons with amputation, as the cortical plasticity associated with both conditions confounds sensorimotor function and functional hand use in both populations [41, 42].

### Conclusions

The purpose of the current study was to explore the potential interaction of DM and sex on tactile function, with consideration of variability in health state measures. The data indicate



significant impacts of sex, age, degree of handedness/laterality, self-identified minority status, and metabolic health on the development of poor tactile sensation. We have discussed the sex-based differences in tactile function with respect to the evidence base, potential non-modifiable bases for these differences, and implications for both clinicians and patients.

## Acknowledgments

We would like to thank Jeff Min-In Yau for his helpful feedback on this project. SLG had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

## Author Contributions

**Conceptualization:** Stacey L. Gorniak, Patrick M. Dougherty.

**Data curation:** Stacey L. Gorniak, Lauren I. Gulley Cox, Aisha Khan, Sahifah Ansari, Beatriz Thames, Haley Ray, Yoshimi F. Lu, Hidetaka Hibino, Nikita Watson.

**Formal analysis:** Stacey L. Gorniak.

**Funding acquisition:** Stacey L. Gorniak, Patrick M. Dougherty.

**Investigation:** Stacey L. Gorniak, Nereyda Ochoa, Lauren I. Gulley Cox, Aisha Khan, Sahifah Ansari, Beatriz Thames, Haley Ray, Yoshimi F. Lu, Hidetaka Hibino, Nikita Watson.

**Methodology:** Stacey L. Gorniak, Nereyda Ochoa, Lauren I. Gulley Cox, Aisha Khan, Sahifah Ansari, Beatriz Thames, Haley Ray, Yoshimi F. Lu, Hidetaka Hibino, Patrick M. Dougherty.

**Project administration:** Stacey L. Gorniak, Lauren I. Gulley Cox, Nikita Watson, Patrick M. Dougherty.

**Resources:** Stacey L. Gorniak, Patrick M. Dougherty.

**Software:** Stacey L. Gorniak, Hidetaka Hibino.

**Supervision:** Stacey L. Gorniak, Nereyda Ochoa, Lauren I. Gulley Cox, Aisha Khan, Haley Ray, Hidetaka Hibino.

**Validation:** Stacey L. Gorniak.

**Visualization:** Stacey L. Gorniak, Hidetaka Hibino.

**Writing – original draft:** Stacey L. Gorniak.

**Writing – review & editing:** Stacey L. Gorniak, Nereyda Ochoa, Lauren I. Gulley Cox, Aisha Khan, Sahifah Ansari, Beatriz Thames, Haley Ray, Yoshimi F. Lu, Hidetaka Hibino, Nikita Watson, Patrick M. Dougherty.

## References

1. National Diabetes Statistics Report, 2017. In: National Diabetes Statistics Report, 2017 [Internet]. [cited 16 Apr 2018]. Available: <http://www.diabetes.org/assets/pdfs/basics/cdc-statistics-report-2017.pdf>
2. Gorniak SL, Khan A, Ochoa N, Sharma M, Phan CL. Detecting Subtle Fingertip Sensory and Motor Dysfunction in Adults with Type II Diabetes. *Exp Brain Res*. 2014; 232: 1283–1291. <https://doi.org/10.1007/s00221-014-3844-x> PMID: 24468726
3. Ochoa N, Gogola GR, Gorniak SL. Contribution of tactile dysfunction to manual motor dysfunction in type II diabetes. *Muscle Nerve*. 2016; 54: 895–902. <https://doi.org/10.1002/mus.25137> PMID: 27061801

4. Ochoa N, Gorniak SL. Changes in sensory function and force production in adults with type II diabetes. *Muscle Nerve*. 2014; 50: 984–990. <https://doi.org/10.1002/mus.24261> PMID: 24710967
5. Gorniak SL, Ray H, Lee B-C, Wang J. Cognitive–Motor Impairment in Manual Tasks in Adults With Type 2 Diabetes: OTJR Occup Particip Health. 2019; 40: 113–121. <https://doi.org/10.1177/1539449219880536> PMID: 31658863
6. Snoek GJ, IJzerman MJ, Hermens HJ, Maxwell D, Biering-Sorensen F. Survey of the needs of patients with spinal cord injury: impact and priority for improvement in hand function in tetraplegics. *Spinal Cord*. 2004; 42: 526–532. <https://doi.org/10.1038/sj.sc.3101638> PMID: 15224087
7. Casanova JE, Casanova JS, Young MJ. Hand function in patients with diabetes mellitus. *South Med J*. 1991; 84: 1111–1113. <https://doi.org/10.1097/00007611-199109000-00013> PMID: 1891732
8. Cederlund RI, Thomsen N, Thrainsdottir S, Eriksson KF, Sundkvist G, Dahlin LB. Hand disorders, hand function, and activities of daily living in elderly men with type 2 diabetes. *J Diabetes Complications*. 2009; 23: 32–39. <https://doi.org/10.1016/j.jdiacomp.2007.09.002> PMID: 18413154
9. Sayer AA, Dennison EM, Syddall HE, Gilbody HJ, Phillips DIW, Cooper C. Type 2 diabetes, muscle strength, and impaired physical function: the tip of the iceberg? *Diabetes Care*. 2005; 28: 2541–2542. <https://doi.org/10.2337/diacare.28.10.2541> PMID: 16186295
10. Allen MD, Kimpinski K, Doherty TJ, Rice CL. Length dependent loss of motor axons and altered motor unit properties in human diabetic polyneuropathy. *Clin Neurophysiol Off J Int Fed Clin Neurophysiol*. 2014; 125: 836–843. <https://doi.org/10.1016/j.clinph.2013.09.037> PMID: 24168843
11. Gorniak SL, Lu FY, Lee BC, Massman PJ, Wang J. Cognitive impairment and postural control deficit in adults with Type 2 diabetes. *Diabetes Metab Res Rev*. 2019; e3089. <https://doi.org/10.1002/dmrr.3089> PMID: 30338902
12. Gorniak SL, Wagner VE, Vaughn K, Perry J, Cox LG, Hernandez AE, et al. Functional neuroimaging of sensorimotor cortices in postmenopausal women with type II diabetes. *Neurophotonics*. 2020; 7: 035007. <https://doi.org/10.1117/1.NPh.7.3.035007> PMID: 32905073
13. Pollonini L, Gullely Cox L, Gorniak SL. Hemodynamic Function of Forearm Muscle in Postmenopausal Women With Type 2 Diabetes. *J Aging Phys Act*. 2020; 1–8. <https://doi.org/10.1123/japa.2019-0221> PMID: 32315982
14. Thames BH, Gorniak SL. Coefficient of Friction at the Fingertips in Type II Diabetics Compared to Healthy Adults. *J Appl Biomech*. 2017; 33: 185–188. <https://doi.org/10.1123/jab.2016-0147> PMID: 27918701
15. Zochodne DW. Diabetes mellitus and the peripheral nervous system: manifestations and mechanisms. *Muscle Nerve*. 2007; 36: 144–166. <https://doi.org/10.1002/mus.20785>
16. Seghieri G, Policardo L, Anichini R, Franconi F, Campesi I, Cherchi S, et al. The Effect of Sex and Gender on Diabetic Complications. *Curr Diabetes Rev*. 2017; 13: 148–160. <https://doi.org/10.2174/1573399812666160517115756> PMID: 27183843
17. Campesi I, Franconi F, Seghieri G, Meloni M. Sex-gender-related therapeutic approaches for cardiovascular complications associated with diabetes. *Pharmacol Res*. 2017; 119: 195–207. <https://doi.org/10.1016/j.phrs.2017.01.023> PMID: 28189784
18. Bialek M, Zaremba P, Borowicz KK, Czuczwar SJ. Neuroprotective role of testosterone in the nervous system. *Pol J Pharmacol*. 2004; 56: 509–518. PMID: 15591638
19. Ko S-U, Simonsick E, Deshpande N, Ferrucci L. Sex-specific age associations of ankle proprioception test performance in older adults: results from the Baltimore Longitudinal Study of Aging. *Age Ageing*. 2015; 44: 485–490. <https://doi.org/10.1093/ageing/afv005> PMID: 25637144
20. Cheng Y, Decety J, Lin C-P, Hsieh J-C, Hung D, Tzeng OJL. Sex differences in spinal excitability during observation of bipedal locomotion. *NeuroReport*. 2007; 18: 887. <https://doi.org/10.1097/WNR.0b013e3280ebb486> PMID: 17515795
21. Riedel BC, Thompson PM, Brinton RD. Age, APOE and Sex: Triad of Risk of Alzheimer’s Disease. *J Steroid Biochem Mol Biol*. 2016; 160: 134–147. <https://doi.org/10.1016/j.jsbmb.2016.03.012> PMID: 26969397
22. Moreau KL. Modulatory influence of sex hormones on vascular aging. *Am J Physiol Heart Circ Physiol*. 2019; 316: H522–H526. <https://doi.org/10.1152/ajpheart.00745.2017> PMID: 30632767
23. Booya F, Bandarian F, Larijani B, Pajouhi M, Nooraei M, Lotfi J. Potential risk factors for diabetic neuropathy: a case control study. *BMC Neurol*. 2005; 5: 24. <https://doi.org/10.1186/1471-2377-5-24> PMID: 16336693
24. Szalat A, Aryan S, Raz I, Itamar R. Gender-specific care of diabetes mellitus: particular considerations in the management of diabetic women. *Diabetes Obes Metab*. 2008; 10: 1135–1156. <https://doi.org/10.1111/j.1463-1326.2008.00896.x> PMID: 18494812

25. Basit A, Hydrie MZI, Hakeem R, Ahmedani MY, Masood Q. Frequency of chronic complications of type II diabetes. *J Coll Physicians Surg—Pak JCPSP*. 2004; 14: 79–83. <https://doi.org/10.2004/JCPSP.7983> PMID: 15228868
26. Aaberg ML, Burch DM, Hud ZR, Zacharias MP. Gender differences in the onset of diabetic neuropathy. *J Diabetes Complications*. 2008; 22: 83–87. <https://doi.org/10.1016/j.jdiacomp.2007.06.009> PMID: 18280437
27. Perreault L, Ma Y, Dagogo-Jack S, Horton E, Marrero D, Crandall J, et al. Sex differences in diabetes risk and the effect of intensive lifestyle modification in the Diabetes Prevention Program. *Diabetes Care*. 2008; 31: 1416–1421. <https://doi.org/10.2337/dc07-2390> PMID: 18356403
28. Fritschi C, Bronas UG, Park CG, Collins EG, Quinn L. Early declines in physical function among aging adults with type 2 diabetes. *J Diabetes Complications*. 2017; 31: 347–352. <https://doi.org/10.1016/j.jdiacomp.2016.06.022> PMID: 27450624
29. Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia*. 1971; 9: 97–113. [https://doi.org/10.1016/0028-3932\(71\)90067-4](https://doi.org/10.1016/0028-3932(71)90067-4) PMID: 5146491
30. Adamo DE, Scotland S, Martin BJ. Upper limb kinesthetic asymmetries: Gender and handedness effects. *Neurosci Lett*. 2012; 516: 188–192. <https://doi.org/10.1016/j.neulet.2012.03.077> PMID: 22490887
31. Chung SJ, Jeon SR, Kim SR, Sung YH, Lee MC. Bilateral Effects of Unilateral Subthalamic Nucleus Deep Brain Stimulation in Advanced Parkinson's Disease. *Eur Neurol*. 2006; 56: 127–132. <https://doi.org/10.1159/000095704> PMID: 16960454
32. Acosta MC, Copley PA, Harrell JR, Wilhelm JC. Estrogen signaling is necessary for exercise-mediated enhancement of motoneuron participation in axon regeneration after peripheral nerve injury in mice. *Dev Neurobiol*. 2017; 77: 1133–1143. <https://doi.org/10.1002/dneu.22501> PMID: 28388831
33. Wisniewski A. SEXUALLY-DIMORPHIC PATTERNS OF CORTICAL ASYMMETRY, AND THE ROLE FOR SEX STEROID HORMONES IN DETERMINING CORTICAL PATTERNS OF LATERALIZATION. *Psychoneuroendocrinology*. 1998; 23: 519–547. [https://doi.org/10.1016/s0306-4530\(98\)00019-5](https://doi.org/10.1016/s0306-4530(98)00019-5) PMID: 9802126
34. Amunts K, Jäncke L, Mohlberg H, Steinmetz H, Zilles K. Interhemispheric asymmetry of the human motor cortex related to handedness and gender. *Neuropsychologia*. 2000; 38: 304–312. [https://doi.org/10.1016/s0028-3932\(99\)00075-5](https://doi.org/10.1016/s0028-3932(99)00075-5) PMID: 10678696
35. Rabinowicz T, Petetot JMcD-C, Gartside PS, Sheyn D, Sheyn T, De Courten-Myers GM. Structure of the cerebral cortex in men and women. *J Neuropathol Exp Neurol*. 2002; 61: 46–57. <https://doi.org/10.1093/jnen/61.1.46> PMID: 11829343
36. Goyal MS, Blazey TM, Su Y, Couture LE, Durbin TJ, Bateman RJ, et al. Persistent metabolic youth in the aging female brain. *Proc Natl Acad Sci*. 2019; 116: 3251–3255. <https://doi.org/10.1073/pnas.1815917116> PMID: 30718410
37. Aaberg ML, Burch DM, Hud ZR, Zacharias MP. Gender differences in the onset of diabetic neuropathy. *J Diabetes Complications*. 2008; 22: 83–87. <https://doi.org/10.1016/j.jdiacomp.2007.06.009> PMID: 18280437
38. American Diabetes Association. *Standards of Medical Care in Diabetes—2019* Abridged for Primary Care Providers. *Clin Diabetes*. 2019; 37: 11–34. <https://doi.org/10.2337/cd18-0105> PMID: 30705493
39. Hugdahl K, Davidson RJ. *The Asymmetrical Brain*. MIT Press; 2004.
40. Witelson SF, Nowakowski RS. Left out axons make men right: a hypothesis for the origin of handedness and functional asymmetry. *Neuropsychologia*. 1991; 29: 327–333. [https://doi.org/10.1016/0028-3932\(91\)90046-b](https://doi.org/10.1016/0028-3932(91)90046-b)
41. Bütefisch CM. Plasticity in the human cerebral cortex: lessons from the normal brain and from stroke. *Neurosci Rev J Bringing Neurobiol Neurol Psychiatry*. 2004; 10: 163–173. <https://doi.org/10.1177/1073858403262152> PMID: 15070490
42. Makin TR, Scholz J, Henderson Slater D, Johansen-Berg H, Tracey I. Reassessing cortical reorganization in the primary sensorimotor cortex following arm amputation. *Brain J Neurol*. 2015; 138: 2140–2146. <https://doi.org/10.1093/brain/aww161> PMID: 26072517