AN EXPLORATION OF DIABETIC FOOT SCREENING PROCEDURES DATA BY A MULTIPLE CORRESPONDENCE ANALYSIS
ANALIZA PODATKOV PRESEJALNEGA TESTA ZA DIABETIČNO NOGO Z MULTIPLO KORESPONDENČNO ANALIZO

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ABSTRACT

Keywords:
diabetic foot,
screening, statistics

Aims. Gangrene and amputation are among most feared complications of diabetes mellitus. Early detection of patients at high risk for foot ulceration can prevent foot complications. Regular foot screening (medical history, foot examination and classification into risk groups) was introduced at the out-patient diabetes clinic in Ljubljana in November 1996. We aimed to explore the relationships between the observed variables, check the appropriateness of the risk status classification and of the post-screening decisions.

Methods. The data of 11.594 patients, obtained in 18 years, were analysed by multiple correspondence analysis (MCA). Most of the observed variables were categorical.

Results. The majority of the screened population was free of foot complications. We demonstrated an increasing frequency and severity of foot problems with an increasing age, as well as the association between the loss of protective sensation and the history of foot ulceration, foot deformity and callus formation, the history of foot ulcer or amputation and acute foot ulceration. A new finding was that the location of foot deformity points was closer to female than male gender, indicating the possible role of fashionable high-heel footwear. The appropriateness of therapeutic decisions was confirmed: the points representing absent foot pulses and referral to vascular specialist were close together, as well as points representing foot deformity and special footwear prescription or callus formation and referral to pedicurist.

Conclusions. MCA was applied to the data on foot pathology in the population attending the out-patient diabetes clinic. The method proved to be a useful statistical tool for analysing the data of screening procedures.

IZVLEČEK

Ključne besede:
diabetično stopalo,
presejanje, statistika

Namen. *Gangrena in amputacija sodita med najhujše zaplete sladkorne bolezni. Zaplete na nogah lahko preprečimo z zgodnjim odkrivanjem ogroženih bolnikov. V Diabetološki ambulanti Ljubljana izvajamo presejalni test za diabetično stopalo od novembra 1996. Test obsega anamnezo, klinični pregled in klasifikacijo glede na ogroženost. Želeli smo raziskati povezanost med opazovanimi spremenljivkami, preveriti pravilnost klasifikacije bolnikov in ustreznost odločitev po pregledu.*

Metode. *Podatke 11.594 bolnikov, dobljene v 18 letih, smo analizirali z multiplo korespondenčno analizo (MCA). Večina opazovanih spremenljivk je bila kategorična.*

Rezultati. *Večina opazovane populacije ni imela zapletov na nogah. Dokazali smo, da pogostnost in izraženost težav z nogami narašča s starostjo ter da obstajajo povezave med izgubo zaščitne občutljivosti in razjedo v anamnezi, med deformacijo nog in tvorbo kalusa, med ulkusom ali amputacijo v anamnezi in akutno razjedo. Nova ugotovitev je lokacija točke, ki označuje deformacijo stopala, bliže ženskemu kot moškemu spolu, kar kaže na možen vpliv modnih čevljev z visokimi petami. Potrdili smo ustreznost terapevtskih odločitev: točke, ki označujejo odsotne stopalne pulze, in tiste, ki označujejo napotitev k angiologu, so bile blizu skupaj, prav tako deformacija nog in predpis posebne obutve ali tvorba kalusa in napotitev k pedikerju.*

Zaključek. *MCA smo uporabili za analizo podatkov o patologiji stopal pri populaciji bolnikov iz naše diabetološke ambulante. Metoda se je izkazala kot uporabno statistično orodje za analizo podatkov o presejalnih testih.*

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1 INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder affecting 8-11% of the general population (1). It is one of the major public health problems worldwide, including Slovenia (2). The disease is characterized by elevated blood sugar levels, which damage blood vessel walls, ultimately leading to end-organ injury. The financial burden of diabetes treatment and its complications is enormous (3). Gangrene and amputation are among the most feared complications of diabetes. More than 50% of all non-traumatic amputations are performed on diabetic patients (4, 5). The initial event is usually a foot ulcer, which affects about 15% of all patients with diabetes mellitus.

The major risk factors for diabetic foot ulceration and gangrene are neuropathy, impaired blood supply, trauma and infection. Other contributing factors include a history of previous foot ulcer, improper footwear, low-quality podiatry service, poor metabolic control, psychological factors, tobacco smoking, old age and low social status. Foot complications usually develop due to an interplay of several component causes (4, 6, 7).

Diabetic neuropathy can involve sensory, motor and autonomic nerves. The most prevalent form is distal symmetric sensory neuropathy (8, 9, 10), which affects vibration, light touch, pain, temperature and proprioceptive sensation. Motor neuropathy leads to muscle atrophy, foot deformity (claw-hammer toes), altered biomechanics of walking, and redistribution of foot pressures during standing and walking. Abundant callus formation on pressure points, together with thinning of the submetatarsal head fat pads, additionally increases the magnitude of plantar pressure, and ultimately results in foot ulceration (11, 12). Neuropathy of sympathetic sudomotoric nerves results in diminished or even absent sweating, which causes dry foot skin, prone to cracks and fissures. The distribution of neuropathic changes is usually symmetrical (9, 10).

Due to impaired or absent pain sensation, patients with sensory neuropathy often neglect warning signs of foot disease. Early detection of high-risk patients by systematic screening enables timely implementation of preventative measures to avoid gangrene and amputation (13).

Screening means examination of asymptomatic people to detect those with a high probability of having a given disease (14). In the past, there used to be mass screening for lung tuberculosis; nowadays, all blood products are screened for the presence of HIV.

Foot screening protocol is a set of simple and inexpensive procedures, which reveal the patients at risk for the development of foot ulceration. It consists of one's medical history (previous foot ulceration, symptoms of neuropathy), foot examination and classification into risk groups.

In Slovenia, there is no national diabetes registry. In 2014, there were 104.550 patients on antidiabetic medications, with the estimated prevalence of diabetes mellitus in the population over 15 years of age being 6.9% (confidence interval 6.3 - 7.6 %) (15). The out-patient diabetes unit at the University Medical Centre Ljubljana is the biggest in Slovenia (with over 11.000 registered patients). Here, we started to perform foot screening in November 1996. The procedure is repeated in every patient at least once a year. In this retrospective survey, we decided to analyse the results of the first screening test. The main analytical tool was multiple correspondence analysis (MCA). The aims of the study were:

1. To reveal the possible new causal relationships among the observed variables and to confirm the causal pathways to foot complications which have already been described before.

2. To evaluate the appropriateness of the classification into risk groups.

3. To evaluate the appropriateness of the post-screening decisions (referral, footwear prescription).

2 METHODS

2.1 Patients and Data Collection

Between November 1996 and December 2014, 11.594 patients with diabetes mellitus were screened (55.2% men, average age 60.81 years): all patients registered at the clinic in November 1996, and afterwards, all newly-diagnosed patients with type 2 diabetes, as well as the patients with type 1 diabetes five years after the diagnosis. For every patient, only the data of the first foot examination were included in the analysis.

The protocol was adopted by the Slovenian Working Group on the Diabetic Foot in 1996, and it is coherent with international recommendations (13). The examination is done by a specialist nurse and evaluated by a diabetologist. The protocol (Appendix 1) includes demographic data (ID, age, sex), medical history (previous foot ulcer, amputation, various symptoms) and foot examination (various deformities, hard skin, ulcer, dry skin, redness, arterial pulses). Risk status classification (groups 1 – 4, Table 1) is done according to the data from medical history and the findings upon foot examination. Therapeutic measures taken after the examination are also recorded: education, footwear prescription, referrals (foot clinic, angiologist, surgeon and chiropodist). The duration of diabetes and the level of metabolic regulation (HbA1c level) are not included in the protocol.

Table 1.   Risk status classification.

Category	Description
1	Normal sensation, palpable pedal pulses, no foot deformity
2	Impaired sensation, no foot deformity
3	Absent pedal pulses, normal sensation, no foot deformity
4	• Combination: foot deformity and impaired sensation and / or absent foot pulses • Previous ulcer or amputation • Charcot foot

The original data set consists of 56 variables. We included the data of both feet about previous and acute ulceration, amputation and foot pulses. As we have previously demonstrated that the data on neuropathy and foot deformity did not differ between the two feet (16), we decided to include only the data of one (right) foot in the analysis. Among the remaining 24 variables under consideration, all except for age and loss of protective sensation were nominal, mostly dichotomous. The list of the analysed variables is shown in Appendix 2. Age has been recoded to 3 age groups (0: under 51 years, 1: 51 – 70, 2: more than 70 years). The loss of protective sensation has been recoded to 3 categories (0: no loss of protective sensation, 1: unable to feel the monofilament on 1 – 3 points, 2: unable to feel the monofilament on 4 or more points). In this way, there were 52 categories to be analysed altogether.

Statistical analysis was performed with the SAS 9.4, procedures Corresp and IML. The correspondence maps were designed with XLSTAT 2015, procedure Multiple Correspondence Analysis (MCA).

2.2 Multiple Correspondence Analysis

The relationship between variables was summarized by cross-tabulations and analysed by multiple correspondence analysis (MCA). MCA is a powerful descriptive statistical technique for handling larger, more complex datasets, including high-dimensional categorical data often encountered in social sciences, marketing, health economics and biomedical research (17). The primary goal of this exploratory statistical method is to transform numerical information into graphical displays ('maps') and related numerical statistics. The position of the category-points in MCA maps is the basis for revealing the relationship among the investigated variables (17, 18).

2.3 Burt Matrix

MCA can be defined as the correspondence analysis of the so-called 'Burt matrix' **B**. It is a partitioned symmetric matrix containing all pairs of crosstabulations among a set of categorical variables. Each crosstabulation $\mathbf{F}_{qq}$ $(q=1,2,...,Q)$ on the main diagonal of the Burt matrix is a diagonal matrix of the marginal frequencies (i.e., a crosstabulation of a variable with itself). Each off-diagonal crosstabulation is an ordinary two-way contingency table $\mathbf{F}_{qq'}$ $(q,q'=1,2,...,Q, q\neq q')$. Each contingency table above the diagonal has a transposed counterpart below the diagonal.

$$\mathbf{B} = \begin{bmatrix} \mathbf{F}_{11} & \mathbf{F}_{12} & \cdots & \mathbf{F}_{1Q} \\ \mathbf{F}_{21} & \mathbf{F}_{22} & \cdots & \mathbf{F}_{2Q} \\ \vdots & \vdots & & \vdots \\ \mathbf{F}_{Q1} & \mathbf{F}_{Q2} & \cdots & \mathbf{F}_{QQ} \end{bmatrix}$$

As mentioned before, we have analysed a data set of 24 variables (Q=24), containing altogether 52 categories (J=52). Therefore, the Burt matrix is a symmetric matrix consisting of 52 rows and columns (Table 2).

Table 2.   The Burt matrix, the presentation of crosstabulations reduced to the first two variables and the last variable (the complete matrix at (19)).

	SEXF	SEXM	NSY0	NSY1	⋯	AMP0	AMP1	*Total*
SEXF	5193	0	2519	2674	⋯	5167	26	124632
SEXM	0	6401	3876	2525	⋯	6357	44	153624
NSY0	2519	3876	6395	0	⋯	6376	19	153480
NSY1	2674	2525	0	5199	⋯	5148	51	124776
⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮
AMP0	5167	6357	6376	5148	⋯	11524	0	276576
AMP1	26	44	19	51	⋯	0	70	1680
Total	124632	153624	153480	124776	⋯	276576	1680	6678144

On the basis of the Burt matrix, one can calculate rows of relative frequencies (the division of row frequencies by the marginal total), called profiles, representing each variable category (Table 3). The marginal row of relative frequencies at the bottom of the table presents the average profile (Total). Categories with similar profiles have similar characteristics for the variables considered. Unfortunately, due to numerous categories, direct inspection of all profiles and formation of homogenous profile groups is impossible. For that reason, the numerical information contained in the Burt matrix has been analysed with MCA.

Table 3. The matrix of row profiles (source: Table 2).

	SEXF	SEXM	NSY0	NSY1	$\cdots$	AMP0	AMP1	*Total*
SEXF	4.1667	0.0000	2.0212	2.1455	$\cdots$	4.1458	0.0209	100
SEXM	0.0000	4.1667	2.5230	1.6436	$\cdots$	4.1380	0.0286	100
NSY0	1.6413	2.5254	4.1667	0.0000	$\cdots$	4.1543	0.0124	100
NSY1	2.1430	2.0236	0.0000	4.1667	$\cdots$	4.1258	0.0409	100
$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$
AMP0	1.8682	2.2985	2.3053	1.8613	$\cdots$	4.1667	0.0000	100
AMP1	1.5476	2.6190	1.1310	3.0357	$\cdots$	0.0000	4.1667	100
Total	1.8663	2.3004	2.2982	1.8684	$\cdots$	4.1415	0.0252	100

2.4 Dimensionality of MCA Solution

Based on the Burt matrix one can form the matrix

$$\mathbf{D_B^{-1/2}(P_B - p_B p_B')D_B^{-1/2}}$$

where $\mathbf{D_B}$ is a diagonal matrix with the elements of the average profile on the main diagonal, $\mathbf{P_B}$ is a matrix of relative frequencies of the Burt matrix (division of Burt matrix by the grand total) and $\mathbf{p_B}$ is an average profile (Table 3). The expression in brackets represents the deviations of observed relative frequencies of the Burt matrix from the model of independence, while $\mathbf{D_B}^{-1/2}$ is a weighting factor matrix.

Basic calculations are made in three steps:

1. Find the eigenvalue-eigenvector decomposition of the matrix (2)

$$\mathbf{D_B^{-1/2}(P_B - p_B p_B')D_B^{-1/2}} = \breve{\mathbf{\Gamma}}\mathbf{D}_\delta\breve{\mathbf{\Gamma}}'$$

where $\breve{\mathbf{\Gamma}}$ is an orthogonal matrix of eigenvectors

$$\breve{\mathbf{\Gamma}}'\breve{\mathbf{\Gamma}} = \mathbf{I}$$

and $\mathbf{D}_\delta$ is a diagonal matrix of eigenvalues δ_j

$$\mathbf{D}_\delta = diag(\delta_1, \delta_2, \ldots, \delta_L)$$

The number of nontrivial singular values is equal to $L = J - Q$ (L=28). In case of the analysis of Burt table, the principal inertias λ_l are defined as the squared values of singular values δ_l.

2. Calculate the matrix of standard coordinates

$$\mathbf{\Gamma} = \mathbf{D_B^{-1/2}}\breve{\mathbf{\Gamma}}$$

3. The corresponding principal coordinates are given by

$$\mathbf{Y} = \mathbf{\Gamma}\mathbf{D}_\delta^{1/2}$$

Table 4. The first two principal coordinates of the matrix **Y**.

	1. principal coordinate	2. principal coordinate
SEXF	0.045545	0.264007
SEXM	-0.036950	-0.214184
NSY0	-0.337288	-0.219527
NSY1	0.414879	0.270028
HVA0	-0.071098	-0.165217
HVA1	0.340644	0.791587
⋮	⋮	⋮
AMP0	-0.011657	-0.010940
AMP1	1.919002	1.801034

MCA includes the fitting of the diagonal submatrices $\mathbf{F}_{qq}\ (q=1,2,...,Q)$ of the Burt matrix. As a result, the total inertia is inflated and thus the proportions of the first few principal inertias as parts of the total inertia are reduced (21, p.155). One way to address this problem, proposed by Benzécri (22), is to consider only those principal axes whose eigenvalues are higher than 1/Q (i.e. 1/24=0.041667 in this application, see Table 5). These adjusted inertias $\tilde{\lambda}_k$ can be calculated according to Benzécri's formula

$$\tilde{\lambda}_k = \left[\frac{Q}{Q-1}\left(\delta_k - \frac{1}{Q}\right)\right]^2 \quad k=1,2,...$$

with the condition that these be calculated for $\delta_k > 1/Q$ only.

The number of inertias has been reduced from 28 to only 9, with strongly dominating values of the first two principal inertias. The values of the adjusted inertias $\tilde{\lambda}_k$ are shown in Table 5.

Table 5. The adjustment of inertias.

	Singular values δ_l	Burt principal inertia λ_l	Adjusted inertia $\tilde{\lambda}_k$	Percentage of adjusted inertia	Cumulative percentage of adjusted inertia	16 32 48 64 80 ----+----+----+----+---
1	0.20583	0.04237	0.02934	66.72182	66.72182	*********************
2	0.11983	0.01436	0.00665	15.12592	81.84773	***
3	0.07324	0.00536	0.00109	2.46806	84.31580	*
4	0.06369	0.00406	0.00053	1.20083	85.51663	
5	0.04969	0.00247	0.00007	0.15938	85.67600	
6	0.04743	0.00225	0.00004	0.08224	85.75824	
7	0.04398	0.00193	0.00001	0.01325	85.77149	
8	0.04196	0.00176	0.00000	0.00021	85.77170	
9	0.04174	0.00174	0.00000	0.00001	85.77171	
⋮	⋮	⋮	⋮			

$\bar{\phi}^2 = 0.04398$

The next question is the quality of the presentation of the position of the profiles based on the first few principal coordinates. M. Greenacre (21) calculates the percentage of inertia as follows

$$\tilde{\lambda}_k\% = 100\frac{\tilde{\lambda}_k}{\bar{\phi}^2} \qquad k = 1,2,\ldots$$

where $\bar{\phi}^2$ is an average of the off diagonal inertias $\phi_{qq'}^2$, i.e.

$$\bar{\phi}^2 = \frac{1}{Q(Q-1)}\sum_{q=1}^{Q}\sum_{\substack{q'=1 \\ q'\neq q}}^{Q}\phi_{qq'}^2$$

where $\phi_{qq'}^2$ is the off-diagonal inertia; e.g., chi-square measure of association (based on particular crosstabulation in the Burt matrix) divided by the number of units observed.

The values of percentages of adjusted principal inertias and the cumulative percentages of adjusted principal inertia are also shown in Table 5. According to the aforementioned Greenacre's approach to the calculation of percentages of inertia, 81.85% of the total inertia is explained by the first two principal axes. Therefore, without losing too much information, the representation of the positions of the profiles (category points) based on the first two principal coordinates (on a two-dimensional map) can serve as a good basis for the thorough analysis of the relationship between considered variables.

Figure 1. A two-dimensional map – a display of all categories (extended labels in Appendix 2).

3 RESULTS: MAPS AND ANALYSIS

The spread of the profiles is evaluated as total inertia. When the cumulative percentage of inertia of the first two dimensions is relatively high, then most of the profiles are well represented in a two-dimensional map (by their projections onto a plane). Thus the two-dimensional solution of our example (Table 4) explaining 81.85% of the total inertia (Table 5) can serve as a good basis for the display of the profiles (Figure 1).

In correspondence analysis, the average profile is represented as a point in the origin of the coordinate system. The deviation of a particular variable category point from the origin is determined by its share in the sample: the lower the share, the farther the category point from the origin.
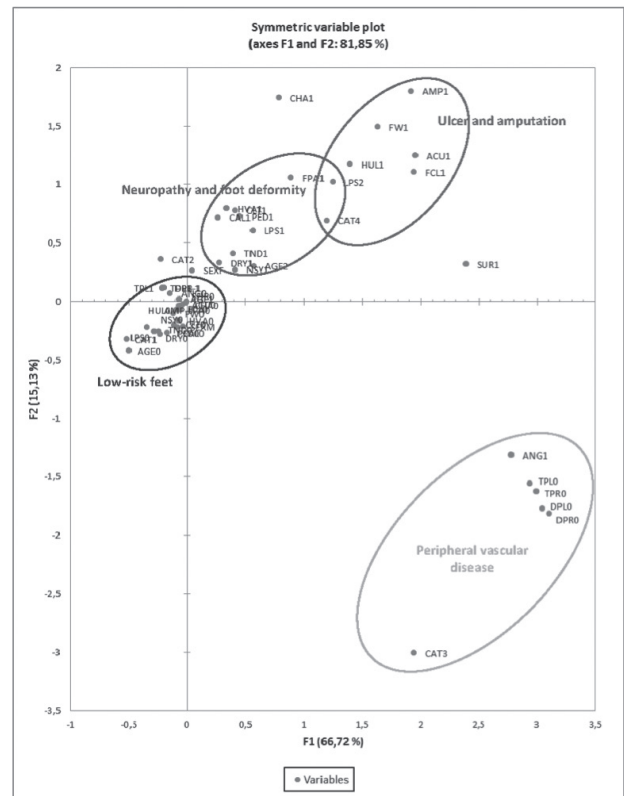
In our case (Figure 1), the categories with high shares (younger age group - AGE0, no history of foot ulcer – HUL0, no loss of protective sensation - LPS0, absence of foot deformities, palpable pulses of pedal arteries) are concentrated in the left lower quadrant, close to the origin.

On the other side, the points representing the presence of particular foot deformities, loss of protective sensation, and acute foot ulceration are distributed in the right upper quadrant.

There is a separate group of category points in the right lower quadrant, which represents the patients with absent foot pulses. Close to them is the point representing referral to vascular specialist. The point representing group 3 (pure ischaemia and no neuropathy) is a little away.
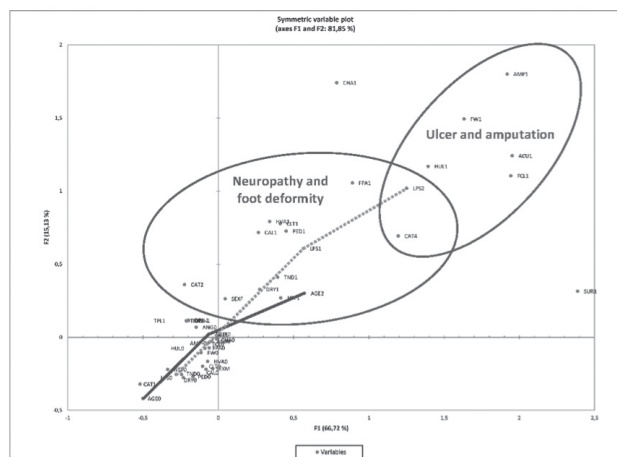
Figure 2. A zoom-in display of the upper part of Figure 2.

The zoomed-in upper part of Figure 1, where the majority of the points are located, is shown in Figure 2.

The points representing the ordinal variables are connected with broken lines. The solid line connecting the age groups (AGE1, AGE2, AGE3) is stretched in the direction from the left lower to the right upper quadrant. The youngest age group (under 50, AGE0) is situated at the left lower end.

The dotted line, representing the ordinal character of protective sensation loss, from LPS0 to LPS2, follows almost the same direction as age groups, with no loss of sensation (LPS0) in the left lower quadrant and loss of sensation (LPS2) in the right upper quadrant.

4 DISCUSSION AND CONCLUSIONS

The decision to conduct the study was based on the belief that it could contribute to improved diabetic foot care in Slovenia. This would be important from the public health aspect, since Slovenia had the second highest age-sex standardised amputation rate per 100 000 population among the observed countries, and the highest age-sex standardised amputation rate per 100 000 people with diabetes, according to the data from the OECD health statistics report published in 2015 (23).

Regular preventative foot examinations are the cornerstone of efficient amputation prevention strategies. With the introduction of a new organisation at the primary health care level, called model practices, the frequency of foot examinations has increased significantly (24).

Our retrospective analysis of the large foot screening data set has confirmed most of the already known relationships in the development of foot pathology, and revealed a stronger association of foot deformity with female than

with male gender. The survey has confirmed that the risk status classification and the post-screening decisions were concordant with the data obtained by screening.

We have decided to use MCA because it has proved to be a strong tool for examining the association between signs and symptoms described by mostly nominal data. In 1989, Crichton described its use on two big data sets of patients with chest pain and acute abdominal pain (25). MCA has been used in the analysis of data in psychiatry (26), rheumatology (27), infectious diseases (malaria) (28) and oral health (29).

Recently, Sacco et al.(30) used MCA to reveal early indicators of diabetic polyneuropathy. Their study included 193 patients without partial or total foot amputation, major vascular complications or severe nephropathy. On the contrary, our study was performed on an unselected population of patients with diabetes. To the best of our knowledge, no analysis of such large data set has been published so far.

Screening is a strategy used in a population to identify the possible presence of an as-yet-undiagnosed disease in asymptomatic individuals. The majority of the screened population is supposed to be disease-free, and the points representing the individuals without a condition are therefore concentrated close to the origin of the coordinate system. As expected, the points representing the absence of impaired blood supply, foot deformity, neuropathic symptoms and previous or current foot ulceration were all located close to the origin.

The decline of neurological functions (in particular vibrating sensation) with aging is well established (31, 32, 33). Accordingly, we found the position of points representing foot deformity and neuropathic symptoms close to the point of the age group over 70 years. Unfortunately, our protocol does not include the data on diabetes duration and metabolic control, which are known risk factors for chronic complications of diabetes (34).

Some other apparently obvious associations have been demonstrated: the category point representing the history of foot ulceration was close to the points representing the loss of protective sensation, acute foot ulceration and fat pad atrophy. The points representing various foot deformities (claw toes, hallux valgus, toenail deformity) were close together and also close to abundant callus. Dry skin (indicating autonomic neuropathy) was close to neuropathic symptoms, and both were close to moderate loss of protective sensation (LPS1).

The location of foot deformity points closer to female than male gender was unexpected, but could possibly be explained by the inappropriate footwear in women.

Foot screening in our centre is done by a nurse and evaluated by a physician –diabetologist. The risk category classification is a subjective decision based on the data from medical history and foot examination, and as such it might be prone to error. We conclude that it was done properly, since the points representing the four risk categories were distributed as expected: The risk group 1 point (normal sensation, no deformity) is among the points representing the absence of particular foot pathologies. The risk group 2 point (the loss of protective sensation, no deformity) is located away from the foot deformity points. The risk group 3 point (absent foot pulses, normal sensation, no deformity) is close to absent foot pulses and far away from neuropathy. The risk group 4 point (previous ulcer or amputation, Charcot, combination of neuropathy, ischemia and foot deformity) is close to those representing neuropathy, foot deformity, ulcer and amputation.

The patients with impaired blood supply form a special group – possibly due to subjective symptoms, they seek help in earlier stages, and are therefore not discovered only by screening. It might be surprising that the point of group 3 (the group with pure ischaemia and no neuropathy) was not closer to the points representing absent foot pulses. A possible explanation is that the patients with poor blood supply may have other problems, a combination of disease changes, which classify them into the risk group 4.

The post-screening decisions were also appropriate: the point representing footwear prescription was close to foot deformity, referral to foot clinic was close to acute foot ulceration, referral to angiologist close to absent foot pulses, and referral to the surgeon closer to acute foot ulceration than to absent pedal pulses.

The main weakness of our study is that it included patients with different duration of diabetes. With longer duration of diabetes, the prevalence of neuropathy and peripheral arterial disease increase. Nevertheless, their influence on the development of foot ulceration mainly depends on their severity and not on duration.

In human medicine, we are often faced with the situations where categorical (nominal and ordinal) variables are predominant. Even some laboratory results, although physical readings, are essentially of ordinal nature. For that reason, we believe that MCA can be useful in the analysis of medical data.

CONFLICTS OF INTEREST

The authors declare that no conflicts of interest exist.

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ETHICAL APPROVAL

The data analysed in this study were collected at the University Medical Centre Ljubljana without information about the identity of individuals. The study was conducted in accordance with the code of Ethics of the World Medical Association (Declaration of Helsinki).

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