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Title: Diabetes and obesity are the main metabolic drivers of peripheral neuropathy

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Abstract

Objective: To determine the associations between individual metabolic syndrome components and peripheral neuropathy in a large population based cohort from Pinggu, China.

Methods: A cross-sectional, randomly selected, population-based survey of participants from Pinggu, China was performed. Metabolic phenotyping and neuropathy outcomes were performed by trained personnel. Glycemic status was defined according to the American Diabetes Association criteria, and the metabolic syndrome using modified consensus criteria (BMI instead of waist circumference). The primary peripheral neuropathy outcome was the Michigan Neuropathy Screening Instrument (MNSI) examination. Secondary outcomes were the MNSI questionnaire and monofilament testing. Multivariable models were used to assess for associations between individual metabolic syndrome components and peripheral neuropathy. Tree based methods were used to construct a classifier for peripheral neuropathy using demographics and metabolic syndrome components.

Results: The mean (SD) age of the 4,002 participants was 51.6 (11.8) and 51.0% were male. 37.2% of the population had normoglycemia, 44.0% pre-diabetes, and 18.9% diabetes. The prevalence of peripheral neuropathy increased with worsening glycemic status (3.25% in normoglycemia, 6.29% in pre-diabetes, and 15.12% in diabetes, $p<0.0001$). Diabetes (odds ratio (OR) 2.60, 95%CI 1.77-3.80) and weight (OR 1.09, 95%CI 1.02-1.18) were significantly associated with peripheral neuropathy. Age, diabetes, and weight were the primary splitters in the classification tree for peripheral neuropathy.

Interpretation: Similar to previous studies, diabetes and obesity are the main metabolic drivers of peripheral neuropathy. The consistency of these results reinforces the urgent need for effective interventions that target these metabolic factors to prevent and/or treat peripheral neuropathy.

Introduction

Peripheral neuropathy is a highly prevalent condition, particularly in older populations.[1-3] This disease affects patients by causing pain, decreased quality of life, falls, ulcerations, and

amputations.[3-5] Unfortunately, outside of medications for neuropathic pain, few therapies exist to help patients with peripheral neuropathy.[4] Even in patients with type 2 diabetes, glycemic control has only a small effect on the prevention of peripheral neuropathy.[6] Furthermore, a significant proportion of patients with peripheral neuropathy have no known underlying cause.[7-10] Therefore, a better understanding of the underlying causes is needed to inform the development of new disease modifying treatments.

Multiple studies have implicated the metabolic syndrome as a potential cause of peripheral neuropathy.[11-14] However, studies that have investigated the contributions of the individual components have revealed mixed results.[15-21] We have recently shown that diabetes, pre-diabetes, and obesity are the main metabolic components associated with peripheral neuropathy in a United States obese population.[22] Similarly, in a United States elderly population, we demonstrated that diabetes, obesity, and the number of metabolic components are associated with peripheral neuropathy.[23] Another group has performed similar studies in Shanghai, China. They found that patients with diabetes and pre-diabetes had a higher prevalence of peripheral neuropathy compared to patients with normoglycemia.[24] Waist circumference and fasting glucose were the main metabolic factors associated with peripheral neuropathy. The same group observed that the peripheral neuropathy prevalence increased as the number of metabolic syndrome components increased.[25] However, the association with metabolic syndrome lost statistical significance when adjusted for insulin resistance.

We aimed to determine the associations between individual metabolic syndrome components and peripheral neuropathy in a large population based cohort from Pinggu, China. In contrast to the previous Chinese study in Shanghai, we included a categorical classification of glycemic status, included interaction terms, limited the analysis to metabolic factors, and avoided potential collinearity in the models. We also investigated the association between the number of metabolic syndrome components. Unlike the previous Chinese study, we evaluated the number of metabolic syndrome components in addition to hyperglycemia and adjusted for the glycemic effect in the models. Finally, we used a tree based approach to build a classifier for peripheral neuropathy based on demographics and metabolic syndrome components. The resulting classification tree allowed identification and characterization of peripheral neuropathy risk groups.

Material and Methods

Population

This study was part of the larger Pinggu metabolic disease study. The study design was a cross-sectional, randomly selected, population-based survey of participants from Pinggu, China. Participants were obtained by a stratified, random sampling method with 5 year age segments of each gender. There are total of 16 towns in the rural area. Five of these towns were randomly selected, and 5 villages were randomly selected from each town. 2,500 participants were randomly sampled from these 25 villages. The remaining 2500 participants were randomly sampled from a randomly chosen urban district (one of two). Individuals were required to be 25–74 year old, born in Pinggu, and lived there for 5 or more years. Pregnant women, individuals who for medical or other reasons would not be able to return for repeat testing over a 2–5 year period were excluded given the longitudinal nature of the larger study. Sexually active women were required to refrain from unprotected sexual intercourse during the course of the study (three weeks). All study protocols were approved by the institutional review board at the University of Michigan.

Metabolic Syndrome components

Individuals filled out surveys including demographic information, and all questions were posed in Chinese via a trained interviewer who recorded responses into a secure computer database. Study team members were present to answer any questions posed by the participants taking the survey. In addition, fasting laboratory assessments were performed included a fasting (10-12 hours) lipid panel and oral glucose tolerance test (75 grams of glucose). Individuals were also measured by a technician for height and weight. Blood pressure was measured in triplicate with the participant's feet flat on the ground.

Diabetes (fasting glucose $\geq$ 126 or 2 hour glucose $\geq$ 200) and pre-diabetes (fasting glucose $\geq$ 100 or 2 hour glucose $\geq$ 140) were defined according to the American Diabetes Association criteria.[26] Consensus metabolic syndrome criteria were used to define the metabolic syndrome and its individual components, with the exception of BMI instead of waist circumference as this data was not available.[27] Specifically, the metabolic syndrome criteria, in addition to the

hyperglycemia definition above, were a BMI>/=30, systolic blood pressure >/= 130 or diastolic blood pressure >/= 85, triglycerides >/= 150mg/dL, and HDL < 40mg/dL in men and < 50mg/dL in women.

Peripheral neuropathy

The MNSI examination and questionnaire were performed by trained personnel as previously described.[28] Monofilament testing was performed with a Semmes Weinstein 5.07/10-g monofilament on the dorsum of the dominant great toe. The primary peripheral neuropathy outcome was an abnormal MNSI examination (≥2.5). Secondary peripheral neuropathy outcomes included an abnormal MNSI questionnaire (≥ 4), and an abnormal monofilament examination (participant is unable to feel 3 or more applications out of 10).[28]

Statistical Analysis

Descriptive statistics were used to describe the demographics and metabolic phenotype of the population. We determined the prevalence of peripheral neuropathy (all three definitions) stratified by glycemic status. We then applied the Cochran-Armitage test to investigate for a trend in the peripheral neuropathy prevalence in the three groups based on glycemic status. Similarly, we determined the prevalence of peripheral neuropathy (primary outcome) stratified by glycemic status and the number of MetS components. We then used the Cochran-Armitage test to determine whether there was a significant trend between peripheral neuropathy and the number of MetS components within each glycemic subgroup.

Multivariable logistic regression was used to model the peripheral neuropathy outcomes as a function of the MetS components (weight as a surrogate for waist circumference, hyperglycemia in the pre-diabetic range, hyperglycemia in the diabetic range, HDL level, triglyceride level, systolic blood pressure), after adjusting for baseline demographic factors (age, sex, height). Interaction effects between glycemic status and the other four MetS components were examined by adding them individually to the multivariable logistic regression models described above.

We performed tree-based analyses (statistical machine learning) to construct a classifier for peripheral neuropathy based on demographics (age, gender, and height) and the MetS

components. In the tree paradigm, the covariate space is partitioned recursively in a binary fashion. Our analyses began with the entire patient cohort and found the best split into two groups based on a variable that makes the resultant two groups most homogeneous within themselves. For our binary outcome of peripheral neuropathy, within group homogeneity was measured using the Gini impurity. The two groups were again partitioned (each group being split on the same or other variables), thereby creating a tree structure. At each step to select the best split the tree-growing paradigm examined every possible cut point for each predictor variable. This process was continued until the groups reached a minimum size (10 patients in each group). Because the resulting tree was overgrown (thereby over fitting the data), a subtree was chosen using cost-complexity pruning.[29, 30] The classification tree was evaluated by examining the percent correct classification (overall, as well as for the peripheral neuropathy cases). We implemented inverse weighting within our classification tree to give proportionally more weight to correct classification of the neuropathy cases. The final tree was selected using a 10-fold cross validation approach.[29, 30] All analyses were performed with SAS 9.3 (Cary, NC) or in R version 3.2.3 using the rpart package.

Results

Demographics and metabolic phenotyping are presented in Table 1 for the 4002 participants. The mean (SD) age was 51.6 (11.8) and 51.0% were male. Normoglycemic participants accounted for 37.2% of the population, pre-diabetes 44.0%, and diabetes 18.9%, which is comparable to the distribution in a previous large Chinese cohort study.[24] The metabolic syndrome was present in 38.0%. The mean (SD) BMI was 26.1 (3.8), SBP 130.1 (18.1), triglycerides 141.2 (130.0), and HDL 45.0 (12.0).

The prevalence of peripheral neuropathy increased with worsening glycemic status regardless of the peripheral neuropathy definition used ($p<0.0001$ for all three peripheral neuropathy outcomes). The prevalence in those with pre-diabetes was higher than those with normoglycemia using the MNSI examination and monofilament definitions ($p<0.0001$), but not using the MNSI questionnaire definition ($p=0.30$). Using the MNSI examination, the prevalence was 3.25% in normoglycemic participants, 6.29% in pre-diabetes, and 15.12% in diabetes. Using the MNSI questionnaire, the prevalence was 1.21% in normoglycemic participants, 1.65% in pre-diabetes,

and 6.08% in diabetes. Using the monofilament definition, the prevalence was 3.70% in normoglycemic participants, 7.29% in pre-diabetes, and 9.13% in diabetes. Controlling for glycemic status, the prevalence of peripheral neuropathy increased with the number of MetS components, particularly in those with normoglycemia (p=0.16) and pre-diabetes (p=0.10), but the result was not statistically significant (Figure 1).

In a multivariable logistic regression model investigating the individual MetS components, hyperglycemia in the diabetic range (odds ratio (OR) 2.60, 95%CI 1.77-3.80) and weight (OR 1.09, 95%CI 1.02-1.18) were significantly associated with the peripheral neuropathy primary outcome (Table 2, MNSI examination). Age, gender, and height were also significantly associated with peripheral neuropathy. For MNSI questionnaire and monofilament, hyperglycemia in the diabetic range was the only MetS component associated with peripheral neuropathy (OR 3.85, 95%CI 2.09-7.09 and OR 1.51, 95%CI 1.01-2.25 respectively). Age and gender were also significantly associated with peripheral neuropathy using these two definitions. Of note, hyperglycemia in the pre-diabetic range had an odds ratio of 1.11-1.41 in the three models, but did not reach statistical significance. No statistically significant interactions between glycemic status and other MetS components were observed. In a multivariable logistic regression model investigating glycemic status and the number of additional MetS components, the number of MetS components (OR 1.17, 95%CI 1.03-1.32) was significantly associated with the peripheral neuropathy primary outcome. Diabetes (OR 2.71, 95%CI 1.86-3.94), but not pre-diabetes (OR 1.25, 95%CI 0.87-1.80, was also significantly associated with peripheral neuropathy in this model.

Using tree analysis, we found that age, glycemic status, and weight were the main demographic and metabolic factors that could help discriminate peripheral neuropathy status (Figure 2). The resulting tree first separates the population into three groups based on age. Patients aged less than 52.5 years old were given a class prediction of “no peripheral neuropathy”, with 97.9% accuracy. Peripheral neuropathy was much more common in those greater than or equal to 67.5 years old (93 out of 360, 25.8%). Those older than 67.5 were predicted to have neuropathy using this classification tree. In those between these two age group, diabetes status, weight and systolic blood pressure were used to split patients into neuropathy groups. For patients aged between 52.5 and 67.5, diabetes status increased the probability of peripheral neuropathy (339 out of 404,

83.9%). Patients in this middle age group that did not have diabetes were further split based on weight and systolic blood pressure to determine their final neuropathy classification.

Discussion

In a large, population-based study in Pinggu, China, we found that diabetes, weight, and the number of MetS components in addition to hyperglycemia are associated with peripheral neuropathy. Participants with pre-diabetes also have a higher prevalence of peripheral neuropathy, but the association does not meet statistical significance in multivariable models. These results are comparable to findings in other populations including those in the United States,[22, 23] another region in China,[24, 25] and the Netherlands.[31] Now that the evidence supporting these specific metabolic drivers of nerve injury is increasingly robust, efforts should turn to interventional studies aimed at weight loss and/or exercise in populations at high risk of peripheral neuropathy. In addition, using statistical machine learning, we demonstrate that age, diabetes, and weight are the key factors that can help clinicians target specific populations for peripheral neuropathy screening. Specifically, patients over the age of 67.5 (25.8%), those over 52.5 with diabetes (83.9%), and those over 52.5 and weighing over 60.75kg (8.5%) are much more likely to have peripheral neuropathy compared to those under the age of 52.5 (2.1%).

While diabetes is the strongest and most well-established metabolic driver of peripheral neuropathy, determining the other metabolic contributors is critical to understand the population at risk and to inform new interventions to prevent and/or treat this common condition. Including this study, five recent investigations reveal that obesity is significantly associated with peripheral neuropathy in multivariable analyses.[22-24, 31] Our results are comparable to those found in 2,035 Han Chinese subjects in Shanghai.[24] Importantly, we were able to address important limitations of the previous study including addressing the effects of interactions between metabolic components and glycemic status, focusing the analysis on metabolic factors, and avoiding collinearity in the multivariable models. Our population demographics were also different with our study including younger participants (51.5 vs. 61.5), with a higher proportion of normoglycermia (37.2% vs. 19.9%), a higher mean BMI (26.1 vs. 24.4), and more males 51.0% vs. 43.3%). Despite the differences in population location and demographics, the definition of neuropathy, and statistical modeling design, the results are consistent. Similarly, studies in obese and elderly populations in the United States,[22, 23] and an older population in the Netherlands[31]

lead to the same conclusion despite study design differences. With strong evidence supporting obesity as a metabolic driver of peripheral neuropathy, we need to start considering obesity as a potential cause of peripheral neuropathy in the non-diabetic obese and design interventions that address this underlying metabolic cause.

In contrast to the evidence supporting obesity, the data supporting pre-diabetes is less clear. We found that the prevalence of peripheral neuropathy was higher in those with pre-diabetes than those with normoglycemia, but the association was not significant in multivariable models. With many previous studies supporting,[16, 32, 33] and some not supporting,[23, 34] an association of pre-diabetes with peripheral neuropathy, our results do not push the overall level of evidence much in either direction. Our study is now the third to show an increased odds ratio in those with pre-diabetes that does not meet statistical significance.[22, 31] Possible explanations are that the study was not adequately powered to detect this small effect size or that pre-diabetes is not the underlying metabolic driver of nerve injury when accounting for other metabolic factors. Another possibility is that definitions of neuropathy that primarily measure large fiber function, such as in our study, may miss the association between pre-diabetes and neuropathy because pre-diabetes may preferentially injure small fiber nerves.[35] Interestingly, the only other study addressing this issue in a Chinese population demonstrated that 2 hour post prandial glucose levels were associated with peripheral neuropathy in the pre-diabetes population.[24] Regardless of whether pre-diabetes is one of the underlying metabolic drivers of peripheral neuropathy, the best interventions to study is unlikely to change. Current data supports weight loss and/or exercise as the best treatment to prevent pre-diabetes from transitioning to diabetes,[36] and these are also the best interventions for the now well-established metabolic driver of peripheral neuropathy, obesity.

Besides diabetes and obesity, we also found that the number of metabolic syndrome components in addition to hyperglycemia was significantly associated with peripheral neuropathy. This finding was observed despite the fact that obesity was the only other metabolic syndrome component significantly associated with peripheral neuropathy. Our finding is comparable to studies performed in China,[25] the United States,[23] and the Netherlands.[31] Unlike the China and Netherlands studies, we did not include hyperglycemia as one of the metabolic syndrome components since this is already the strongest and most well established risk factor for peripheral

neuropathy. The United States study used a similar modeling strategy with comparable results. Like some previous studies, we did not find associations of peripheral neuropathy with systolic blood pressure, triglycerides, or HDL levels.[22-24] Therefore, our data would support interventions that target the metabolic syndrome as a whole rather than concentration on blood pressure and/or cholesterol management. However, it should be noted that some studies have revealed an association with triglycerides and neuropathy.[21, 31]

Another key finding is that we were able to use statistical machine learning to define the populations most at risk of peripheral neuropathy including evaluating for potential important interactions. This information is crucial for physicians so that they can screen for peripheral neuropathy in the appropriate groups. Emphasizing this point, screening tests have the best performance in populations with a higher prevalence of disease. We found that age alone is a key variable with participants over the age of 67.5 at much higher risk of peripheral neuropathy than those under 52.5 even with no other metabolic abnormalities. Diabetes substantially increases the prevalence of peripheral neuropathy in those over 52.5 to the point where the vast majority of this population has highly morbid condition. Weight is another metabolic factor identified, with those older than 52.5 and weighing more than 60.75 kg have a slightly increased risk of peripheral neuropathy. This data highlights the importance of age and peripheral neuropathy. Previous studies have shown that the prevalence of peripheral neuropathy, particularly idiopathic peripheral neuropathy, rises dramatically with age.[37] Furthermore, these results reveal that diabetes has a much greater impact on peripheral neuropathy than obesity. Diabetes continues to be the strongest metabolic driver of peripheral neuropathy and new disease modifying treatments are desperately needed in this population.

Limitations include the cross sectional study design and lack of waist circumference, diabetes duration, and medication data. Furthermore, the generalizability of these results to other populations is unclear. However, the population-based methodology and size of the population are strengths. Furthermore, the consistency of results with other investigations utilizing different populations and study designs support the data's generalizability and validity. The neuropathy definition was based on standardized examination and questionnaires, but not on a neurologist's history and examination or confirmatory measures (nerve conduction studies or skin biopsies). On the other hand, the MNSI questionnaire and examination are validated measures of

neuropathy and have been used successfully in both type 1 and type 2 diabetic cohorts.[28, 38-40] While the MNSI instruments have not been validated in Asian populations, the prevalence of neuropathy was comparable to a previous large Chinese cohort study using a different neuropathy definition.[24] We also were unable to adjust our models for potential confounders such as alcohol consumption and comorbidities.

A consensus is emerging that diabetes and obesity are the main metabolic drivers of peripheral neuropathy. As a result, intervention studies are needed to demonstrate whether treatment of these underlying abnormalities can lead to the prevention and/or treatment of this common condition. Weight loss and/or exercise regimens may be the most promising given that they can be effective in those with diabetes, obesity, and pre-diabetes. Given the lack of current disease modifying therapies, funding for new treatments should be a priority.

Author contributions:

Brian Callaghan was involved in the study design, interpretation of the statistical analysis, and wrote the manuscript. Evan Reynolds and Mousumi Banerjee were involved in the statistical analyses, interpretation of the data, and critical revisions of the manuscript. Eva Feldman, Rodica Pop-Busui, and Linong Ji were involved in the study design, interpretation of the data, and critical revisions of the manuscript. LeiLi Gao, Yufeng Li, and Xianghai Zhou were involved in the interpretation of the data and critical revisions of the manuscript.

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Brian Callaghan is the principal author and takes full responsibility for the data, analyses, interpretation, and the conduct of the research. He has full access to all of the data used in this manuscript and has the right to publish any and all data separate and apart from any sponsor.

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Disclosures:

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Figure 1 Title: The prevalence of DSP with increasing metabolic syndrome components stratified by glycemic status.

Figure 1 Legend: DSP was defined as those with a MNSI Examination score > 2. Glycemic status was determined by the glucose tolerance test according to the Expert Committee on the diagnosis and classification of diabetes mellitus. Metabolic syndrome components were defined using modified consensus criteria.

Figure 2 Title: Classification tree analysis for peripheral neuropathy based on demographics and the MetS components

Figure 2 Legend: A tree based approach was used to build a classifier for peripheral neuropathy based on demographics and metabolic syndrome components. The resulting classification tree allowed identification and characterization of peripheral neuropathy risk groups.

Table 1: Demographics of the Pinguu population stratified by glycemic status

Variable	Total	Normoglycemia	Pre-diabetes	Diabetes
Subjects, N (%)	4002 (100%)	1487 (37.2%)	1758 (44.0%)	757 (18.9%)
Age, mean (SD)	51.6 (11.8)	47.2 (11.8)	53.2 (11.3)	56.7 (9.9)
Male, N (%)	2039 (51.0%)	885 (59.5%)	816 (46.4%)	338 (44.7%)
Height (cm), mean (SD)	162.6 (8.4)	162.3 (8.4)	162.7 (8.2)	162.9 (8.6)
Fasting glucose (mg/dL), mean (SD)	109.5 (29.4)	93.0 (4.8)	105.8 (7.5)	150.9 (46.0)
2 hour glucose (mg/dL), mean (SD)	133.1 (46.4)	106.9 (19.0)	136.4 (8.2)	228.3 (64.7)
BMI (kg/m^2), mean (SD)	26.1 (3.8)	24.9 (3.6)	26.5 (3.8)	27.4 (3.8)
SBP (mm Hg), mean (SD)	130.1 (18.1)	123.6 (17.0)	132.5 (17.1)	137.5 (18.3)
DBP (mm Hg), mean (SD)	78.7 (11.4)	75.8 (10.7)	80.2 (11.3)	81.1 (11.7)
Cholesterol (mg/dL), mean (SD)	190.6 (38.1)	183.0 (33.8)	193.7 (37.4)	198.2 (44.4)
Triglycerides (mg/dL), mean (SD)	141.2 (130.0)	106.3 (85.5)	150.7 (134.7)	187.8 (167.9)
HDL (mg/dL), mean (SD)	45.0 (12.0)	46.9 (12.2)	44.4 (11.8)	42.7 (11.6)
LDL (mg/dL), mean (SD)	111.3 (31.5)	107.2 (29.0)	114.0 (31.5)	112.9 (35.1)
Metabolic syndrome, N	1519	138	900	481

(%)	(38.0%)	(9.3%)	(51.2%)	(63.5%)

1

2 BMI=body mass index, SBP=systolic blood pressure, DBP=diastolic blood pressure, HDL=high
3 density lipoprotein cholesterol, LDL=low density lipoprotein cholesterol

4

5 Table 2:Multivariable logistic regression evaluating the association of MetS components and
6 neuropathy

	Primary outcome	**Secondary outcomes**	
Variable	**MNSI Examination OR (95%CI)**	**MNSI Questionnaire OR (95%CI)**	**Monofilament OR (95%CI)**
Demographics			
Age	1.10 (1.09,1.12)*	1.07 (1.05,1.10)*	1.10 (1.08,1.12)*
Male (reference female)	1.68 (1.14,2.47)*	2.03 (1.05,3.91)*	1.56 (1.05,2.31)*
Height unit=5 cm	1.20 (1.05,1.37)*	0.89 (0.71,1.10)	1.14 (1.00,1.15)
MetS Components			
Diabetes Pre-diabetes (reference normal)	2.60 (1.77,3.80)* 1.21 (0.84,1.75)	3.85 (2.09,7.09)* 1.11 (0.60,2.06)	1.51 (1.01,2.25)* 1.41 (1.00,1.99)
Weight	1.09 (1.02,1.18)*	1.00 (0.98,1.03)	1.00 (0.98,1.01)

unit=5 kg			
SBP unit=10 mm Hg	1.04 (0.96,1.11)	0.93 (0.82,1.05)	1.07 (0.99,1.15)
Triglycerides unit=50 mg/dL	1.01 (0.96,1.06)	0.90 (0.79,1.02)	0.94 (0.87,1.01)
HDL unit=10 mg/dL	0.99 (0.87,1.12)	0.87 (0.69,1.08)	1.03 (0.91,1.16)

*=p<0.05, MNSI=Michigan Neuropathy Screening Instrument, MetS=metabolic syndrome, SBP=systolic blood pressure, HDL=high density lipoprotein cholesterol

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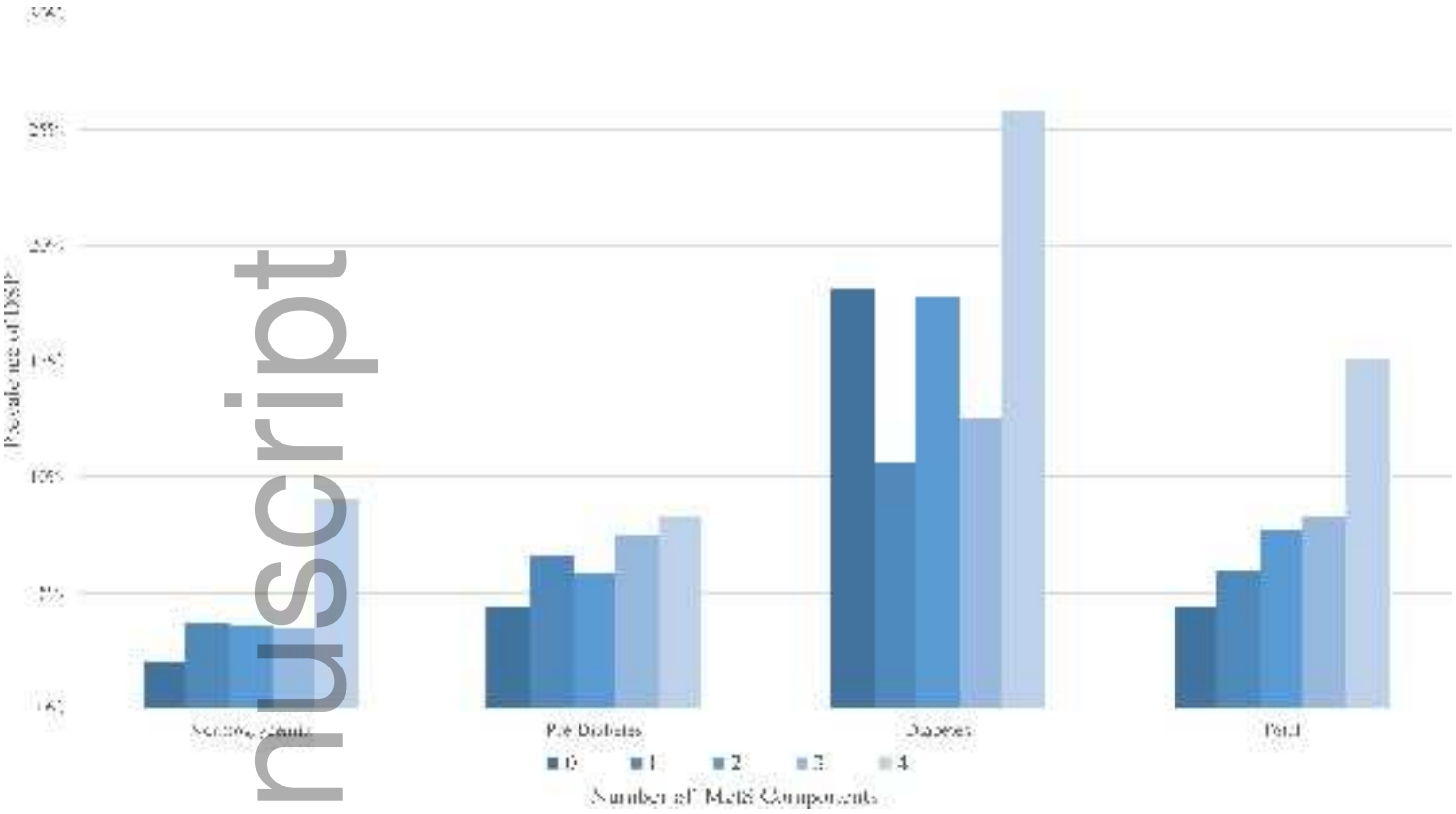

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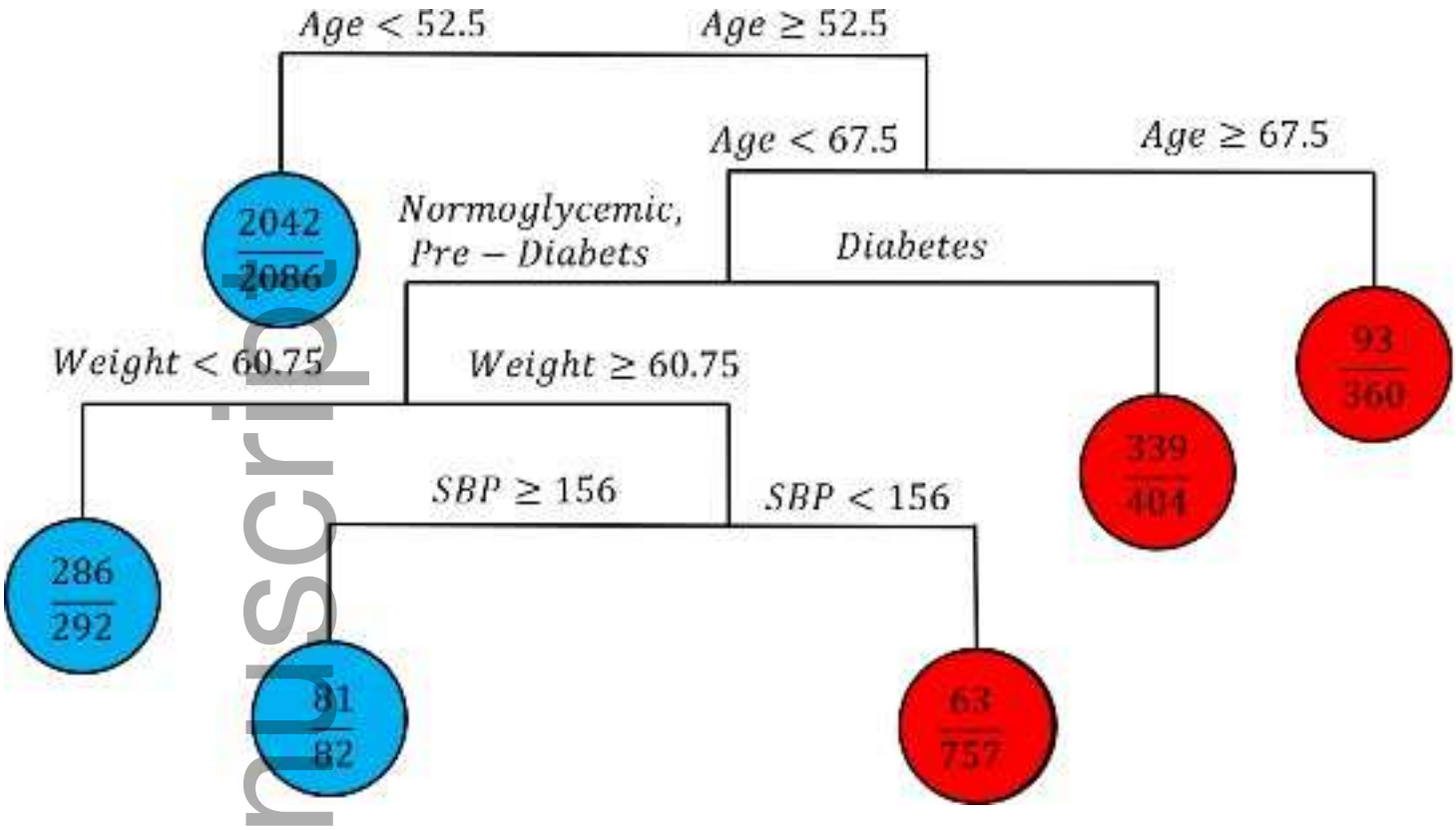

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