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A smartphone-based tool for screening diabetic neuropathies: A mHealth and 3D printing approach

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ABSTRACT

Diabetic neuropathy, a nerve damage associated with diabetes mellitus, can lead to severe disabilities, morbidity, and mortality, if not diagnosed in a timely manner. Diabetic neuropathies represent a huge economic burden and are a growing problem in sub-Saharan Africa, where they affect up to 61% of the diabetic population. Therefore, the United Nations (UN) has included the reduction of the diabetes-related mortality, as a priority in the Sustainable Development Agenda. A review of the current existing solutions for diabetic patients highlighted the fact that many are focused on lifestyle management and glycemia monitoring, while less are available for diabetic neuropathies screening, in particular in the digital health field. Beyond cutting-edge screening methods, which are time-consuming and equipment-heavy, traditional ones are effective, but they require specialised knowledge, which often lacks in low-resource settings. These settings, specifically those in low-income countries, are challenged by the lack of expertise, funds, spare parts, and consumables and harsh environmental conditions, which hinder the safe use of medical devices. This paper proposes a smart-tool for the screening of diabetic neuropathies based on the effective combination of three already established methods, through 3D-printed accessories and a smartphone app, aiming at contributing towards the UN's Sustainable Development Goal 3, as well as the fourth industrial revolution in healthcare. Moreover, an on-field evaluation for this smart-tool is ongoing. So far, we recruited 11 normosubjects as a pilot study. The results demonstrate that it could be a viable solution to improve the standard of care of diabetic patients, specifically in the field of diabetic neuropathy screening, globally, as well as locally in low-resource settings.

1. Introduction

Diabetic neuropathies, the top cause of neuropathy in the world, are nerve damages associated with diabetes mellitus [1]. Although their aetiology is multifactorial, one of the main causes behind nerve damage is the direct effect of long-term hyperglycemia, which reduces nerve perfusion [2–4]. A recent editorial by Papanas [5] pointed to diabetic peripheral neuropathy as the most common form of diabetic neuropathy and the most frequent manifestation of diabetes mellitus in the nervous system. A distinction should be made between type 1 and type 2 diabetes, because in patients with type 2 diabetes, even when blood glucose levels are under control, there is a high risk of developing neuropathy [6]. Among the different kinds of diabetic neuropathies, sensorimotor polyneuropathy affects nerve cells, fibers and coverings, causing nerve signal transmission to be harmed to the point that a nerve's activity is completely halted [7]. Symptoms include burning and/or deep pain, hyperesthesia, loss of touch, vibration, pressure, and temperature, beginning in the toes and gradually ascending to the lower limbs. This reduced sensitivity can increase the chances of developing non-healing ulcers and infections, which can lead to amputations and eventually death [8–10]. Early diagnosis of such condition is, therefor, key [5].

The prevalence of diabetes has been increasing since the 1980s, reaching 463 millions in 2019 and is expected to reach 700 million cases in 2045, worldwide. About 79% of the cases are from low- and middle-income countries (LMICs), which are also those that experienced a faster surge. In fact, diabetes is among the most prevalent noncommunicable diseases (NCDs) in sub-Saharan Africa (SSA) and has been responsible for an ever-growing number of disabilities, morbidity, and mortality since 1990 [11,12]. Specifically, diabetic neuropathy, one of the most recurrent diabetes-related health issues [13], is an increasing problem in SSA, where it affects up to 61% of people with diabetes [14]. In addition, the annual costs of diabetic peripheral neuropathies and their complications were estimated to be 4.6–13.7 billion

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US dollars in 2001 in the US only, representing a huge economic burden [15,16]. More recent costs were reported by Chapman et al. [17], who reported that the average inpatient and outpatient costs per patient with severe neuropathies were greater than €8700, over than 13 times higher than patients without any diagnosed neuropathy. In another recent study, Kiyani et al. [18] reported that the costs associated with painful diabetic peripheral neuropathies were 20 to 31% higher than diabetic controls (*p*-val less than 0.001). These higher costs were also directly linked to increased odds of using opioids, anticonvulsants, and antidepressants.

As a consequence, the United Nations (UN) enlisted the reduction of diabetes-related mortality rates as an indicator of their Sustainable Development Goal 3 (SDG3) – Good health and wellbeing – target 3.4, which aims at reducing "by one third premature mortality from NCDs through prevention and treatment" and promoting "mental health and well-being" by 2030 [19].

Screening for diabetic peripheral neuropathies, which is crucial for their prevention and treatment, is highly recommended in most clinical guidelines (e.g., the American Diabetes Association) [20]. According to both the International Diabetes Federation and the American Diabetes Association, all diabetic patients should have their foot checked annually [21]. Notwithstanding, this is often neglected due to the lack of consensus on the screening methods, of quick and reliable screening methods, as well as of preventative pharmacological therapies that are neuropathy-specific [20,21].

Throughout this paper, we demonstrate how a frugal and contextualised engineering approach, leveraging circular economy, mHealth and the wide availability of smartphones in LRSs, can be applied when designing medical devices (as also described and proved elsewhere [22–25]). In particular, the aim of this project was to design, develop, and test a smartphone app complemented by 3D-printed accessories, which could dramatically improve the screening for diabetic neuropathies and inform decisions of healthcare operators, worldwide, fostering the shift towards Care 4.0 [26] and circular economy through the use of protocyclers, which are 3D printer filament makers/extruders and recyclers. This could be of benefit not only to LRSs in high-income countries, but also (and perhaps foremost) to those in low-income countries.

This paper follows the frugal design criteria that were pinpointed downstream of our field studies with a Delphi study technique, which are duly explained in [23]. In fact, since 2016, members from our lab, i.e., the Applied Biomedical Signal Processing Intelligent eHealth Lab[1], have been performing field studies in SSA, specifically in Benin, Ethiopia, South Africa, and Uganda. During these field studies we were able to meet local biomedical engineers and technicians as well as healthcare workers, while assessing the conditions of local healthcare locations, and the available medical devices [27–29]. As it resulted from our field studies, and during focus groups at world congresses and fora with experts of different backgrounds (e.g., biomedical and clinical engineering, medical device design, additive manufacturing, eHealth, health technology assessment, usability engineering, etc.),[2] mHealth and 3D printing-based solutions are very relevant and feasible for this kind of settings (especially in LMICs), where the lack of resources, funds, expertise, and medical devices (MDs), as well as harsh environmental conditions, are barriers to healthcare delivery, and are the cause of morbidity and deaths [30–32]. Despite all the above-mentioned challenges, LMICs (e.g., those in Sub-Saharan Africa) can rely on a wide diffusion of wireless telecommunication, young populations, and a fast-growing MD market with a compound annual growth rate of 6.8% (4.7% for Europe) [33,34]. Hence, empowering local communities, by leveraging local production, 3D printing, mHealth, and building capacity among new generations, is one of the first crucial steps in reducing the gap between LRSs and high-resource ones, and for a more equitable access to healthcare, worldwide.

2. Methods

2.1. Literature review: state of the art and gaps

Before delving into the design of the medical app, a literature review was performed by applying the snowballing technique [35] to relevant literature published in scientific journals. This allowed to highlight the state of the art and gaps about this topic and to inform the design process in terms of requirements and specifications.

2.2. Smartphone application

The app was developed in Android Studio [36], using Java for the implementation of functions and XML for the design of the user interface, targeting Android-based smartphones with an API level of at least 21 (i.e., Android 5.0 Lollipop). This choice allows 94.1% of Android users to use our app, since, according to [37], only 5.9% of the Android-based smartphones are provided with an API level lower than 21 worldwide (and similar trends can be found in Africa)(from Android Platform/API version distribution — Android Studio). The app was designed to walk the user through three tests, namely the Neuropathy Total Symptom Score-6 (NTSS-6), the two-point discrimination test, and the vibration perception test. These tests were selected based on the literature and guided by a professional podologist.

1. **NTSS-6**. NTSS-6 is a validated neuropathy sensory symptom scale, evaluating individual neuropathy sensory symptoms in patients affected by diabetes mellitus and diabetic peripheral neuropathy. It was introduced by Bastyr et al. [38]. The questionnaire focuses on the frequency and intensity of six symptoms, namely numbness and/or insensitivity, prickling and/or tingling, burning sensation, aching pain and/or tightness, sharp, shooting, lancinating pain, and allodynia and/or hyperalgesia. The possible scores for the NTSS-6 range from 0 to 21.96, where a score greater than 6 indicates clinically significant symptoms.
2. **The two-point discrimination test**. The two-point discrimination test evaluates whether a subject can identify two close points on a small area of skin, and how finely they can be discriminated [39]. Different areas of the body will feature different sensitivity levels with the hands and feet among the most sensitive areas, and the lower back and thigh among the least sensitive ones [40]. With this test, the minimal distance, at which the subject can distinguish if one or two points of a caliper are held against their skin, can be assessed [41]. For these reasons, it is a measure of agnosia and a proxy for the presence of diabetic neuropathy [39,42]. Any instrument used for this kind of measurement will feature millimeter readings to facilitate the examination.
3. **Vibration perception test**. The vibration perception test assesses whether a subject can perceive vibration. The vibration perception threshold can be considered a valid indicator of proprioceptive capacity [43]. A diminished vibration perception can, in fact, be predictive of future foot ulceration [44]. Normally 128-Hz tuning forks or biothesiometers are used to

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[1] https://warwick.ac.uk/fac/sci/eng/research/grouplist/biomedicaleng/abspie/

[2] The Fourth World Health Organisation Global Forum on Medical Devices (Visakhapatnam, India, 2018), the First International Conference on Collaborative Biomedical Engineering for Open Source Medical Technologies (Pisa, Italy, 2018), the International Union for Physical and Engineering Sciences in Medicine (IUPESM) World Congress (Prague, Czech Republic, 2018), the Third International Clinical Engineer and Health Technology Management Congress (ICEHTMC) (Rome, Italy, 2019), and the International Conference on Medical and Biological Engineering (CMBEBIH) (Banja Luka, Bosnia Herzegovina, 2019).

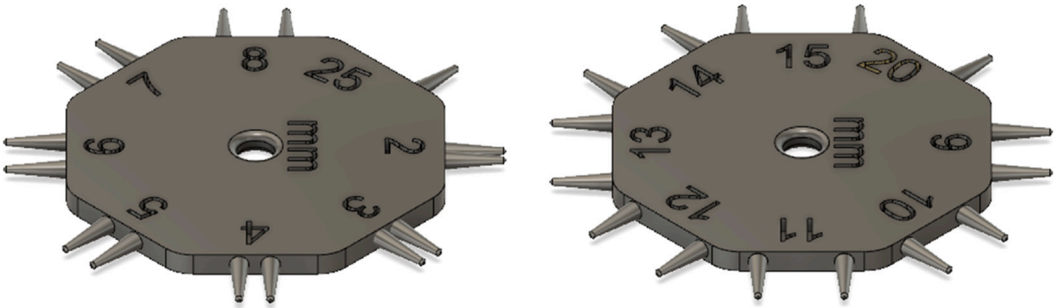


Fig. 1. Two-point discriminators with different discriminator distances.

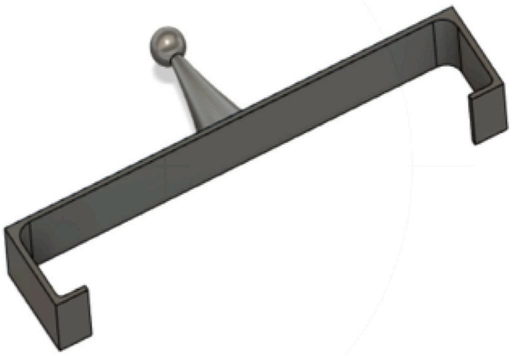


Fig. 2. Smartphone add-on for vibration testing.

perform this test [45] and evaluate the ability of a subject to perceive vibrations in specific bony parts of the lower extremities.

For data collection purposes, a fourth activity was introduced, namely a screening form activity, to collect personal information about the subjects.

2.3. CAD design and 3D printing

3D printing was used to create specific parts that would complement the app, i.e., two two-point discriminators for the two-point discrimination test (see Fig. 1), and one smartphone-add-on tip (see Fig. 2) for the vibration perception test. Such 3D printed parts were designed on Autodesk Fusion360 [46], sliced on Ultimaker Cura [47] and printed with the available 3D printer (Creality Ender3), which has a maximum layer resolution of 0.1 mm and a print precision of ±0.1 mm, using RepRap black polylactic acid (PLA), as it is a very versatile and biocompatible material.

In particular, the two-point discriminators were designed to have an octagonal shape with a circular hole in the middle, to facilitate holding in one's hand. Each side of the octagon features two pins that are distanced at increasing distances (i.e., 1–8 mm and 25 mm for one, and 9–15 mm and 20 mm for the other one). The smartphone-add-on tip was designed to fit a Doogee S60 Lite, i.e., a rugged smartphone, but thought to be potentially adapted to any kind of smartphone. The tip is characterised by a conic pin that extends for 22 mm terminating in a spherical tip. All these items were printed with 0.16 mm layer height and 50% infill, 200 °C nozzle temperature and 40 °C bed temperature.

2.4. Testing for normal thresholds

An on-field research was planned to evaluate normosubjects using the many tests allowed by the smart tool in order to test the initial prototype of this smart tool., i.e., the NTSS-6 questionnaire, the two-point discrimination test, and the vibration perception test (see Fig. 3). Eleven subjects were included in the study, with an average age of 32.18 years (no subject older than 65 was involved) (see Fig. 4). Personal information regarding the subjects and their medical history was recorded using an ad-hoc activity of the app. This was essential to include only normosubjects and exclude potential outliers due to other concomitant diseases or factors that could interfere with peripheral nerve conduction (e.g., hypothyroidism, kidney disorders, recent lower limb injury, rheumatoid arthritis, etc.). Furthermore, only people under the age of 65 were included in the study in order to reduce heterogeneity in the sample, since the two-point discrimination and vibration perception thresholds decrease with age. [48–50]. The full list of questions can be found in Additional File 1. After this screening, the patients were first tested with the NTSS-6 questionnaire, then with the two-point discrimination test, and, finally, with the vibration perception test. To fine tune and benchmark the vibration perception test, also a commercial tool (Vibratip [51]) was tried on the subjects as a last step. The perception of the vibrations generated by both tools, specifically the regions were such vibrations were perceived, were recorded and compared. In particular, the two-point discrimination test was performed on the sole of the hallux and the small toe for both feet in an antero-posterior direction, as the two branches of the planter nerve (medial and lateral), arising from the posterior branch of the tibial nerve, innervate these two parts [52]. Specifically, the examination started with larger thresholds alternating two-tip and one-tip touches, gradually using tips closer to each other, until the subject could not correctly distinguish anymore between one- or two-tip touches. The vibration perception test was performed on the bony part of the distal interphalangeal joint (followed by the lateral malleolus, the lateral femoral condyle, and the hip crest).

These experiments were done in concordance with ethical approval BSREC 05/20-21. The data were then pseudonymised and statistically analyzed using Microsoft Excel.

2.4.1. Statistical analysis

Data normality was investigated by applying the Kolmogorov–Smirnov test. The data are presented as Average and Standard Deviation (SD). Outliers were individuated by applying a modified Thompson's τ test. The deviations for this test were calculated according to Eq. (1), where δ is the deviation, x_i is the ith value and $\bar{x}$ is the average value:

$$\delta_i = \left| x_i - \bar{x} \right| \tag{1}$$

The maximum deviation was then compared to the thresholds from Eq. (2), where t is the threshold, S is the sample standard deviation and τ is the modified Thompson's τ (tabled value):

$$t = S \cdot \tau \tag{2}$$

Depending on the results of the Kolmogorov–Smirnov test, either the paired t-test (in case of normality) or the Wilcox sum-rank test was used to investigate statistical differences between two groups (left versus right part of the body). A p-value lower than 0.05 was considered significant.

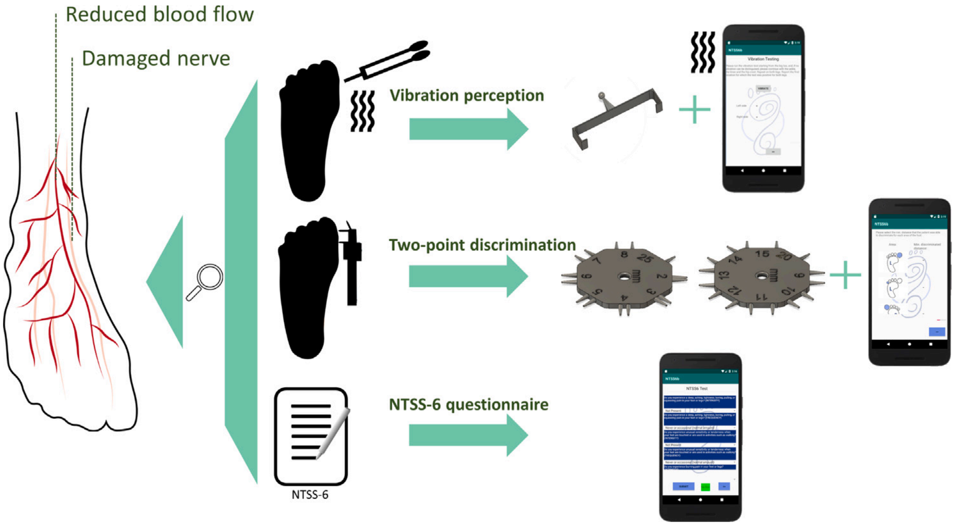


Fig. 3. The testing diagram. The diagram shows diabetic neuropathies are damages to the nerves due to reduced blood flow. The idea behind our smart tool is to combine three different validated tests, i.e., the vibration perception test, the two-point discrimination test, and the NTSS-6 questionnaire, using 3D-printed accessories and a smartphone app. Finally, an artificial-intelligence-based algorithm will calculate the risk of neuropathy.

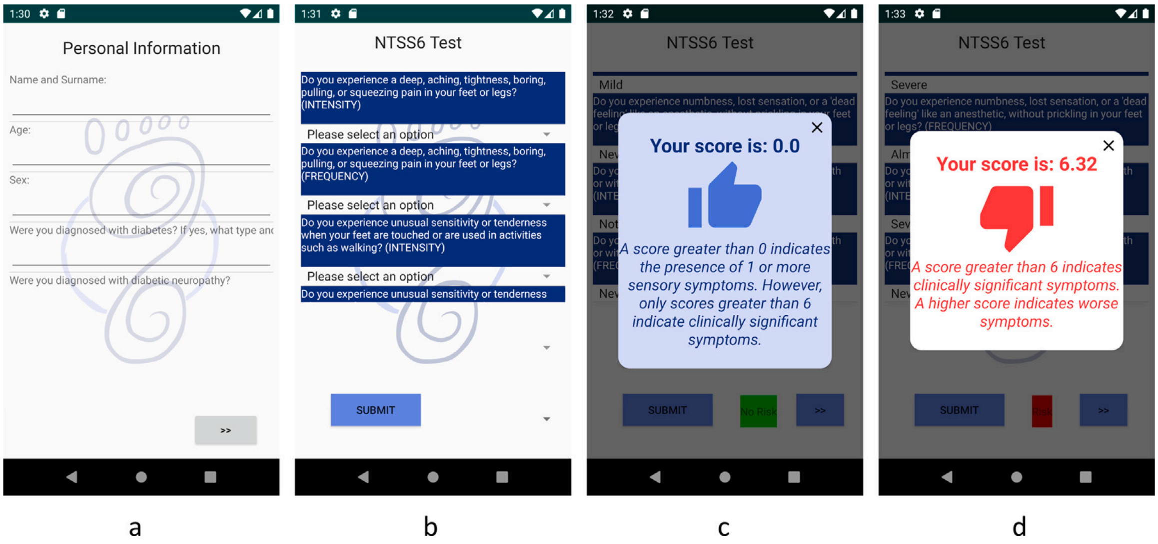
Fig. 4. The two-point discrimination test being performed on a subject.

3. Results

3.1. Literature review: state of the art and gaps

From the literature review, it was possible to understand what the current practices and gaps in the field are. When it comes to methods for screening and assessing diabetic peripheral neuropathies, both questionnaires [38], composite neurological scores, and quantitative sensory or nerve conduction testing are relevant clinically validated methods [20,53]. In 2021, the World Health Organisation [54], included the 128 Hz tuning fork, the reflex hammer, the 10-g monofilament, and diabetic foot ulcer risk scales in the list of specific priority medical devices for clinical assessment interventions for diabetes. More equipment-heavy, time-consuming and invasive methods were proposed in the recent years, such as skin biopsies, corneal confocal microscopy, thermography-based on automatic segmentation of the foot sole, nerve conduction studies [20,55]. Other techniques, which still have limited evidence for use in clinical practice, include electrochemical skin conductance, sweat gland activity, laser Doppler examinations, neuropathic itch, Neurometer, DPN-Check and Sudomotor Testing [20,56].

Traditional methods, supported by the American Diabetes Association, include vibration perception tests through tuning forks or biothesiometers, 2-point discrimination tests, and monofilaments [21,50]. These methods are used for assessing the sensory loss linked to diabetic neuropathies and evaluating different somatosensory functions that are progressively affected by diabetes [57]. In particular, vibratory sensitivity has been proven to be highly sensitive [21], with lower frequencies being a better indicator of developing diabetic foot ulcers, gait or balance problems, or foot drop [50]. In general, combinations of more than one test were shown to improve sensitivity in detecting diabetic peripheral neuropathies [21], with values reaching more than 87% [58,59]. In regard to this, Chicharro-Luna et al. [21] assessed the variability of different methods for diagnosing diabetic neuropathies. They demonstrated that the type of test that had the highest degree of agreement is the one coming from the International Working Group of the Diabetic Foot Criteria, based on the combined use of a monofilament, cotton wisp and tuning fork. When it comes to mHealth and digital solutions for diabetes, their focus is on blood glucose levels monitoring and diabetic management [60,61]. Kap et al. [61], in fact, claimed that, by 2020, 222 Android and 123 iOS diabetes-related applications were released. Such applications can be divided into four main functionalities, that is, management (to monitor glucose levels and unit conversions), supportive (to receive feedback and support from doctors), informative (to provide diet and nutrition advice), and multifunctional. This flourishing has also been possible thanks to recent developments in smartphone cameras that allowed the development of highly accurate and selective colorimetric detection systems that work with bodily fluid samples (e.g., sweat, tears) to monitor glucose levels and enable patient-specific insulin therapies [61]. A great



1:30

Personal Information

Name and Surname:

Age:

Sex:

Were you diagnosed with diabetes? If yes, what type anc

Were you diagnosed with diabetic neuropathy?

1:31

NTSS6 Test

Do you experience a deep, aching, tightness, boring, pulling, or squeezing pain in your feet or legs? (INTENSITY)

Please select an option

Do you experience a deep, aching, tightness, boring, pulling, or squeezing pain in your feet or legs? (FREQUENCY)

Please select an option

Do you experience unusual sensitivity or tenderness when your feet are touched or are used in activities such as walking? (INTENSITY)

Please select an option

Do you experience unusual sensitivity or tenderness

1:32

NTSS6 Test

Mild

Your score is: 0.0

A score greater than 0 indicates the presence of 1 or more sensory symptoms. However, only scores greater than 6 indicate clinically significant symptoms.

1:33

NTSS6 Test

Severe

Do you experience numbness, lost sensation, or a 'dead feeling' like an anesthetic, without prickling in your feet or legs? (FREQUENCY)

Your score is: 6.32

A score greater than 6 indicates clinically significant symptoms. A higher score indicates worse symptoms.

Fig. 5. Screenshots of the app: (a) the personal information activity; (b) the NTSS6 questionnaire activity; (c) and (d) two cardviews representing the feedback of the questionnaire.

share of the diabetes-related app sector is then populated by apps for self-management, lifestyle modification, and medication adherence motivation (e.g., Glucose Buddy, VoiceDiab). As with mHealth in general, these apps and technologies can facilitate timely referral of those on the edge of foot ulceration for timely intervention care [62]. Moreover, they can greatly improve the quality of life of people with diabetes, particularly those living in low-resource settings (LRSs) [60]. Doupis et al. [60] reported existing smartphone applications relevant in this field and supported by prospective randomised controlled trials. Among these, Intelligent Diabetes Management, University of Alberta, supports type 1 diabetes patients with a glucose and meal tracker, similarly to Glucose Buddy. In addition to these functionalities, Diabetes manager, VoiceDiab and Diabetes diary provide for an insulin dose calculator. Similarly, Dbees, Diabetes Interactive Diary, and D-partner are equipped with similar features and also can rely on telemedicine for further patient support. Similar apps with similar features exist for patients with type 2 diabetes, such as Diabeo, Diabetes Pal, BlueStar and Bant2. However, mHealth apps or tools are not yet used to screen diabetic peripheral neuropathies and help for a fast referral to a specialised doctor. In fact, no previous smart tool based on 3D-printed accessories and a smartphone app has ever been devised for screening diabetic neuropathies, to the best of the authors' knowledge. There are few studies in the literature concerning similar solutions for this purpose, as confirmed by [63–65]. In 2017, May et al. [63] demonstrated that mobile phone vibrations via an ad-hoc app (Neurapathy app) could be used to detect diabetic peripheral neuropathy with the highest accuracy, by comparing it with a 10-g Semmes–Weinstein monofilament and a 128-Hz tuning fork. It resulted that the vibrating mobile phone had the highest accuracy (i.e., 88%), compared to the other tools. In 2018, Jacobs et al. [65] described the PeriVib, a portable smartphone-based peripheral neuropathy test platform, which uses a smartphone-controlled external motor to generate vibrations and test the perception. Differently from the world of diabetes management and blood glucose monitoring, which is characterised by numerous mHealth solutions, as presented above, the world of diabetic neuropathy screening still needs to further evolve towards a more digital approach.

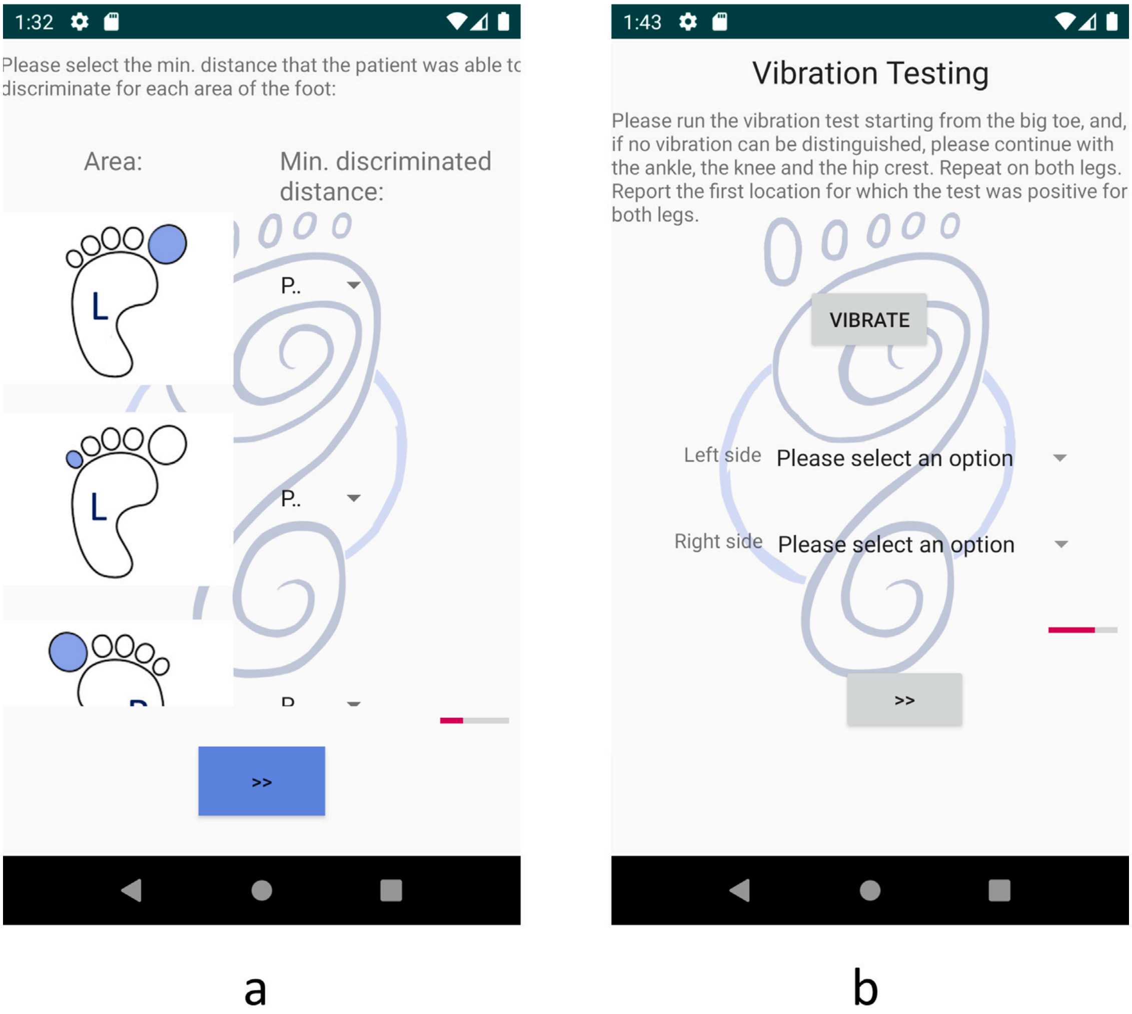
3.2. CAD design and 3D printing

The final CAD models were prepared (using Autodesk Fusion 360) and sliced with Cura using the previously indicated values before being sent to a Creality Ender 3 3D printer for printing. Additional File 2 contains the technical drawings of the parts. The two two-point discriminators, with their octagonal shape and progressively-distanced tips, can be seen in Fig. 1. The print turned out defect-free and all the numerical inscriptions (i.e., those indicating the distance) resulted to be readable. Furthermore, when measured using a ruler, all of the tips were found to be properly spaced. Overall, the 3D-printed two-point discriminators resulted to be lightweight, sturdy, and easy to manoeuvre in an average adult's hand. Similarly, the smartphone add-on for vibration testing, comprising of a spherical tip attached to a truncated cone pin, can be seen in Fig. 2. Also in this case, the smartphone add-on resulted to be defect-free. Upon clipping on the smartphone (i.e., a Doogee S60 Lite), it fit satisfactorily. However, by adding a third side clip to the current design, the fit might be even better.

3.3. Smartphone application

When first clicking on the icon, the app guides the user through four main activities, after showing the splash screen with the logo. Figs. 5 and 6 are screenshots of the different activities. Fig. 7 shows both the Unified Modeling Language (UML) use case diagram and the activity diagrams for the most relevant activities. There are four main activities:

1. Screening form activity, which collects personal information about the subject (e.g., the relevant past medical history). This is useful to understand whether the subject is already suffering from diabetes or other conditions (e.g., hypothyroidism, Lyme disease, rheumatoid arthritis, etc.) that could alter their neurological pathways and perceptions;
2. The NTSS-6 questionnaire activity, which collects the answers related to the frequency and intensity of diabetic neuropathy specific symptoms (e.g., numb feeling in the hands, arms or legs, prickling or tickling feeling in the hands, arms or legs), and gives a final score as well as a recommendation, based on the interpretation given to the total score by Bastyr et al. presented [38]. Such recommendation is given through ad-hoc cardviews in the same activity;
3. The two-point discrimination activity, in which the user can input the minimum two-point discriminator thresholds that the



Please select the min. distance that the patient was able tc discriminate for each area of the foot:

Vibration Testing

Please run the vibration test starting from the big toe, and, if no vibration can be distinguished, please continue with the ankle, the knee and the hip crest. Repeat on both legs. Report the first location for which the test was positive for both legs.

Fig. 6. Screenshots of the app: (a) the discrimination test activity; (b) the vibration test activity.

subject perceived during the two-point discriminator test performed with the ad-hoc 3D printed tool;

4. The vibration perception activity, in which the user can decide whether activating the vibration mode or not by clicking on a button, before placing the spherical tip of the smartphone add-on tool in contact with the different bony parts of the subject. In the same activity, the user can then record the body region where the vibration/non-vibration was felt and correctly individuated.

3.4. *Testing for normal thresholds*

Eleven subjects (eight males, three females) volunteered to take part to the study, after reading the participant's information leaflet. No subject decided at any point to withdraw from the study, nor to withdraw their data within the cooling-off period.

3.4.1. *Statistical analysis*

Table 1 reports the data collected on the 11 normosubjects enrolled in this study. The collected data for each subject included age, sex, the NTSS-6 score, the two-point discrimination thresholds (in millimeters) and the body regions where the vibration was felt first. An additional column collects further comments that are related to the use of Vibratip as a benchmark for the vibration perception test.

By observing Table 1 it is possible to notice that subject ID 4 scored values that are apparently distant from the rest of the group. In order to understand whether subject ID 4 is an outlier, modified Thompson's tau technique was used [66]. In particular, the deviations δ for 2PD LLT (two-point discrimination left little toe), 2PD RH (two-point discrimination right hallux), and 2PD RLT (two-point discrimination right little toe), resulted all to be greater than the threshold value given by the multiplication of Thompson's tau and the standard deviation of the sample, as shown in Table 2. For these reasons, subject ID 4 was considered an outlier and removed from further analysis.

The Kolmogorov–Smirnov test showed that the four variables resulted to be normally distributed (for LH D=0.2 and p-value = 0.749; for LLT D = 0.29 and p-value = 0.317; for RH D=0.23 and p-value = 0.614; for RLT D = 0.23 and p-value = 0.61). The paired t-test could not reject the null hypothesis that the paired samples came from populations with equal means (Hallux p-value = 0.49; Little toe p-value = 0.21) (see Fig. 8).

4. Discussion

An overview of the currently available technologies developed for diabetic patients brought to light the fact that, as opposed to the field of glycemia screening and lifestyle management, not much has been done in the field of mHealth for the screening of diabetic neuropathies, which are a major health burden, worldwide. In fact, as regards the former, as afore-mentioned in the introduction section, there are numerous mHealth solutions aimed at facilitating and improving the quality of life

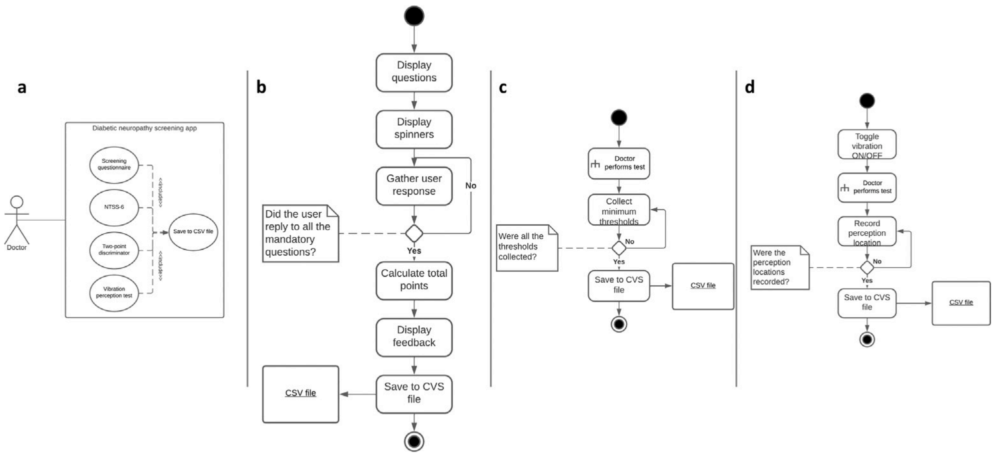


Fig. 7. UML diagrams: (a) UML use case diagram; (a, b, c) activity diagrams respectively for the NTSS-6, two-point discrimination and vibration perception activities.

Table 1
The collected data for each subject. 2PD stands for two-point discrimination; LH stands for left hallux; LLT stands for left little toe; RH stands for right hallux; RLT stands for right little toe; LAPV stands for left area perceived vibration; RAPV stands for right area perceived vibration; avg stands for average; std stands for standard deviation; *the averages and the standard deviations reported in the table are those calculated after the removal of the outlier (ID 4).

ID	Age	Sex	NTSS-6	2PD LH	2PD LLT	2PD RH	2PD RLT	LAPV	RAPV	Comments
1	22	M	2	9	11	9	9	Big Toe	Big Toe	
2	58	F	2	8	9	8	8	Knee	Knee	Vibratip felt on big toe
3	28	M	0	10	8	7	8	Big Toe	Big Toe	
4	62	M	0	10	14	13	15	Knee	Knee	Vibratip felt on big toe
5	27	F	0	8	8	8	7	Big Toe	Big Toe	
6	38	M	0	7	7	6	8	Knee	Knee	Vibratip felt on big toe
7	21	M	0	7	8	8	7	Big Toe	Big Toe	
8	31	F	0	10	9	10	9	Knee	Knee	Vibratip felt on big toe
9	21	M	0	4	8	7	7	Knee	Knee	Vibratip felt on big toe
10	27	M	0	8	8	8	10	Big Toe	Big Toe	
11	19	M	0	9	9	4	4	Big Toe	Big Toe	
Avg*				8	8.5	7.5	7.7			
Std*				1.76	1.08	1.65	1.64			

Table 2
The deviations and thresholds for the two-point discrimination variables. The * denotes values over the threshold.

	2PD LH	2PD LLT	2PD RH	2PD RLT
δ	1.82	5*	5*	6.64*
Threshold	3.23	3.54	4.14	4.89

of diabetic patients, by allowing them to check and log their glycemia levels and blood pressure, record their daily food intake, medication, and physical activities, as well as access advice from a real health coach or communicate with healthcare professionals, as presented in the introduction [60,61]. In particular, Kap et al. [61] reviewed several smartphone-based methods, relying on the collection of bodily fluids (e.g., saliva, sweat, etc.) samples through ad-hoc microfluidic devices to measure the amount of glucose levels. The latter can be manually or automatically recorded along with the daily diet and exercise on specific apps, as reported by Doupis et al. [60].

Conversely, as regards the screening of diabetic neuropathies, the currently available cutting-edge methods found in the existing literature, such as the automatic sole segmentation and thermography method reported by Arteaga-Marrero et al. [55], or the methods relying on nerve conduction studies, skin biopsies, corneal confocal microscopy, and electrochemical skin conductance as described by Roikjer et al. [20], or those additionally reported by Yang et al. [56] based on the assessment of the retinal nerve fiber layer thickness through optical coherence tomography, pupil responsiveness, or sudomotor testing, require more equipment and time, compared to traditional clinical practice. As a result, we believe that our solution, which relies on a combination of different tests as suggested by Chicharro-Luna et al. [21], represents a more simple and cost-effective way to test for diabetic neuropathies, both in high- and low-resource settings, where it could empower less-skilled healthcare personnel to perform such screening procedures, as well as foster telemedicine and Care 4.0.

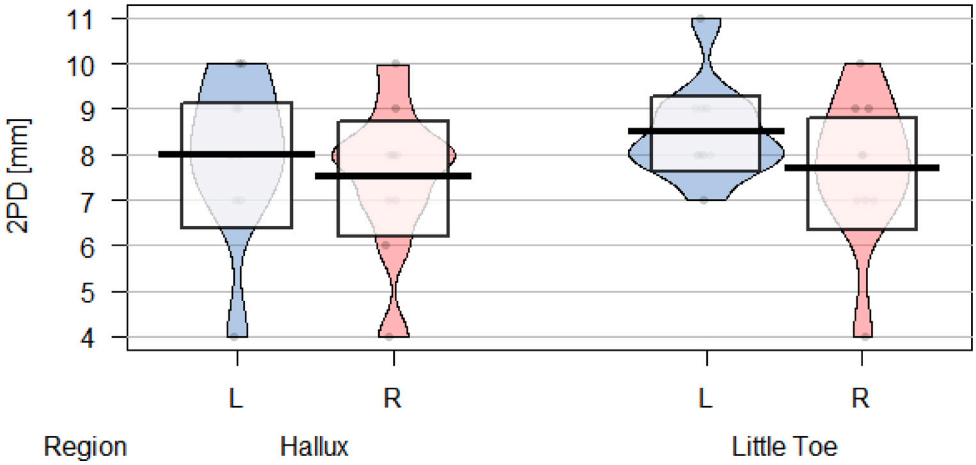


Fig. 8. (a) The pirate plots for the 2PD of both halluces (left VS right) and little toes (left VS right).

Other technologies [51] relying on the vibration perception threshold measurement only, although proven reliable, cannot warrant the same sensitivity and specificity of the combinations of different sensory tests [21,58,59]. Moreover, to the authors' best knowledge, the only available smartphone-based solutions are solely reliant on vibration perception [63,65] and, in particular, the tool developed by Jacobs et al. [65] makes use of a specific additional platform/motor that may not be accessible or so easy to reproduce in LRSs.

In light of this, this paper presented the design, prototyping, and feasibility study of a smart tool for screening diabetic neuropathies relying on a combination of methods, which can be a goad to a global healthcare evolution towards Care 4.0 as well as foster the socio-economic growth of LRSs, thanks to contextualised design and circular economy approaches. In fact, during the design of this smart tool, a frugal engineering perspective was adopted, leveraging on contextual needs, specific material selection that allowed for 3D printing and its recycling and reuse at the end of life through protocyclers, and mHealth. The results proved that this system can be easily manufactured and used by lay users to produce reliable results. This is of utter importance for a timely referral and screening, and also for those remote areas of both LMICs and high-income countries, which are often challenged by the lack of specialised personnel. In this regard, this smart tool would allow a more equitable access to the screening of diabetic neuropathies, globally.

In particular, as it can be observed from the results, the average two-point discrimination thresholds (8 mm and 7.5 mm, respectively for the left and right halluces) are in line with other results presented in the literature. Lederman et al. [67] report a figure taken from previous studies from Weinstein [68], which shows an average two-point discrimination threshold of approximately 12.5 mm on the hallux. As regards the vibration perception, six subjects could feel and distinguish vibrations on their hallux, while five of them could perceive it on their knee. Notwithstanding, the latter were able to distinguish the vibration coming from Vibratip on their halluces. This highlights the current limitations of the add-on system for applying the vibration. This is probably linked to the fact that an optimal vibration frequency for this test is 128 Hz [69] and due to further attenuation provided by the smartphone components. However, it is currently not possible to set the vibration frequency in smartphones. As a consequence, in order to tackle this, future designs might need to focus on optimising/enhancing the vibration transmission by considering the modal frequencies of the add-on device. Nonetheless, May et al. [63] previously proved that a smartphone without add-ons could be used for this purpose. In light of this, it is also possible that future releases will discard the add-on and only use the mobile phone for vibration testing.

5. Conclusions

This smart tool seems novel in the way that it represents a frugally engineered device that makes use of 3D printed accessories and mHealth, which improves its global accessibility and reproducibility. Moreover, compared to the existing state of the art in mHealth for screening diabetic neuropathies, this tool is less equipment-heavy, more sensible, easy to use, and reliable, thanks to the combination of different methods, namely, a scientifically-validated symptom-based questionnaire, a vibration perception test, and a two-point discrimination test. Its portability and compactness add to its potential to improve the quality of care in terms of time and resource utilisation by expediting and motivating the screening of diabetic neuropathies around the world. Eventually, this smart tool can also be a great input tool for a clinical decision support system based on machine learning. The future integration of artificial intelligence and/or decision support systems to process the results from the above-mentioned tests, can further complement this smart tool.

CRediT authorship contribution statement

Davide Piaggio: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Rossana Castaldo:** Methodology, Formal analysis, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Gianluca Garibizzo:** Methodology, Validation, Writing – review & editing. **Ernesto Iadanza:** Validation, Project administration, Supervision, Writing – review & editing. **Leandro Pecchia:** Project administration, Supervision, Funding acquisition, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Davide Piaggio reports was provided by University of Warwick. Davide Piaggio, the lead author of this manuscript, is one of the co-guest editors for the special issue to which this manuscript is being submitted.

Data availability

Data will be made available on request.

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Ethical approval

We obtained clearance to conduct this study from the University of Warwick Ethical BSREC Committee (BSREC 05/20-21). Additionally, we obtained consent from every participant prior to data collection.

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