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Associations between diabetes-related symptoms, glucose management, and health-related quality of life in adult Samoans

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ABSTRACT

Introduction: The prevalence of type 2 diabetes in Samoa has increased substantially over the last 30 years. Identifying common symptoms in those living with diabetes may be instrumental in directing those at risk to seek early evaluation, diagnosis, and treatment. Additionally, identifying associations between diabetes experiences and health-related quality of life is useful for understanding the lived experience of having diabetes in this setting. Here we present the first description of diabetes-related symptoms in an adult cohort of Samoans with diabetes and prediabetes and describe associations between symptom presence and sex, suboptimal glycemia (HbA1c ≥ 8.0%), and health-related quality of life (HRQL). We also assessed whether reported symptoms were independently associated, when adjusting for other factors, with increased odds of having diabetes.

Methods: Analyses were conducted on n = 123 adult Samoan participants selectively sampled from the observational cohort Soifua Manuia (2017-2019) study in Samoa. These participants were originally recruited for a 2010 Genome Wide Association Study (GWAS) and were selectively recruited for the 2017-2019 follow-up study based on their rs373863828 genotypes and were resident on 'Upolu Island. Participants included in this analysis were only those who were living with either prediabetes or diabetes and completed a series of anthropometric, biochemical, and questionnaire measures including the Revised Diabetes Symptoms Checklist (DSC-R) questionnaire between 2017-2019. Differences in symptom presence by sex, diabetes status (prediabetes vs. diabetes), optimal vs. suboptimal glycemia (HbA1c < or ≥ 8.0%), and HRQL were assessed using Independent Sample T-tests, Mann Whitney U tests and Chi-square tests of association. Multivariate logistic regression was used to assess which symptoms, when controlling for other factors, were associated with increased odds of having diabetes.

Findings/Outcomes measure: In a small sample of adult Samoans, we observed high symptom burdens among those with prediabetes and diabetes, and sex differences in the reported impact of diabetes symptoms on health-related quality of life. We identified three specific symptoms – frequent urination, difficulty thinking clearly, and chest/heart pains – that may be useful indicators of diabetes in this setting,

Conclusions: A high prevalence of symptoms was observed among those with prediabetes and among those with diabetes. It is recommended that individuals experiencing any of the measured symptoms seek early evaluation and engage in diabetes self-care behaviours to prevent diabetes-related complications and/or progression to diabetes among those at risk.

Key words: type 2 diabetes, Samoa, DSC-R, health-related quality of life

INTRODUCTION

Pacific Islanders, like Samoans, are at high risk for type 2 Diabetes (hereafter referred to as diabetes). This risk is exacerbated by the escalating prevalence of key diabetes risk factors such as obesity[1]; additionally, rapid modernisation in the region has shifted diets towards low-quality, calorically dense foods and reduced opportunities for subsistence living/occupation-related physical activity.[1, 2] In Samoa, between 1978 and 2013, age-adjusted diabetes prevalence increased from 2.2% to 19.5% among women and from 1.2% to 19.6% among men.[3] In the *Soifua Manuia* study— a cohort of n=519 Samoan adults recruited in 2010 and re-recruited in 2017-2019— we found that diabetes prevalence at the time of re-recruitment, based on fasting glucose levels, was 29.2%;[4] however, less than half of those affected (41.8%) were aware of their condition and had received a formal diagnosis.[4] Identifying common symptoms in those living with diabetes

may be instrumental in directing those at risk to seek early evaluation, diagnosis, and treatment.[5, 6] Doing so will also illuminate whether reported symptoms among Samoan adults differ by sex or between individuals with optimal and suboptimal glycemia, and/or whether the presence of diabetes symptoms is associated with mental or physical health-related quality of life (HRQL) (associations which have all been observed in other settings).[7-10] These data are critical for informing targeted efforts to identify those with diabetes and understanding the lived experience of having diabetes in Samoa. Furthermore, these investigations may help to illuminate what symptoms may be already present in those with prediabetes (a risk factor for the development of micro- and macrovascular complications).[11]

Pacific Islanders globally also experience a disproportionate burden of diabetes and prediabetes. For example, in New Zealand Pacific Islanders experience a disproportionately higher prevalence of prediabetes (29.8%) than New Zealand/European groups (24.6%).[12] Additionally, a recent study of the PORTAL network (which includes 10 sites and 3 healthcare systems within the US) demonstrated that in a population of 4,906,238 US adults, the prevalence of both prediabetes (36.7%) and diabetes (27.7%) among Native Hawai'ians and Pacific Islanders was the highest compared to all other analyzed ethnic groups, and disproportionately higher than the prevalence of prediabetes (31.0%) and diabetes (12.2%) observed among non-Hispanic White patients.[13] Therefore, this study may be relevant for Samoan diaspora communities and other Pacific Islanders.

Here we present the first description of diabetes-related symptoms in an adult cohort of Samoans with HbA1c ≥ 6.5% (classified here as glycemia indicative of diabetes) or HbA1c ≥ 5.7% to < 6.5% (classified here as glycemia indicative of prediabetes). Our goals were to 1) describe the frequency of reported symptoms in men and women; 2) measure unadjusted associations between (a) symptom presence and diabetes status, (b) symptom presence and sex, (c) symptom presence and optimal/suboptimal glycemia (HbA1c < or ≥ 8.0%), and (d) symptom presence and mental and physical HRQL; and 3) determine whether reported symptoms were independently associated, when adjusting for other factors, with increased odds of having diabetes.

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presence and mental and physical HRQL; and 3) determine whether reported symptoms were independently associated, when adjusting for other factors, with increased odds of having diabetes.

METHODS

Setting

Samoa is an independent Polynesian island nation with a population of approximately 203,774.[14] Participants from three of four Samoan census regions are represented in this study: the Apia Urban Area (AUA; Apia is the capital), Northwest 'Upolu (NWU), and the Rest of 'Upolu (ROU).

Study Population

Participants included in these analyses were selectively sampled from adult men and women (age ≥ 32.5 -72 years; n=519 total) who took part in the 2017-2019 *Soifua Manuia* ("Good Health") study[15]. The study aimed to characterize associations between a missense variant (rs373863828) in CREB3 regulatory factor (CREBRF) and metabolic and behavioral traits. Inclusion criteria for the study have been reported previously.[15] Among other criteria, those who were enrolled were between the ages of 32.5-72 years and had previously participated in a 2010 Genome Wide Association Study (GWAS) study without regard to any health conditions; a subsample was selectively

recruited for the 2017-2019 follow-up study. The 2017-2019 study was designed to enroll participants, resident on 'Upolu Island, at an approximate a ~2:2:1 ratio of GG:AG:AA rs373863828 genotypes (the A allele has been previously found to be associated with reduced odds of type 2 diabetes).[16] Participants included in the analyses presented here (n = 123) were only those who had HbA1c ≥ 5.7% to < 6.5% (prediabetes) or HbA1c ≥ (diabetes) and completed a series of questionnaire measures including the 34-item revised Diabetes Symptoms Questionnaire (DSC-R).[17, 18]

Study Measures

The DSC-R groups symptoms into eight domains: psychological-fatigue, psychological-cognitive, neuropathic pain, neuropathic sensory, cardiovascular, ophthalmologic, hypoglycemic, and hyperglycemic. Although the questionnaire asks about both presence and severity of symptoms, this study only assessed symptom presence. In the original *Soifua Manuia* study design, the DSC-R was to be administered only to participants with diabetes (those who either reported a prior diabetes diagnosis and/or presented with HbA1c values ≥6.5%). However, this strategy changed during study implementation and administration of the DSC-R was expanded to all participants, regardless of their diabetes status; this change allowed us to examine whether symptoms included on the DSC-R were unique to people living with diabetes in this setting. Nonetheless, the timing of the change during study implementation meant that completed DSC-R questionnaire data was obtained from only n = 130 participants.

Participants also completed the Short Form 8 (SF-8™)[19] assessing health-related quality of life (HRQL), from which physical health component scores (PCS) and mental health component scores (MCS) were calculated. For both, higher scores indicate better self-reported HRQL. In addition, participants reported sociodemographic (i.e., age, sex, census region of residence, education levels) and health information including other chronic condition diagnoses. Participants were categorized as having other chronic conditions if they reported prior diagnoses of heart disease, hypertension, heart attack, stroke, or angina. All questionnaire measures were translated and back-translated by trained Samoan researchers bilingual in Samoan and English; the Short Form 8 (SF-8™)[19] had been previously used in a Samoan population in American Samoa.

Blood Pressure (BP) was measured three times, with a three-minute rest period between measurements, using an Omron HEM-907XL automated blood pressure monitor (Omron Healthcare). The last two BP measures were averaged for analyses. If participants had an averaged measured BP indicative of hypertension during the study assessment (Systolic BP ≥ 140mmHg and/or Diastolic BP ≥ 90mmHg), they were also categorized as having chronic conditions (hypertension). Calculated body mass index (kg/m^2) is also reported here to characterize the study population. All measures were collected using standard procedures.[15]

Diabetes status was determined based on point of care HbA1c (DCA vantage analyzer, Siemens Healthcare GmbH). Participants were categorized as not having diabetes if their HbA1c was < 5.7%; participants were categorized as having prediabetes if their HbA1c was ≥5.7% and < 6.5%, or as having diabetes if their HbA1c was ≥ 6.5% (with the acknowledgement that HbA1c values collected at one time are not adequate for clinical diagnosis). Additionally, individuals were also classified as having diabetes based on self-report of a prior clinical diagnosis or use of diabetes medication, regardless of HbA1c. Individuals with HbA1c ≥ 8.0% were classified as having suboptimal glycemia.[20-23] Associations between medication use and symptoms were assessed statistically.

Statistical Analyses

Of the n = 130 participants with data collected from the DSC-R questionnaire, analyses were conducted only on those classified as having diabetes or prediabetes (n = 71 with diabetes and n=52 individuals with prediabetes), yielding an analytic sample of n = 123. We chose to exclude n = 7 individuals who completed the DSC-R and had neither prediabetes nor diabetes (HbA1c < 5.7%) due to the small sample size. A sex-stratified sensitivity analysis of associations between symptom presence and diabetes status including these n = 7 excluded participants can be viewed in Supplementary Table 1.

Differences in sociodemographic, anthropometric, and health characteristics by sex, diabetes status, and optimal/suboptimal glycemia were examined using independent sample T-tests for normally distributed variables, Mann-Whitney U tests for non-normally distributed variables, and X^2 tests for categorical variables (**Table 1**). Sex-stratified associations between symptom presence and diabetes status (prediabetes or diabetes) were assessed using X^2 tests (**Table 2**). Analyses were sex-stratified due to associations between sex and chronic disease health behaviors, attitudes, and symptom reporting recorded in other settings.[8, 24-26] Symptoms were initially grouped into their respective domains for analysis; based

on poor internal consistency for many of the domain groupings (calculated using Cronbach's α) (**Table 2**), we chose to examine symptoms individually. Sex-stratified associations between symptom presence and optimal/suboptimal glycemia (HbA1c 6.5% to <8.0% vs ≥ 8.0%) among those with diabetes were examined using X^2 tests of association (Supplementary Table 2). Sex-stratified associations between symptom presence and SF-8™ MCS and PCS HRQL scores were assessed using Mann-Whitney U tests of association for non-normally distributed data (Supplementary Table 2). Fishers Exact Tests were used for all categorical analyses if cell sizes <5.

Using stepwise logistic regression (to reduce the number of independent variables due to small sample size), we assessed which of the symptoms, after adjusting for other factors, were independently associated with odds of having diabetes. We subjectively chose to include only those symptoms that varied between those with prediabetes and diabetes in the sex-stratified unadjusted analyses using the cutoff of p<0.1. Diabetes (ref: prediabetes) was the dependent variable, and age, sex, BMI, presence of other chronic conditions, and the symptoms were independent variables. Non-symptom independent variables were chosen *a priori* based on their association with diabetes risk.[27-30] Removal criterion for the backwards stepwise procedure was set at p<0.15, and model fit was assessed to avoid issues of collinearity between symptoms. To maintain statistical power when analyzing multiple variables in a small sample, the model was not stratified by sex but included sex as a covariate. Due to missing data in several of the variables, the final model included n = 108 participants (**Table 3**).

It is possible that the use of blood glucose lowering diabetes medications, if taken as prescribed, may influence the presence of hyperglycemia-related symptoms.[31, 32] Preliminary analyses (not shown) did not identify statistical associations between medication use and either optimal/suboptimal glycemia, or reported symptoms. Therefore, analyses do not control for medication use.

Ethical Review

The study underwent initial and annual continuing ethical review by institutional review boards (IRBs) at Yale and Brown Universities (Yale served as the IRB of record, IRB#1604017547). The study was also approved by the Health Research Committee of the Samoan Ministry of Health. All participants provided their written informed consent

RESULTS

Sample characteristics

The sample included n=123 Samoans (n=68 women) with a mean age of 55.5 ± 9.3 years and BMI of 35.9 kg/m^2 ± 7.9 (**Table 1**). Of the sample, 42.3% had prediabetes and 52.7% had diabetes. A significantly higher proportion of women compared to men had diabetes (66.2% vs. 47.3%, p = 0.035). Median HbA1c for the sample was 6.8% (IQR: 4.6%) and 69.1% of participants with diabetes had suboptimal glycemia. The presence of other chronic conditions was recorded in 44.7% of participants. Compared to those with prediabetes, a significantly higher proportion of participants with diabetes also had other chronic conditions (p = 0.001). SF-8™ mental and physical health summary scores did not significantly differ between men and women, among participants with prediabetes vs. diabetes, or among participants with optimal vs. suboptimal glycemia.

Symptoms

Among men, significant variation by diabetes status (prediabetes vs. diabetes) was observed for the following symptoms (**Table 2**): frequent need to empty their bladders, lack of energy, overall sense of fatigue, increasing fatigue over a day, fuzzy feeling in the head/difficulty thinking clearly, sleepiness or drowsiness, shortness of breath during exertion, pains in the breast or heart region, tingling in the hands, an odd feeling in their legs when touching, and deteriorating vision. In all cases, a greater proportion of men with diabetes reported experiencing the symptoms compared to men with prediabetes.

Among women, significant variation by diabetes status was observed for the following reported symptoms: experiencing a fuzzy feeling in their head/difficulty thinking clearly, deteriorating vision, seeing black flashes or spots in their vision, experiencing alternating clear and blurred vision, and a sudden deterioration in vision (**Table 2**). In all cases, a higher proportion of women with diabetes reported experiencing the symptoms compared to women with prediabetes. The only significant difference in symptom reporting between the sexes was that a higher proportion of women reported experiencing a 'fuzzy' head/difficulty thinking clearly compared to men; all other symptoms did not significantly vary between sexes.

Table 1: Participant characteristics: Tests of associations conducted via Mann-Whitney U tests, Chi-square tests of association. Means and standard deviations or n (%) presented.

Variables	**Total (n=123)**	**Men (n=55)**	**Women (n=68)**	**Differences by sex P < 0.05**	**Prediabetes (n=52)**	**Diabetes (n=71)**	**Differences by Diabetes status p< 0.05**	**Optimal glycemia (HbA1c <8.0%) (n = 21) ***	**Suboptimal glycemia (HbA1c ≥ 8.0%) (n =47)**	**Differences between optimal vs. suboptimal glycemia (HbA1c < or ≥ 8.0%) P < 0.05**
Age (years)	55.5 (9.3)	57.6 (8.9)	53.8 (9.3)	0.026	53.1 (10.3)	57.2 (8.1)	**0.012**	58.8 (9.5)	56.3 (1.0)	0.122
≥50 years (%)	52 (42.3%)	29 (52.7%)	23 (33.8%)	0.035	28 (53.8%)	58 (81.7%)	0.066	12 (57.1%)	23 (48.9%)	0.605
Census region of residence										
Apia Urban Area (%)	21 (17.1%)	11 (20.0%)	10 (14.7%)	0.146	9 (17.3%)	12 (16.9%)	0.320	4 (19.0%)	7 (14.9%)	0.937
Northwest 'Upolu (%)	32 (26.0%)	18 (32.7%)	14 (20.6%)		10 (19.2%)	22 (31.0%)		6 (28.6%)	14 (29.8%)	
Rest of 'Upolu (%)	70 (56.9%)	26 (47.3%)	44 (64.7%)		33 (63.5%)	37 (52.1%)		11 (52.4%)	26 (55.3%)	
Education (≥ secondary school completed) (%)	91 (73.9%)	36 (65.4%)	55 (80.9%)	0.052	42 (80.8%)	51 (69.0%)	0.142	13 (61.9%)	33 (70.2%)	0.579
Anthropometrics										
BMI (kg/m^2)	35.9 (7.9)	35.1 (6.5)	36.6 (8.8)	0.293	35.7 (8.5)	36.1 (7.4)	0.558	37.5 (6.1)	35.7 (8.0)	0.259
SBP (mmHg)	128.4 (19.4)	130.7 (15.1)	126.4 (22.3)	0.123	123.2 (16.6)	132.2 (20.5)	**0.012**	136.9 (20.9)	129 (19.9)	0.186
DBP (mmHg)	77.8 (11.7)	79.1 (10.2)	76.7 (12.9)	0.277	78.0 (11.0)	77.6 (12.3)	0.865	76.5 (12.8)	77.6 (12.1)	0.736
Hba1c (%) *¶	6.8 (4.6)	6.3 (2.8)	7.2 (4.9)	0.115	6.0 (0.4)	9.9 (4.5)	**<0.001**	6.1 (0.5)	11.3 (3.7)	**<0.0001**
Prediabetes (%)	52 (42.3%)	29 (52.7%)	23 (33.8%)	0.035	-	-	-	-	-	-
Diabetes (%)	71 (57.7%)	26 (47.3%)	45 (66.2%)	0.035	-	-	-	-	-	-
Previously diagnosed with diabetes (%) *	49 (69.0%)	19 (73.1%)	30 (66.7%)	0.607	-	49 (69.0%)	-	10 (47.6%)	37 (78.7%)	**<0.010†**
Suboptimal glycemia (HbA1c ≥ 8.0%) (%) *	47 (69.1%)	17 (30.9%)	30 (46.1%)	0.088	-	47 (69.1%)	-	-	-	-
Other chronic conditions (%)	55 (44.7%)	26 (44.1%)	30 (42.2%)	0.835	14 (26.9%)	41 (57.7%)	**0.001**	15 (71.4%)	23 (48.9%)	0.084
Health-related Quality of Life (HRQL)										
Physical Health subscale score	41.2 (7.6)	41.7 (7.4)	40.7 (7.8)	0.510	42.3 (6.3)	40.3 (8.4)	0.129	38.3 (8.0)	41.2 (8.7)	0.208
Mental Health subscale score	45.2 (10.3)	46.4 (10.9)	44.2 (9.8)	0.864	45.1 (10.2)	45.3 (10.4)	0.967	45.8 (11.9)	45.4 (10.1)	0.956

Tests of association were conducted using Mann-Whitney U tests, and Kruskal-Wallis tests for all variables except Systolic and Diastolic BP.
Associations between Sex and Systolic BP, and optimal/suboptimal glycemia, and Systolic BP conducted using independent samples T-test. Associations between Sex and Diastolic BP, and optimal/suboptimal glycemia and Diastolic BP conducted using independent samples T-test.
¶Median HbA1c calculated from n=19 men, and n=28 women; median and interquartile range calculated due to non-normal distribution of HbA1c
*n=2 women missing HbA1c measures
†Assessed only among individuals who had diabetes (n=71)
* n = 3 participants missing HbA1c measures, so diabetes control not assessed; Optimal vs. suboptimal glycemia was only assessed among individuals with diabetes
Bold font indicates association is significant at p < 0.05

Table 2: Sex-stratified tests of association between individual symptom presence and diabetes status (prediabetes vs. diabetes), and tests of association between symptom presence and sex

			Men		Associations between symptoms and diabetes status	Women		Associations between symptoms and diabetes status	Associations between symptoms and sex
DSC-R domains	**Cronbach's α**	**Have you experienced any of the following symptoms?**	**Prediabetes (n=29)**	**Diabetes (n=26)**	**p-values**	**Prediabetes (n=23)**	**Diabetes (n=45)**	**p-values**	**p-values**
Hyperglycemic	0.65	Very thirsty (%)	14 (48.3%)	18 (69.2%)	0.116	15 (65.2%)	31 (68.9%)	0.759	0.179
		Dry mouth (%)	10 (34.5%)	14 (53.8%)	0.148	11 (47.8%)	24 (53.3%)	0.727	0.281
		Drink a lot (%)	11 (37.9%)	15 (57.7%)	0.143	15 (65.2%)	26 (57.8%)	0.553	0.092
		Frequent need to empty bladder (%)	6 (20.7%)	19 (73.1%)	**<0.0001**	9 (39.1%)	22 (48.9%)	0.434	0.914
Hypoglycemic	0.63	Moodiness (%)	12 (41.4%)	16 (61.5%)	0.097	12 (52.2%)	26 (57.8%)	0.802	0.773
		Easily annoyed or irritated (%)	15 (51.7%)	17 (65.4%)	0.305	10 (43.5%)	29 (64.4%)	0.195	0.816
		Irritability before a meal (%)	10 (34.5%)	10 (38.5%)	0.835	5 (21.7%)	19 (42.2%)	0.118	0.885
Psychological fatigue	0.81	Lack of energy (%)	10 (34.5%)	17 (65.4%)	**0.019**	12 (52.2%)	27 (60.0%)	0.595	0.235
		Overall sense of fatigue (%)	8 (27.6%)	15 (57.7%)	**0.024**	8 (34.8%)	25 (55.6%)	0.140	0.275
		Fatigue in the morning when getting up (%)	7 (24.1%)	12 (46.2%)	0.086	7 (30.4%)	24 (53.3%)	0.097	0.183
		Increasing fatigue during the course of a day (%)	2 (6.9%)	10 (38.5%)	**0.005**	4 (17.4%)	18 (40.0%)	0.074	0.154
Psychological cognitive	0.53	Fuzzy feeling in head/difficulty thinking clearly (%)	3 (10.3%)	10 (38.5%)	**0.024**	4 (17.4%)	22 (48.9%)	**0.016**	**0.038**
		Sleepiness or drowsiness (%)	1 (3.4%)	7 (26.9%)	**0.014**	4 (17.4%)	13 (28.9%)	0.394	0.079
		Difficulty concentrating (%)	5 (17.2%)	6 (23.1%)	0.589	4 (17.4%)	10 (22.2%)	0.670	0.815
		Difficulty staying attentive (%)	14 (48.3%)	16 (61.5%)	0.324	10 (43.5%)	29 (64.4%)	0.139	0.867
Cardiovascular	0.56	Shortness of breath during physical exertion (%)	7 (24.1%)	13 (50.0%)	**0.047**	9 (39.1%)	19 (42.2%)	0.918	0.380
		Shortness of breath at night (%)	4 (13.8%)	9 (34.6%)	0.181	3 (13.0%)	12 (26.7%)	0.230	0.984
		Palpitations (%)	5 (17.2%)	9 (34.6%)	0.140	3 (13.0%)	7 (15.6%)	0.836	0.171
		Pains in the breast or heart region (%)	2 (6.9%)	9 (34.6%)	**0.010**	3 (13.0%)	16 (35.6%)	0.062	0.189
Neuropathic pain	0.76	Aching calves when walking (%)	11 (37.9%)	15 (57.7%)	0.143	10 (43.5%)	21 (46.7%)	0.926	0.947
		Shooting pains in the legs (%)	9 (31.0%)	13 (50.0%)	0.152	10 (43.5%)	20 (44.4%)	0.938	0.441
		Burning pain in the calves at night (%)	2 (6.9%)	4 (15.4%)	0.313	2 (8.7%)	12 (26.7%)	0.097	0.150
		Burning pain in the legs during the day (%)	4 (13.8%)	5 (19.2%)	0.586	3 (13.0%)	9 (20.0%)	0.498	0.781
Neuropathic sensory	0.84	Loss of sensation in the hands (%)	13 (44.8%)	14 (53.8%)	0.504	13 (56.5%)	24 (53.3%)	0.801	0.265
		Loss of sensation in the feet (%)	12 (41.4%)	15 (57.7%)	0.213	11 (47.8%)	32 (71.1%)	0.091	0.086
		Tingling/prickling in the hands or fingers (%)	16 (55.2%)	21 (80.8%)	**0.043**	14 (60.9%)	32 (71.1%)	0.714	0.536
		Tingling/prickling in the feet or lower legs (%)	16 (55.2%)	20 (76.9%)	0.054	15 (65.2%)	30 (66.7%)	0.901	0.691
		Odd feeling in the legs/ feet when touching (%)	5 (17.2%)	13 (50.0%)	**0.010**	5 (21.7%)	13 (28.9%)	0.593	0.530
		Tingling in the limbs at night (%)	8 (27.6%)	12 (46.2%)	0.153	6 (26.1%)	19 (42.2%)	0.287	0.680
Ophthalmologic	0.86	Persistently blurred vision (even with glasses) (%)	14 (48.3%)	15 (57.7%)	0.571	11 (47.8%)	31 (68.9%)	0.133	0.347
		Deteriorating vision (%)	7 (24.1%)	13 (50.0%)	**0.047**	5 (21.7%)	25 (55.6%)	**0.011**	0.298
		Flashes or black spots in vision (%)	6 (20.7%)	11 (42.3%)	0.083	4 (17.4%)	23 (51.1%)	**0.010**	0.338
		Alternating clear and blurred vision (%)	17 (58.6%)	19 (73.1%)	0.260	9 (39.1%)	32 (71.1%)	**0.012**	0.563
		Sudden deterioration in vision (%)	10 (34.5%)	10 (38.5%)	0.759	4 (17.4%)	24 (53.3%)	**0.006**	0.753

Bold font indicates association is significant at $p < 0.05$

A higher proportion of men with suboptimal glycemia (HbA1c ≥ 8.0%) reported excessive thirst, a frequent need to empty their bladder, and having difficulty staying attentive compared to men with controlled diabetes (**Supplementary Table 2**). Notably, a higher proportion of men with optimal glycemia reported experiencing aching calves when walking. Men who reported feeling irritable before a meal, experiencing burning pains in the legs during the day, and a sudden deterioration in vision had significantly lower SF-8™ MCS scores (worse mental HRQL) than men who did not report those symptoms.

Men who reported feeling irritable before a meal, an overall sense of fatigue, sleepiness or drowsiness, burning pain in the calves at night, an odd feeling in the leg upon touch, a tingling sensation in the limbs at night, and reporting flashes or black spots in their vision had significantly lower SF-8™ PCS scores (worse physical HRQL) than men who did not report those symptoms.

A higher proportion of women with suboptimal glycemia (HbA1c ≥ 8.0%) reported experiencing an overall sense of fatigue, and a 'fuzzy' head compared to women with optimal glycemia. Women who reported feeling easily irritated or annoyed, irritability before a meal, having an overall sense of fatigue, and having difficulty staying attentive had significantly lower SF-8™ MCS scores. Notably, women who reported palpitations had higher SF-8™ MCS scores than those who did not. Women experiencing shortness of breath at night had lower SF-8™ PCS scores than women who did not report that symptom.

Factors associated with odds of diabetes (multivariable analysis)

After backward stepwise selection the following factors were associated with increased odds of diabetes: each additional year of age (1.06, CI 1.00-1.13), female sex (OR 3.16, CI 1.08-9.21), presence of other chronic conditions (OR 3.01, CI 1.02-8.89), a frequent need to empty the bladder (OR: 4.72, CI: 1.67-13.31), a loss of sensation in the feet and lower legs (OR: 2.16, 0.78-5.94), a 'fuzzy' feeling in the head (OR: 3.85, CI: 1.22-12.09), and pains in the breast and heart region (OR: 3.91, CI 1.10-13.84) (**Table 3**)

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Table 3: Logistic regression predicting odds of having diabetes (n=108)

Model variables	Odds Ratio	Confidence intervals	Standard Error	p-values
Age (years)	1.06	1.00-1.13	0.03	**0.045**
Sex (ref: male)	3.16	1.08-9.21	1.72	**0.035**
Other chronic conditions (ref: no)	3.01	1.02-8.89	1.66	**0.046**
Frequent need to empty bladder (ref: no)	4.72	1.67-13.31	2.49	**0.003**
Loss of sensation in feet (ref: no)	2.16	0.78-5.94	1.11	0.136
'Fuzzy' Head/difficulty thinking clearly (ref: no)	3.85	1.22-12.09	2.25	**0.021**
Pains in the breast/heart region (ref: no)	3.91	1.10-13.84	2.52	**0.034**

Symptoms that varied between diabetes status (prediabetes vs. diabetes) at p<0.1 were included as predictors in the backwards selection logistic regression model, along with age, sex, BMI, and the presence of other chronic conditions. Removal criterion was set at p < 0.15. Symptoms included: frequent need to empty the bladder, lack of energy, an overall sense of fatigue, fatigue in the morning when getting up, increasing fatigue during the course of a day, a 'fuzzy' feeling in the head, sleepiness/drowsiness, shortness of breath during physical exertion, pains in the breast or heart region, tingling in then hand and fingers and the in feet and legs, an odd feeling in legs upon touch, deteriorating vision, flashes or black spots in vision, alternating clear and blurred vision, a sudden deterioration of vision, burning pains in the calves at night, and a loss of sensation in the feet and lower legs.

DISCUSSION

In this first description of symptoms experienced by those with diabetes and prediabetes in Samoa, we identified common diabetes-related symptoms and noted three symptoms that were associated with increased odds of diabetes. We also identified differences in the reporting of symptoms by sex as well as differences in the reported impact of diabetes symptoms on mental and physical health-related quality of life.

There were several symptoms that were reported by a higher proportion of men and women with diabetes compared to their peers with prediabetes: frequent urination, irritability,

low energy and fatigue, shortness of breath during physical exertion, heart palpitations, symptoms associated with peripheral neuropathy (i.e., tingling sensations in the limbs), and vision-related problems. These results are notable as they suggest that both sexes are at risk for peripheral neuropathy and vision problems, even though other studies have found that men are considered more at risk for microvascular complications related to diabetes (i.e., neuropathy, nephropathy, and retinopathy).[33-35] Additionally, diabetic neuropathy has been found to manifest earlier,[36, 37] and be experienced more frequently[38] in men compared to women. The current prevalence of diabetic neuropathy in Samoa is unknown; however, global estimates indicate that upwards of 50% of those with diabetes will develop peripheral neuropathy that can lead to foot ulceration, lower limb amputation, pain, restricted activities, and poor quality of life.[39] Based on the high prevalence of symptoms and a high proportion of participants with suboptimal glycemia (a major risk factor for peripheral neuropathy[39]) in this sample, it should be considered a major concern. Diabetic retinopathy is also a likely, but understudied, concern in this setting. In a cohort study conducted in 1991 in Samoa, diabetic retinopathy was observed in 43.2% of n = 88 individuals with known diabetes and 15.4% of n = 103 newly diagnosed individuals.[40] In 2018, non-proliferative diabetic retinopathy was observed in 2.9% of n=206 of adult Samoans (30.5-50 years old) living with prediabetes or diabetes.[41] However, the vision-related symptoms observed here may also be due to hypertensive retinopathy[42] given a concurrent high prevalence of hypertension.

A greater number of symptoms varied by diabetes status (prediabetes vs. diabetes) in men compared to women. Other studies have found that women generally report more disease symptoms (including those related to chronic conditions) than men,[8] which may account for the absence of significant variation in symptom reporting between women with prediabetes and women with diabetes. As diabetes-related symptoms—including those related to neuropathy[43, 44] and diabetic retinopathy[45, 46]—can start to impact people with prediabetes, it is not unexpected that symptoms may also be present in these individuals. Further research is needed to understand why a higher proportion of men with prediabetes are either not experiencing or not reporting these symptoms as frequently.

Nonetheless, based on the limited number of symptoms overall that were differentially reported by those with diabetes compared to those with prediabetes (especially in women), the results suggest that symptom presence, for many of the items, may not be unique to only those living with diabetes. Clinical identification and recognition of these symptoms as also indicative of prediabetes should be communicated by clinicians to high-risk patients and the wider public to help people understand the risk factors for diabetes development [12]. Additionally, recognition of these symptoms as indicative of prediabetes may be useful in linking high-risk individuals to the healthcare system for early screening and helping direct patients towards lifestyle changes and early health-seeking behaviors that prevent progression to diabetes and/or microvascular complications. These actions have the potential to reduce the prevalence of comorbidities related to diabetes- and other chronic conditions.

Notably, we observed that few symptoms varied based on optimal vs. suboptimal glycemia; the exceptions observed were that a higher proportion of men with suboptimal glycemia reported a frequent need to empty their bladders, difficulty staying attentive, and excessive thirst compared to men with optimal glycemia. Additionally, a higher proportion of women with suboptimal glycemia reported experiencing a fuzzy feeling in their head and overall sense of fatigue compared to women with optimal glycemia. The relatively few number of reported symptom differences by optimal or suboptimal glucose status was unexpected given that suboptimal glycemia are a major risk factor for many symptoms related to diabetic retinopathy,[47, 48] neuropathy[38] and cognitive decline.[49] These findings suggest that symptom burden may not be a reliable indicator for patients to assess their management over their condition and support the need for ongoing engagement in diabetes care and regular blood glucose monitoring.

Several symptoms (i.e., irritability, limb pain and numbness, fatigue, and deteriorating vision) in men were associated with worse mental and physical HRQL. Several—though fewer—symptoms in women were associated with worse mental and physical HRQL and included those related to irritability, overall fatigue, attentiveness, and shortness of breath. These results are like those observed in other studies[7, 10] where the presence of diabetes-associated symptoms (assessed using different questionnaires than used here) was associated with worse HRQL. For example, negative associations between diabetes symptom burden and HRQL were observed in 3,716 US adults with diabetes.[10] Similarly, in n = 1,664 Dutch patients with diabetes, symptoms of hyperglycaemia,

neuropathy, and hypoglycaemia were associated with lower HRQL scores.[50] Nonetheless, it is surprising that more symptoms were not associated with worse HRQL given the high prevalence of symptoms reported in the sample. Elsewhere, response shift[51, 52] (changes in quality of life valuations), and adaptation to disease states and events over time[53] have been posited as explanations for better-than-expected chronic condition-related self-evaluation and HRQL. Participants may have integrated and accepted the presence of diabetes symptoms into their personal, social, and spiritual lives—thereby no longer noticing them as aberrant—as a means of coping, reducing disruptions, and overcoming an illness identity.[54, 55]

This latter explanation could be better explored and assessed in future qualitative studies designed using Pacific-specific frameworks and models such as the Fonofale model of health [56] or the Fa'afaletui framework.[57] The former integrates multiple perspectives and values of Samoan and Pacific Islander culture including spiritual beliefs, lifestyles, family and cultural values, and culturally constructed definitions of spiritual, mental, and physical health to assess wellbeing.[56] Similarly, the Fa'afaletui framework weaves together different Samoan cultural values and multiple perspectives, using multi-level and mixed methods approaches, to gain deeper and holistic understandings of experiences.[57] Methods like these would be useful to understand whether the presence or absence of reported symptoms goes beyond individual experiences and are instead illness behaviours or resilience reactions shaped by the wider cultural environment.

Experiencing a frequent need to empty their bladders, a 'fuzzy' head/difficulty thinking clearly, and pains in the breast and heart region were independently and significantly associated with increased odds of having diabetes, when adjusting for age, sex, BMI, and the presence of other chronic conditions.

The absence of more symptoms as independent predictors of diabetes, in contrast to what was observed in a similar study conducted in the US,[5] indicates that 1) for many symptoms, their presence may be related to participants' age and/or presence of other chronic conditions,[58-61] and/or 2) as supported by our findings, many of these symptoms are already present in those with prediabetes. Therefore, many of the measured symptoms are not particularly useful for distinguishing between diabetes or prediabetes; we caution that symptom presence should be investigated in conjunction with additional chronic condition evaluation tools.

Strengths/Limitations

These data address the paucity of information about the presence of diabetes-related symptoms and the association of these symptoms on HRQL and optimal vs. suboptimal glycemia in Samoa. Our findings are limited by a focus only on questionnaire measures; further, while some of these questionnaires have been used in previous studies with Samoan adults, it is possible that cultural differences or biases in translation may have reduced the accuracy of these measures in capturing the full illness experience in this setting. Additionally, the small sample size and selectively sampled cohort here preclude the findings from being representative of the population. We advocate for further investigation, using mixed methods, into whether diabetes symptom reports in Samoa may be constrained or influenced by sociocultural factors, symptom severity, diabetes-related knowledge, depression, or diabetes duration, which have been demonstrated elsewhere to modify perceptions of HRQL and symptom reporting in relation to diabetes.[53, 62-71] This understanding will facilitate the construction of more efficient and context-specific symptom-based diabetes evaluation tools.

CONCLUSION

The study provides important insight regarding diabetes symptoms and experiences in Samoa. In a sample of adult Samoans, we observed high symptom burden among those with both prediabetes and diabetes, identified three specific symptoms – the frequent need to empty one's bladder, difficulty thinking clearly, and chest/heart pains – that may be useful indicators of diabetes in this setting, and described sex differences in the reported impact of diabetes symptoms on health-related quality of life. Given the high prevalence of symptoms reported by both those with prediabetes and those with diabetes, it is recommended that individuals experiencing any of the measured symptoms seek early evaluation and engage in diabetes self-care behaviors to prevent diabetes-related complications and/or progression to diabetes in those at risk.

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Conflict of Interest

The authors have no conflict of interest to declare

Author Contributions

ACR conceived the research question, conducted analyses, led manuscript development and drafting; AP aided in study design and manuscript revision; AIW aided in study design and manuscript revision; SV provided mentorship and manuscript revision; TN provided supervision of data collection; MSR aided in data collection; EEK provided mentorship, manuscript revision; STM led study design and implementation, and manuscript revision; NLH provided mentorship, led study design, implementation and data collection, and provided analytical and manuscript revision.

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Supplementary Table 1: Sex-stratified tests of association between individual symptom presence and diabetes status and tests of association between symptom presence and sex: Including those with neither diabetes nor prediabetes

		Men			**Associations between symptoms and diabetes status**	**Women**			**Associations between symptoms and diabetes status**	**Associations between symptoms and sex**
DSC-R symptom domains	**Have you experienced any of the following symptoms?**	**No diabetes or no prediabetes (n=4)**	**Prediabetes (n=29)**	**Diabetes (n=26)**	**p < 0.05**	**No diabetes or no prediabetes (n=3)**	**Prediabetes (n=23)**	**Diabetes (n=45)**	**P<0.05**	**P < 0.05**
Hyperglycemic	Very thirsty (%)	2 (50.0%)	14 (48.3%)	18 (69.2%)	0.273	3 (100.0%)	15 (65.2%)	31 (68.9%)	0.663	0.179
	Dry mouth (%)	2 (50.0%)	10 (34.5%)	14 (53.8%)	0.324	2 (66.7%)	11 (47.8%)	24 (53.3%)	0.917	0.281
	Drink a lot (%)	1 (25.0%)	11 (37.9%)	15 (57.7%)	0.269	2 (66.7%)	15 (65.2%)	26 (57.8%)	0.827	0.092
	Frequent urination (%)	2 (50.0%)	6 (20.7%)	19 (73.1%)	**<0.001**	0 (0.0%)	9 (39.1%)	22 (48.9%)	0.273	0.914
Hypoglycemic	Moodiness (%)	2 (50.0%)	12 (41.4%)	16 (61.5%)	0.246	0 (0.0%)	12 (52.2%)	26 (57.8%)	0.187	0.773
	Easily annoyed or irritated (%)	1 (25.0%)	15 (51.7%)	17 (65.4%)	0.294	1 (33.3%)	10 (43.5%)	29 (64.4%)	0.316	0.816
	Irritability before a meal (%)	0 (0.0%)	10 (34.5%)	10 (38.5%)	0.428	1 (33.3%)	5 (21.7%)	19 (42.2%)	0.263	0.885
Psychological fatigue	Lack of energy (%)	0 (0.0%)	10 (34.5%)	17 (65.4%)	**0.007**	1 (33.3%)	12 (52.2%)	27 (60.0%)	0.573	0.235
	Overall sense of fatigue (%)	0 (0.0%)	8 (27.6%)	15 (57.7%)	**0.019**	1 (33.3%)	8 (34.8%)	25 (55.6%)	0.359	0.275
	Fatigue in the morning when getting up (%)	0 (0.0%)	7 (24.1%)	12 (46.2%)	0.129	0 (0.0%)	7 (30.4%)	24 (53.3%)	0.072	0.183
	Increasing fatigue in the course of a day (%)	0 (0.0%)	2 (6.9%)	10 (38.5%)	**0.012**	0 (0.0%)	4 (17.4%)	18 (40.0%)	0.099	0.154
Psychological cognitive	Dull head (%)	0 (0.0%)	3 (10.3%)	10 (38.5%)	**0.025**	1 (33.3%)	4 (17.4%)	22 (48.9%)	**0.029**	**0.038**
	Sleepiness or drowsiness (%)	0 (0.0%)	1 (3.4%)	7 (26.9%)	**0.037**	1 (33.3%)	4 (17.4%)	13 (28.9%)	0.625	0.079
	Difficulty concentrating (%)	0 (0.0%)	5 (17.2%)	6 (23.1%)	0.675	0 (0.0%)	4 (17.4%)	10 (22.2%)	0.879	0.815
	Difficulty staying attentive (%)	2 (50.0%)	14 (48.3%)	16 (61.5%)	0.657	0 (0.0%)	10 (43.5%)	29 (64.4%)	**0.046**	0.867
Cardiovascular	Shortness of breath during exercise (%)	0 (0.0%)	7 (24.1%)	13 (50.0%)	**0.045**	1 (33.3%)	9 (39.1%)	19 (42.2%)	1.00	0.380
	Shortness of breath at night (%)	1 (25.0%)	4 (13.8%)	9 (34.6%)	0.169	2 (66.7%)	3 (13.0%)	12 (26.7%)	0.118	0.984
	Palpitations (%)	1 (25.0%)	5 (17.2%)	9 (34.6%)	0.324	1 (33.3%)	3 (13.0%)	7 (15.6%)	0.594	0.171
	Pains in the breast or heart region (%)	0 (0.0%)	2 (6.9%)	9 (34.6%)	**0.029**	1 (33.3%)	3 (13.0%)	16 (35.6%)	0.114	0.189

Neuropathic pain	Aching calves when walking (%)	1 (25.0%)	11 (37.9%)	15 (57.7%)	0.346	2 (66.7%)	10 (43.5%)	21 (46.7%)	0.841	0.947
	Shooting pains in the legs (%)	1 (25.0%)	9 (31.0%)	13 (50.0%)	0.351	2 (66.7%)	10 (43.5%)	20 (44.4%)	0.839	0.441
	Burning pain in the calves at night (%)	1 (25.0%)	2 (6.9%)	4 (15.4%)	0.266	1 (33.3%)	2 (8.7%)	12 (26.7%)	0.219	0.150
	Burning pain in the legs during the day (%)	1 (25.0%)	4 (13.8%)	5 (19.2%)	0.650	1 (33.3%)	3 (13.0%)	9 (20.0%)	0.546	0.781
Neuropathic sensory	Loss of sensation in the hands (%)	1 (25.0%)	13 (44.8%)	14 (53.8%)	0.610	2 (66.7%)	13 (56.5%)	24 (53.3%)	1.000	0.265
	Loss of sensation in the feet (%)	1 (25.0%)	12 (41.4%)	15 (57.7%)	0.289	2 (66.7%)	11 (47.8%)	32 (71.1%)	0.205	0.086
	Tingling/prickling in the hands or fingers (%)	1 (25.0%)	16 (55.2%)	21 (80.8%)	**0.032**	2 (66.7%)	14 (60.9%)	32 (71.1%)	0.899	0.536
	Tingling/prickling in the feet or legs (%)	1 (25.0%)	16 (55.2%)	20 (76.9%)	**0.039**	2 (66.7%)	15 (65.2%)	30 (66.7%)	1.000	0.691
	Odd feeling in the legs/ feet when touching (%)	1 (25.0%)	5 (17.2%)	13 (50.0%)	**0.031**	1 (33.3%)	5 (21.7%)	13 (28.9%)	0.899	0.530
	Tingling in the limbs at night (%)	1 (25.0%)	8 (27.6%)	12 (46.2%)	0.369	2 (66.7%)	6 (26.1%)	19 (42.2%)	0.382	0.680
Ophthalmologic	Blurred vision (also with glasses) (%)	1 (25.0%)	14 (48.3%)	15 (57.7%)	0.469	0 (0.0%)	11 (47.8%)	31 (68.9%)	**0.034**	0.347
	Deteriorating vision (%)	0 (0.0%)	7 (24.1%)	13 (50.0%)	**0.045**	0 (0.0%)	5 (21.7%)	25 (55.6%)	**0.010**	0.298
	Flashes or black spots in vision (%)	1 (25.0%)	6 (20.7%)	11 (42.3%)	0.237	0 (0.0%)	4 (17.4%)	23 (51.1%)	**0.012**	0.338
	Fluctuating clear and blurred vision (%)	2 (50.0%)	17 (58.6%)	19 (73.1%)	0.516	0 (0.0%)	9 (39.1%)	32 (71.1%)	**0.003**	0.563
	Sudden deterioration in vision (%)	2 (50.0%)	10 (34.5%)	10 (38.5%)	0.773	0 (0.0%)	4 (17.4%)	24 (53.3%)	**0.007**	0.753

Bold font indicates association is significant at $p < 0.05$

Supplementary table 2: Sex-stratified associations between diabetes symptoms and diabetes control, and SF8 Mental and Physical Health summary scores

	Men					**Women**				
			Associations between symptoms and optimal vs. suboptimal glycemia (HbA1c 6.5 to < 8.0% or ≥ 8.0%)	Associations between symptoms and SF8 Mental Component Summary scores	Associations between symptoms and SF8 Physical Component Summary scores			Associations between symptoms and optimal vs. suboptimal glycemia (HbA1c 6.5 < 8.0% or ≥ 8.0%)	Associations between symptoms and SF8 Mental Component Summary scores	Associations between symptoms and SF8 Physical Component Summary scores
Have you experienced any of the following symptoms?	**HbA1c 6.5% to < 8.0% (n=9)**	**HbA1c ≥ 8.0% (n=17)**	p-values*	p-values†	p-values†	**HbA1c 6.5% to < 8.0% (n=12)**	**HbA1c ≥ 8.0% (n = 30)**	p-values*	p-values†	p-values†
Very thirsty (%)	3 (33.3%)	15 (88.2%)	**0.008**	0.181	0.205	7 (58.3%)	21 (70.0%)	0.469	0.261	0.532
Dry mouth (%)	4 (44.4%)	10 (58.8%)	0.683	0.261	0.657	7 (58.3%)	14 (46.7%)	0.558	0.639	0.431
Drink a lot (%)	3 (33.3%)	12 (70.6%)	0.103	0.615	0.306	7 (58.3%)	16 (53.3%)	0.769	0.080	0.389
Frequent need to empty bladder (%)	4 (44.4%)	15 (88.2%)	**0.028**	0.908	0.114	5 (41.7%)	15 (50.0%)	0.490	0.535	0.225
Moodiness (%)	3 (33.3%)	13 (76.5%)	0.087	0.407	0.067	7 (58.3%)	17 (56.7%)	0.921	0.080	0.418
Easily annoyed or irritated (%)	4 (44.4%)	13 (76.5%)	0.194	0.238	0.418	5 (41.7%)	22 (73.3%)	0.053	**0.014**	0.285
Irritability before a meal (%)	3 (33.3%)	7 (41.2%)	1.000	**0.031**	**0.027**	3 (25.0%)	16 (53.3%)	0.169	**0.007**	0.343
Lack of energy (%)	4 (44.4%)	13 (76.5%)	0.359	0.175	0.869	5 (41.7%)	19 (63.3%)	0.158	0.541	0.689
Overall sense of fatigue (%)	4 (44.4%)	11 (64.7%)	0.419	0.220	**0.008**	3 (25.0%)	20 (66.7%)	**0.020**	**0.010**	0.085
Fatigue in the morning when getting up (%)	4 (44.4%)	8 (47.1%)	1.000	0.835	0.605	4 933.3%)	18 (60.0%)	0.175	0.978	0.609
Increasing fatigue during the course of a day (%)	3 (33.3%)	7 (41.2%)	1.000	0.795	0.365	3 (25.0%)	15 (50.0%)	0.180	0.097	0.060
Fuzzy feeling in the head (%)	2 (22.2%)	8 (47.1%)	0.399	0.466	0.557	2 (16.7%)	20 (66.7%)	**0.012**	0.273	0.273
Sleepiness or drowsiness (%)	3 (33.3%)	4 (23.5%)	0.661	0.742	**0.014**	3 (25.0%)	9 (30.0%)	1.000	0.889	0.264
Difficulty concentrating (%)	2 (22.2%)	4 (23.5%)	1.000	0.268	0.287	2 (16.7%)	7 (23.3%)	0.702	0.794	0.183
Difficulty staying attentive (%)	3 (33.3%)	13 (76.5%)	**0.046**	0.136	**0.003**	7 (58.3%)	20 (66.7%)	0.611	**0.003**	0.106
Shortness of breath during physical exertion (%)	3 (33.3%)	10 (58.8%)	0.411	0.151	0.943	5 (41.7%)	13 (43.3%)	1.000	0.669	0.064
Shortness of breath at night (%)	1 (11.1%)	8 (47.1%)	0.098	0.686	0.259	4 (33.3%)	8 (26.7%)	0.715	0.067	**0.027**
Palpitations (%)	5 (55.6%)	4 (23.5%)	0.194	0.828	0.828	1 (8.3%)	5 (16.7%)	0.655	**0.028‡**	0.860
Pains in the breast or heart region (%)	5 (55.6%)	4 (23.5%)	0.194	0.576	0.931	6 (50.0%)	9 (30.0%)	0.222	0.703	0.771
Aching calves when walking (%)	8 (88.9%)	7 (41.2%)	**0.036**	0.729	0.368	6 (50.0%)	12 (40.0%)	0.554	0.332	0.169
Shooting pains in the legs (%)	7 (77.8%)	6 (35.3%)	0.097	0.183	**0.008**	7 (58.3%)	12 (40.0%)	0.281	0.143	0.228

Burning pain in the calves at night (%)	3 (33.3%)	1 (5.9%)	0.104	0.129	0.457	2 (16.7%)	10 (33.3%)	0.453	0.510	0.916
Burning pain in the legs during the day (%)	3 (33.3%)	2 (11.8%)	0.302	**0.034**	0.329	1 (8.3%)	8 (26.7%)	0.240	0.706	0.706
Loss of sensation in the hands (%)	7 (77.8%)	7 (41.2%)	0.110	0.723	0.597	7 (58.3%)	14 (46.7%)	0.629	0.541	0.887
Loss of sensation in the feet (%)	7 (77.8%)	8 (47.1%)	0.229	0.826	0.557	8 (66.7%)	21 (70.0%)	1.000	0.470	0.437
Tingling/prickling in the hands or fingers (%)	8 (88.9%)	13 (76.5%)	0.628	0.428	0.319	9 (75.0%)	20 (66.7%)	0.722	0.730	0.549
Tingling/prickling in the feet or lower legs (%)	8 (88.9%)	12 (70.6%)	0.621	0.423	0.285	9 (75.0%)	18 (60.0%)	0.485	0.966	0.431
Odd feeling in the legs/ feet upon touch (%)	6 (66.7%)	7 (41.2%)	0.411	0.053	**0.012**	2 (16.7%)	10 (33.3%)	0.453	0.601	0.127
Tingling in the limbs at night (%)	5 (55.6%)	7 (41.2%)	0.683	0.084	**0.002**	5 (41.7%)	13 (43.3%)	0.921	0.484	0.338
Persistently blurred vision (even with glasses) (%)	5 (55.6%)	10 (58.8%)	1.000	0.249	0.491	7 (58.3%)	23 (76.7%)	0.235	0.244	0.233
Deteriorating vision (%)	4 (44.4%)	9 (52.9%)	1.000	0.209	0.053	7 (58.3%)	17 (56.7%)	0.921	0.511	0.053
Flashes or black spots in vision (%)	4 (44.4%)	7 (41.2%)	1.000	0.067	**0.014**	4 (33.3%)	18 (60.0%)	0.175	0.648	0.388
Fluctuating clear and blurred vision (%)	6 (66.7%)	13 (76.5%)	0.661	0.299	0.790	9 (75.0%)	21 (70.0%)	1.000	0.248	0.519
Sudden deterioration in vision (%)	3 (33.3%)	7 (41.2%)	1.000	**0.013**	0.298	6 (50.0%)	17 (56.7%)	0.695	0.093	0.352

*Associations between symptoms and optimal vs. suboptimal glycemia were only calculated among individuals with diabetes

†Associations between symptoms and SF8 Mental and Physical health component summary scores are calculated among n = 118 participants (MCS and PCS scores missing from n =1 man, and n = 4 women)

‡ Direction of associations between all MCS and PCS scores and symptoms demonstrates that lower MCS and PCS scores (indicating reduced quality of life) are associated with the presence of symptoms except for palpitation presence in women. Women who experienced palpitations have higher (better HRQL) than women who did not report ever experiencing palpitations.

Bond font indicates association is significant at $p < 0.0$