Original Article

Moderating effect for illness uncertainty on the relationship of depressive and anxiety symptoms among patients with type 1 diabetes in Taif region, Saudi Arabia

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Abstract

Background: Illness uncertainty was found to be associated with the development of depressive and anxiety symptoms among patients with type 1 diabetes and chronic illness in general. However, the moderating effect of illness uncertainty was not examined in sufficient depth. The current study evaluates how the path from diabetes distress to depression and anxiety is mediated by illness uncertainty, ambiguity, symptoms and course predictability, and illness complexity. **Method:** Descriptive cross-sectional survey of a large-scale sample of patients living with type one diabetes in Saudi Arabia. We utilized structural equation modelling mediation analysis to examine the effect of illness uncertainty and its subcategories (illness-related ambiguity, symptoms and course predictability, and illness complexity) on depressive and anxiety symptoms. **Results:** The current survey analyzed data pertaining to (n = 536) type one diabetes patients. Mean Mishel Uncertainty of Illness Scale score was 80.8 points (Cronbach's α = 0.91) signifying moderate uncertainty among our patients. Diabetes-related uncertainty was associated with marriage (t = 3.337, P = 0.0009937), diabetes complications (t = 5.257, P < 0.00001), pain (r = 0.2247, P < 0.00001), and children count (correlation coefficient r = 0.195, P < 0.00001). The prevalence of depression was (n = 367, 68.5%) and for anxiety was (n = 173, 30.3%). Illness uncertainty correlated with depressive (r = 0.2484, P < 0.00001) and anxiety (r = 0.2548, P < 0.00001) symptoms' scores. Illness uncertainty exerted a partial moderating effect on both anxiety (β = 0.060, P < 0.001) and depressive symptoms (β =0.056, P < 0.001). We observed a partial moderating effect for diabetes-related ambiguity and diabetes-related symptom unpredictability in terms of depressive and anxiety symptoms. However, for diabetes-related course unpredictability, the moderating effect was significant only for anxiety. Diabetes-related complexity did not exert a significant moderating effect on either depressive or anxiety symptoms. **Discussion:** We confirmed high levels of depression and anxiety among patients with type one diabetes in Saudi Arabia. Our findings suggest that illness uncertainty affects both diabetes-related distress and depression constructs and is likely to be affected by them.

Keywords: Anxiety, depression, illness ambiguity, illness complexity, illness uncertainty, illness unpredictability, mediation analysis, Saudi Arabia, Taif, type one diabetes

Introduction

Diabetes is a chronic disease with complex symptoms and complications that pose substantial challenges to patients.[1] Type 1 diabetes requires substantial therapeutic demands that put pressure on patients' neuropsychological and financial

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well-being.[2,3] A diagnosis of type 1 diabetes is a life-changing event for patients and for their families. Type 1 diabetes is associated with reduced life quality in several multitudes.[4]

Type 1 diabetes is an autoimmune disorder that is associated with significant physical and psychological morbidity and premature mortality particularly when diagnosis is delayed and treatment resources are limited.[5,6] It carries considerable anxiety and depression risk. A third of all patients with insulin-dependent diabetes were found to have significant depressive or anxiety symptoms.[7] Living with type 1 diabetes was shown to be affected by several social and psychological factors. These include a sense of autonomy among patients, level of dysfunction among their families, and mental wellbeing.[8] Such an array of sociopsychological factors functions in a multidirectional way to potentiate the development of depressive and anxiety symptoms among patients with diabetes type 1.[8]

The concept of illness uncertainty was coined in the early 1980s by Michel in an attempt to understand the interaction between individuals and their chronic illnesses. Illness uncertainty occurs when patients fail to coherently judge the meaning and composition of their illness. Clearly, illness uncertainty has different degrees of severity.[9] At its most severe form, patients would be unable to utilize their strengths in educational or social functioning in comprehending their illness or fully accessing care.[9] Illness uncertainty constitutes a significant barrier against adapting to diagnosis, processing illness-related information, or preventing complications. Vice versa, as symptoms burden increase, illness uncertainty deepens.[10] Illness uncertainty correlated well with the development of high stress levels and deterioration in patients' mental health.[11] Even carers can be affected psychologically if they have high levels of illness uncertainty with regards to their cared-for individual.[12,13]

Illness uncertainty and illness intrusiveness were found to be associated with the development of depressive and anxiety symptoms among patients with type 1 diabetes and chronic illness in general (except bronchial asthma).[14] However, the moderating effect of illness uncertainty was not examined in sufficient depth. Mishel's theory puts forward four drivers for illness uncertainty, in the context of type 1 diabetes or other chronic illnesses.[15] First, unclear disease symptoms such as those related to hypoglycaemia or hyperglycaemia, or diabetes complications, can affect certainty about the nature of diabetes. Second, complex diabetes treatment and care resulting from frequent changes in insulin dosages, the need to calculate carbohydrates and calories incessantly, and having to keep medications in certain physical conditions, such as optimum temperature, lead to reduced diabetes illness certainty among patients and their careers. Third, uncertainty can be driven by a lack of information related to the diabetes, its severity, and its complications. Fourth, how diabetes behave is quite unpredictable. Diabetic emergencies do occur and usually necessitate the involvement of emergency services and/or hospitalization.

We hypothesise that diabetes-related illness uncertainty plays a key role in the development of depressive and anxiety symptoms, likely more in anxiety disorder than the depressive disorder.

Depression and anxiety are extremely common among patients living with diabetes type 1. However, their etiopathology remained elusive. Very few studies examined the evolution of depressive and anxiety symptoms in Saudi patients with type 1 diabetes. Recently rates of depression as high as 80% were found among patients with type diabetes in Saudi Arabia.[16] One recent study attempted to explore the effect of 'trust in care' and the development of depressive and anxiety symptoms among Saudi patients with diabetes.[17] However, it did not use validated uncertainty tools devised by Michel. No studies, however, to the best of our knowledge, attempted to explore the moderating effect of illness uncertainty on the development of depressive and anxiety symptoms in diabetes patients in Saudi Arabia. Our study, to the best of our knowledge, is the first in the region to adopt such a validated and advanced approach in the measure of illness uncertainty among diabetes patients and link that to their psychological well-being.

Although no studies explicitly assessed diabetes-related illness uncertainty and depressive or anxiety symptoms in Saudi Arabia, one orphan study attempted to evaluate the 'trust in care' effect on psychological well-being.[17] They interviewed a large sample of nearly 400 patients. A clear negative relationship between depressive symptoms and trust in care was found. They also asserted that the poorer the trust in care the higher the anxiety symptomatology. They clearly advocated for improvement in trust by adopting patient-centred approach in care.

AlHadi et al. [2021][18] surveyed over 3000 Saudi subjects during the current COVID-19 pandemic to measure the relationship between uncertainty and psychological sequelae of the pandemic. They found the severity of depressive and anxiety symptoms to be associated with uncertainty. Although they did not use the validated illness uncertainty tool, clearly their results tally well with international findings.

We found a recent study by *Abu Tabar et al.* [2021][19] that surveyed patients with chronic obstructive pulmonary disease. They found a strong association between illness uncertainty, anxiety, and life quality.

At the regional level, a well-conducted study among 120 patients with chronic renal disease[11] investigated the association between depressive symptoms, family dysfunction, and illness uncertainty. It was clear that depression correlated positively with illness uncertainty and renal symptoms, but negatively with family functioning.

Zhang et al. [2018][20] attempted to evaluate the interplay between illness uncertainty, anxiety, and depression in 360 Chinese cataract and glaucoma patients. Illness uncertainty was found

to strongly mediate the relationship between visual impairment and depressive/anxiety symptoms.

A survey of 200 Chinese women with systemic lupus erythematosus (SLE) was conducted recently.[21] Structural equation modelling (SEM) statistical methods were adopted in order to investigate the path that governs the relationship between illness uncertainty and depression and anxiety disorder. Illness uncertainty was the primary mediator between SLE symptoms and mood/anxiety symptoms. Such a strong correlation was affected by the inclusion of 'hope' in the model. They clearly delineated that while illness uncertainty worsens depression and anxiety symptoms, hope may be able to alleviate their burden.

At the wider international level, one single American study[14] screened nearly 500 college students suffering from a range of chronic illnesses including type 1 diabetes, in contrast with 900 healthy volunteers. The illness uncertainty questionnaire was completed online by the surveyed students. Chronic illness was associated with higher anxiety and depressive symptoms. The paper gave clear evidence of the association between illness uncertainty and anxiety and mood symptoms.

In a study that was conducted on over 100 patients with inflammatory bowel disease,[22] perceived illness stigma was found to be associated with increased depressive symptoms. They identified a path that leads from illness stigma to illness uncertainty to depressive symptoms. However, this path was moderated significantly with mindfulness (being present-focused). They established that illness uncertainty could be the conduit through which stigma interferes with adaptive coping.

We believe that the goalkeeper of the health care system is the primary physician and all of these symptoms can be detected and treated properly in the primary care setting, if the family physician is aware of this relation.

The primary aim of the current investigation was to estimate the prevalence and severity of depressive and anxiety symptoms in type 1 diabetes patients in Saudi Arabia and examine the role of illness uncertainty as a moderator in their development. A range of secondary objectives were also considered appropriate for our survey: the effect of background clinical and demographic characteristics on depressive and anxiety symptoms, and examination of the psychometric properties of the Arabic version of Mishel Uncertainty of Illness Scale.

Methodology

Study design: The study was a questionnaire-based observational investigation to be conducted among patients with type one diabetes.

Study population: All type 1 adult patients attending specialist diabetes and endocrine centre and family medicine clinic.

Eligibility criteria:

Inclusion criteria:
1. adult patients (over 18 years of age)
2. established diagnosis of type 1 diabetes (in for any duration)
3. attending the specialist diabetes and endocrine centre and family medicine clinic
4. literate with sound cognitive abilities

Exclusion criteria:
1. Paediatric patients (below the age of 18)
2. Patients with severe cognitive impairment such as dementia or delirium
3. Patients unwilling to give written consent to participate.
4. Acutely suicidal or psychotic patients

Study area: The tertiary specialist diabetes and endocrine centre and family medicine clinic.

Sample size: Based on the survey carried out by *Mullins et al.* [2017][14], we require at least (n = 512) participants.

Sampling technique: We adopted a simple random sampling scheme when choosing participants for the current study. The sampling frame was constructed using data of all patients attending the specialist diabetes and endocrine centre and family medicine clinic during the last 24 months. A series of computer-generated random digits were used to identify potential participants to be included in the study. All were contacted and during their usual visit they were approached by the main researcher and invited to participate.

Data collection tools:
1. Primary Health Questionnaire (PHQ-9): This is a widely used psychometric tool in the assessment of depressive disorder in primary health care settings in Arabic-speaking communities.[23,24] It was found to have robust psychometric properties and satisfactory sensitivity in capturing depressive patients. However, specificity analysis was suboptimum, meaning that it may include healthy subjects as depressed in many cases. Sensitivity and specificity estimates were 77 and 46%, respectively.[25]
2. Mishel Uncertainty of Illness Scale: The scale consists of 32 questions that measure a range of uncertainty domains about chronic illness. It relies on the cognitive concept that uncertainty is the product of the inability to form cognitive schema. The four main domains measured by the scale are (a) illness state ambiguity, (b) treatment plan complexity, (c) diagnosis and prognosis lack of information, and (d) unpredictability of the disease trajectory.[26] A total score between 32 and 74.7 indicates a low uncertainty level, whereas a score between 74.8 and 117.4 corresponds to a moderate uncertainty level, with a score from 117.5 to 160 points indicating a high level of illness uncertainty.[27]
3. Generalized Anxiety Disorder (GAD-7): This is a short scale for the measurement of anxiety symptoms. It has shown excellent estimates for internal consistency and psychometric abilities.

However, recent evaluations indicated low sensitivity and specificity when compared to clinical diagnosis.[25] Nonetheless, it remains in wide use among Arabic-speaking researchers.[24]

Data collection technique: Patients were interviewed by the principal researcher. The study purpose was explained in simple plain Arabic and they were given ample opportunity to ask questions about the study. They were provided with pen and papers containing the four tools that measured the anxiety symptoms, depressive symptoms, aspects of illness uncertainty, visual functioning, and demographic factors.

Data entry and analysis: Data were entered into an Excel file document as they were collected. The document was saved on the personal computer device of the principal researcher. It was password protected. We will conduct an SEM analysis similar to the technique used in[21] study. With regards to the moderating effect of illness uncertainty, we modelled the direct path between diabetes distress and both anxiety and depression. We, thereafter, included an indirect path going through illness uncertainty from diabetes distress to both anxiety and depression.

Results

In our current study, we included a total of (n = 536) participants who were living with type one diabetes and consented in writing for their data to be included in the final analysis and for the collective results to be published.

We estimated a Cronbach's α for the Arabic version of Mishel Uncertainty of Illness Scale (MUIS) to be 0.91 (95% from 0.91 to 0.94), indicative of excellent reliability and internal consistency.

The mean MUIS score was 80.8 points (ranging between 41 and 138 points), and the SD was 17.9 points. The median MUIS score was 81 points.

With regards to demographic characteristics of our sample, the mean age was 50.0 years (SD = 17.1 years, ranging between 18 and 87 years). The median age was 53 years.

Among the participants, (n = 119, 22.2%) were single and (n = 412, 76.9%) were married. The mean uncertainty score was higher among married patients (μ =82.1 points) compared to single patients (μ =76.5 points). The difference was statistically significant (t = 3.337, P = 0.0009937).

The mean number of participants' children was 4.5 children (SD = 3.8 children) and the median children count was 5. The correlation was positive between kids' count and MIUS (correlation coefficient r = 0.195, P < 0.00001).

The shear majority of participants were Saudi (n = 530, 98.9%), with only (n = 6, 1.1%) who were non-Saudis.

Furthermore, men were (n = 315, 58.8%) whereas women were (n = 221, 41.2%). However, gender did not affect MIUS score (mean MUIS among male participants was 81.0 points compared to MIUS mean among females which was 80.4 points, t = 0.40923, P = 0.6825).

Some (n = 261, 48.7%) reported presence of diabetes complications whose mean MIUS score was 84.8 points. The rest (n = 275, 51.3%) reported no diabetes complications, with a mean MIUS score of 76.9 points. The difference was statistically significant (t = 5.257, P < 0.00001) indicating higher uncertainty levels among patients who developed diabetes complications.

The mean pain score was 2.94 points (median = 3.0 points, SD = 1.24 points). Pain score correlated positively with MIUS score (r = 0.2247, P < 0.00001).

The mean diabetes distress score was 2.7 points (SD = 1.29 points), ranging between 0 and 5 points. The median distress score was three points. Distress and MIUS scores were positively correlated (r = 0.2626, P < 0.00001).

In terms of depressive symptoms, prevalence of severe depression among our participants was (n = 57, 10.6%), with (n = 61, 11.4%) with moderately severe depression, (n = 94, 17.5%) with moderately depressive symptoms, (n = 155, 28.9%) with mild symptoms, and only (n = 169, 31.5%) who had minimal depressive symptoms. The point prevalence for any depressive symptoms was (n = 367, 68.5%). The mean PHQ9 was 9.2 points (SD = 7.2 points, median = 7 points, ranging between 0 and 32 points). We identified positive correlation between PHQ9 and MIUS score (r = 0.2484, P < 0.00001) [see Figure 1].

On the other hand, the prevalence for severe anxiety was (n = 70, 13.1%), and for moderate anxiety was (n = 103, 19.2%), with (n = 363, 67.7%) with minimal anxiety. The point prevalence for any anxiety symptom was (n = 173,

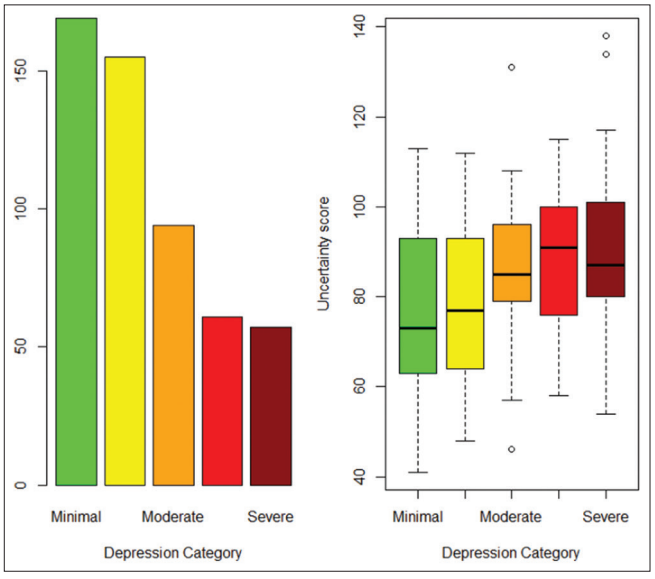

Figure 1: The distribution of depressive symptom categories among the study participants and its unadjusted effect on uncertainty score

30.3%). The mean GAD7 score was 14.6 points (SD = 6.9 points). The median GAD7 was 13 points (ranging between 0 and 35 points). The correlation between GAD7 and MIUS was significant statistically ($r = 0.2548$, $P < 0.00001$) [see Figure 2].

For a comprehensive display of demographic and clinical variables along with their unadjusted effect on illness uncertainty, see Table 1 and Supplementary file 1.

With regards to the moderating effect of illness uncertainty, we modelled the direct path between diabetes distress and both anxiety and depression. We, thereafter, included an indirect path going through illness uncertainty from diabetes distress unto both anxiety and depression.

In terms of the path effect, as sketched in Figure 3 and estimates for coefficients detailed in Table 2, it was clear that illness uncertainty exerted a partial moderating effect on both anxiety ($\beta = 0.060$, $P < 0.001$) and depressive symptoms ($\beta = 0.056$, $P < 0.001$). It was notable that the total indirect effect from diabetes-related distress passing through uncertainty towards anxiety was also significant ($\beta = 2.184$, $P < 0.001$). Additionally, the total indirect effect from diabetes-related distress passing through uncertainty towards depression was statistically significant ($\beta = 2.438$, $P < 0.001$).

When we examined the moderating effect for the subcategories of the uncertainty, similar partial moderating effect were obtained for diabetes-related ambiguity in terms of depressive and anxiety

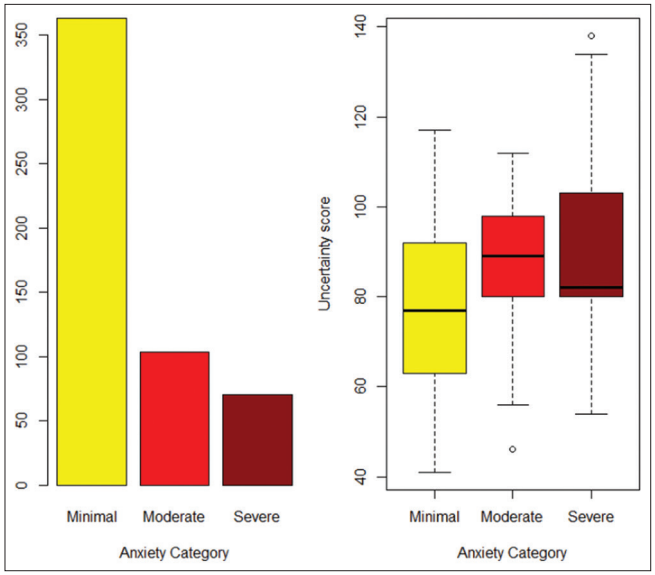

Figure 2: The distribution of anxiety symptom categories among the study participants and its unadjusted effect on uncertainty score

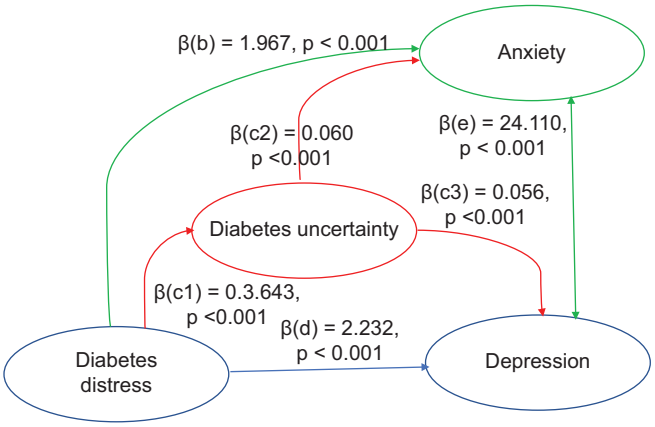

Figure 3: The SEM mediation analysis for illness uncertainty on the path from diabetes duration to anxiety and from diabetes duration to depression among the study participants

Table 1: Demographic and clinical distribution of study participants and the effect of demographic and clinical variables on the level of illness uncertainty about diabetes

Factor	Count/Mean	Proportion/SD	Mean MIUS score/correlation coefficient	Statistical test	*P*
Age	μ=50.0 years	SD=17.1 years	r=0.2623	*t*=6.2806	<0.00001
Marital status					
Married	412	76.9%	82.1 points	*t*=3.337	0.00099
Single	119	22.2%	76.5 points		
Kids count	μ=4.5 kids	SD=3.8 kids	r=0.1946	*t*=4.5838	<0.00001
DM duration	μ=50.0 years	SD=14.2 years	r = -0.0413	*t*=-0.9550	0.34
Nationality					
Saudi	530	98.9%	80.6 points	*t*=4.0203	0.00760
Non-Saudi	6	1.1%	92.7 points		
Sex					
Male	315	58.8%	81.0 points	*t*=0.4092	0.6825
Female	221	41.2%	80.4 points		
DM complication					
Yes	261	48.7%	84.8 point	*t*=5.257	<0.00001
No	275	51.3%	76.9 points		
Pain score	μ=2.94 points	SD=1.24 points	*r*=0.2247	*t*=5.3283	<0.00001
Distress score	μ=2.74 points	SD=1.2915	*r*=0.2626	*t*=6.2655	<0.00001
PHQ9 score	μ=9.21 points	SD=7.18 points	*r*=0.2484	*t*=5.925	<0.00001
GAD7 score	μ=14.56 points	SD=6.87	*r*=0.2548	*t*=6.088	<0.00001

Table 2: Estimates for the SEM path analysis of the moderating effect for uncertainty on depressive and anxiety symptoms among type 1 diabetes patients

Path	β estimate	Standard error	*Z*	*P*
Uncertainty~Diabetes distress (c1)	3.643	0.580	6.277	<0.001
Anxiety~Uncertainty (c2)	0.060	0.016	3.840	<0.001
Depression~Uncertainty (c3)	0.056	0.016	3.517	<0.001
Anxiety~Diabetes distress (b)	1.967	0.215	9.141	<0.001
Depression~Diabetes distress (d)	2.232	0.222	10.050	<0.001
Anxiety ~~ Depression (e)	24.110	2.004	12.034	<0.001
Product of indirect path (distress-anxiety)	0.217	0.066	3.276	0.001
Product of indirect path (distress-depression)	0.205	0.067	3.068	0.002
Total direct and indirect path (distress-anxiety)	2.184	0.211	10.376	<0.001
Total direct and indirect path (distress-depression)	2.438	0.217	11.242	<0.001

symptoms. However, for diabetes-related course unpredictability, the moderating effect was significant for anxiety, but not so for depressive symptoms. On the other hand, diabetes-related symptom unpredictability exerted a significant partial moderating effect in terms of both depressive and anxiety symptoms. Diabetes-related complexity did not exert a significant moderating effect on either depressive or anxiety symptoms. See **Supplementary file 1** for detailed display of estimates for the four models.

Discussion of Key Findings

The current survey analysed data pertaining to 536 type one diabetes patients who reside in Taif in Saudi Arabia. It is one of the largest studies in terms of sample size in the region. To overcome one of the design flaws in past studies, we utilized a well-validated measure for uncertianity, the MUIS, and, based on our dataset, we confirmed its excellent internal consistency with a 0.91 Cronbach's α estimate.

A dynamic multifaceted psychosocial system was proposed as causal in the development of depressive and anxiety symptoms among patients with type one diabetes.[8] Evaluation of the dynamics of such a system required the utilization of robust and advanced statistical techniques such as SEM mediation analysis modelling. That was to capture the effect of uncertainty on the path between diabetes distress and anxiety and depressive symptoms.

One landmark finding from our investigation was the moderate illness uncertainty level among our sample of patients given the mean MUIS score of 80.8 points. One earlier exploration of uncertainty levels among patients with type 2 diabetes identified low levels of illness-related uncertainty and linked that to better motivation for engagement in treatment.[28] However, no previous studies of illness uncertainty among patients with type 1 diabetes clearly identified such estimate, making our finding unique and referential. It indeed awaits further confirmation and reproduction by future academic exploration.

We reiterated the established association between distress and uncertainty within the context of type one diabetes. Research did confirm that a direct relationship exists between high uncertainty levels and high psychological distress levels among young adults with type 1 diabetes related to, but not moderated by 'perceived control'.[29] Indeed, uncertainty could lead to an array of negative emotions and a range of treatment process-related difficulties theorized to increase the risk of diabetes mismanagement and, hence, outcomes.[30] Development of illness certainty and forming clear strategies to cope with diabetes were recently identified as essential components for resilience among type 1 diabetes patients.[31] Furthermore, illness-related uncertainty was shown to enhance patients' anxiety regarding glycaemic control and increase the risk for eating disorders.[32]

Our unique results indicated that higher levels of illness uncertainty were associated with married status, presence of diabetes complications, diabetes duration, and larger family size. Speculation would involve complex bidirectional relationship between complications, illness duration, and uncertainty. The research in connection between illness uncertainty and diabetes complications is, unexpectedly, quite dearth. One study indicated a negative relationship between illness uncertainty and healthy dietary behaviour among patients with diabetes-related kidney disease.[33] One recent academic endeavour showed increased levels of uncertainty about prognosis among diabetes patients who developed foot ulcer complications.[34] One could also theorize that illness uncertainty, based on recent research findings, could worsen general health care and self-regulation[35] and, therefore, accelerate progression to complications. Indeed, longitudinal research is the only approach that could prove or disprove such assertion.

One further pivotal finding from our current work is the identification of a 68.5% prevalence for depression (with 10.6% were categorized as severe depression) in addition to a 30.3% estimate for anxiety prevalence and 13.1% for severe anxiety prevalence. Illness uncertainty correlated positively with both anxiety and depressive symptoms among our sample of patients living with type 1 diabetes. Our results corroborate findings from large-scale systematic reviews for epidemiological estimates for depression and anxiety among type 1 diabetes patients. A recent pooled estimate indicated prevalence of 30% for depressive symptoms and 32% for anxiety symptoms in this group of diabetes patients.[7] Updated regional estimates from Asian

countries showed higher prevalence for depressive symptoms among patients with diabetes, namely 42%.[36] Such variations could be related to timeline with regards to COVID-19 crisis rather than genuine geographical variations. Our results of 68.5% for depressive symptoms are indeed quite impressive, exceeding a 30.8% prevalence found in a recent Saudi Arabian survey,[37] but that could be explained with our data collection process during and immediately after COVID-19 pandemic. A recent Saudi survey postpandemic identified depressive estimates in diabetes close to our estimates, namely 62.5%.[38] Among paediatric population of patients with diabetes, figures were substantially lower than adult counterparts, with 22.2% for depressive disorder and 17.7% for anxiety disorder.[39] The predominance of depressive symptoms among patients with diabetes motivated some authors to call for considering depression as a diabetes-related complication rather than an associated phenomenon[40] with some researchers emphasizing the precedency of depression before the occurrence of diabetes.[41] Other groups were more inclined to propose a biochemical role for inflammatory cytokines in the potentiation of both diabetes and depressive symptoms[42] or the presence of multimorbidity with a third chronic illness on top of diabetes.[43] A third group of academics considered the overlap between diabetes-related distress and diabetes burnout in triggering and perpetuating depressive symptoms.[44]

Our findings confirmed that diabetes-related illness uncertainty exerted a partial moderating effect on both anxiety and depressive symptoms. We demonstrated that the path from diabetes distress to anxiety and to depression was significantly mediated by illness uncertainty without impairing the direct relationship between distress and anxiety or between distress and depression. Our findings provide an explanatory direction to the poorly understood bidirectional underpinnings for anxiety and depression in the context of diabetes mellitus.[45] It is established that distress and depression are closely related constructs when it comes to the psychological effects of diabetes.[46] Our findings suggest that illness uncertainty affects both these constructs and is likely to be affected by them. Diabetes-related distress affects over a third of type one diabetes patients leading to poor management of diabetes[47] glycaemic and metabolic dysfunction in addition to increasing the risk for diabetes complications.[48] Distress was also shown to be associated with high levels of anxiety and fear, particularly fear of hypoglycaemia among diabetes patients.[49]

Depression and anxiety among patients with diabetes are highly correlated with proposed common etiopathology related to impairment in immune-mediated anti-inflammatory mediators.[50] Anxiety and distress were found to correlate with each other in the diabetes context and exert a negative effect on glycaemic control.[51] Uncertainty was also instrumental in explaining a significant part of the association between distress and anxiety among our participants. Uncertainty can be viewed as closely related to a lack of control over worry that was found to bridge the association between diabetes-related distress and anxiety.[52]

One further novice finding from our investigation is the moderating effect of diabetes-related ambiguity and diabetes-related symptom unpredictability in terms of depressive and anxiety symptoms. This can be difficult to explain with confidence given the paucity of research into the effect of subcategories of uncertainty on emotional disorders in diabetes. However, a recent qualitative review indicated that patients with chronic illness experience emotional distress as they have to deal with difficult medical terminology and cope with the complex connection between psychological and physical well-being.[53] Earlier studies showed that diabetes symptoms' ambiguity could have a role into the development of depressive and anxiety symptoms.[54] Other studies confirmed that the unpredictable symptoms of diabetes are perceived (even by a spouse or partner), the higher the risk for emotional difficulties.[55] Our results incorporate a unique dimension to the distress–anxiety relationship but should be reproduced in future evaluations.

Our data show that diabetes-related course unpredictability mediates anxiety but not depressive symptoms. We also observed that diabetes-related complexity did not exert a significant moderating effect on neither depressive nor anxiety symptoms. Such findings can be difficult to explain as literature is lacking on the association between diabetes disease complexity and psychological disorders.

One important limitation for our current work is the potential for overestimation of depressive and anxiety symptoms as a consequence of reliance on subjective self-filled questionnaires rather than direct, costly, clinical consultation.[56] Also, we considered diabetes-related distress as a starting point in direct and indirect paths to depression and anxiety. Prospective authors may arguably consider diabetes burden of disease or diabetes burnout as starting points in the causation of anxiety and depressive symptoms.

Future research endeavours should attempt longitudinal investigation of the effect of illness-related uncertainty on the development of various diabetes complications and examine potential clinical and demographic moderators of such relationship if proved. Also, qualitative research on underpinnings of illness-related uncertainty is required to further understand meaning and implications of its concept among patients with type 1 diabetes especially by their primary physician.

Ethical approval

All experimental protocols were approved by research ethical committee of armed forces centre-western region.

All methods were carried out in accordance with relevant guidelines and regulations. Informed consent was obtained for study participation.

Consent of publication

Not Applicable.

Availability of data and materials

All data supporting our results and discussions are available as part of the article and no additional sources data are available.

Authors contributions

AA (Abdulaziz Alfadhly) conceptualized the study and originated its idea, and planned its design and practicalities. AM (Ayah Mohammed) directed data collection and analysis and wrote the first draft of the manuscript. BA (Basim Almalki), SA (Saad Alfaez), and AM (Ali Mubarak) cosupervised the study running and contributed to write up of the manuscript. EA (Eman Alotaibi), GA (Ghaida Alotaibi), NA (Norah Alshamrani), JA (Jmeela Almathami), RA (Rehab Abdullah), and NB (Njood Bazhair) contributed to data collection, entry, analysis, and the write-up.

All authors state that the manuscript has been read and approved by her as the all of them, that the requirements for authorship as stated earlier in this document have been met, and that she believes that the manuscript represents honest work.

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Conflicts of interest

There are no conflicts of interest.

References

1. Lotfy M, Adeghate J, Kalasz H, Singh J, Adeghate E. Chronic complications of diabetes mellitus: A mini review. Curr Diabetes Rev 2017;13:3-10.
2. Henríquez-Tejo R, Cartes-Velásquez R. Impacto psicosocial de la diabetes mellitus tipo 1 en niños, adolescentes y sus familias. Revisión de la literatura [Psychosocial impact of type 1 diabetes mellitus in children, adolescents and their families. Literature review]. Rev Chil Pediatr 2018;89:391-8. [Spanish].
3. Cameron FJ, Northam EA, Ryan CM. The effect of type 1 diabetes on the developing brain. Lancet Child Adolesc Health 2019;3:427-36.
4. Souza MA, Freitas RWJF, Lima LS, Santos MAD, Zanetti ML, Damasceno MMC. Health-related quality of life of adolescents with type 1 diabetes mellitus. Rev Lat Am Enfermagem 2019;27:e3210. doi: 10.1590/1518-8345.2961.3210.
5. Desai S, Deshmukh A. Mapping of type 1 diabetes mellitus. Curr Diabetes Rev 2020;16:438-41.
6. Rawshani A, Rawshani A, Franzén S, Eliasson B, Svensson AM, Miftaraj M, *et al.* Mortality and cardiovascular disease in type 1 and type 2 diabetes. N Engl J Med 2017;376:1407-18.
7. Buchberger B, Huppertz H, Krabbe L, Lux B, Mattivi JT, Siafarikas A. Symptoms of depression and anxiety in youth with type 1 diabetes: A systematic review and meta-analysis. Psychoneuroendocrinology 2016;70:70-84.
8. Turin A, Drobnič Radobuljac M. Psychosocial factors affecting the etiology and management of type 1 diabetes mellitus: A narrative review. World J Diabetes 2021;12:1518-29.
9. Moreland P, Santacroce SJ. Illness uncertainty and posttraumatic stress in young adults with congenital heart disease. J Cardiovasc Nurs 2018;33:356–62.
10. Mishel M, Clayton MF, Dean M. Theories of Uncertainty in Illness: Middle Range Theory for Nursing. 4th ed. Springer Publishing Company; 2018.
11. Kim O, Yeom EY, Jeon HO. Relationships between depression, family function, physical symptoms, and illness uncertainty in female patients with chronic kidney disease. Nurs Health Sci 2020;22:548-56.
12. Alaradi MI. Predictors of uncertainty, stress, anxiety, and depressive symptoms of parents of preterm infants in the neonatal intensive care unit. Electronic Theses and Dissertations. Paper 25. 2014. Available from: https://doi.org/10.18297/etd/25.
13. Szulczewski L, Mullins LL, Bidwell SL, Eddington AR, Pai ALH. Meta-analysis: Caregiver and youth uncertainty in pediatric chronic illness. J Pediatr Psychol 2017;42:395-421.
14. Mullins AJ, Gamwell KL, Sharkey CM, Bakula DM, Tackett AP, Suorsa KI, *et al.* Illness uncertainty and illness intrusiveness as predictors of depressive and anxious symptomology in college students with chronic illnesses. J Am Coll Health 2017;65:352-60.
15. Dong L, Chen L, Ding S. Illness uncertainty among patients with COVID-19 in the Mobile Cabin Hospital. Nurs Open 2021:10.1002/nop2.924. doi: 10.1002/nop2.924.
16. Alaqeel A, Almijmaj M, Almushaigeh A, Aldakheel Y, Almesned R, Al Ahmadi H. High rate of depression among Saudi Children with type 1 diabetes. Int J Environ Res Public Health 2021;18:11714. doi: 10.3390/ijerph 182111714.
17. AlRuthia Y, Alwhaibi M, Almalag H, Almosabhi L, Almuhaya M, Sales I, *et al.* The relationship between trust in primary healthcare providers among patients with diabetes and levels of depression and anxiety. PLoS One 2020;15:e0239035. doi: 10.1371/journal.pone. 0239035.
18. AlHadi AN, Alarabi MA, AlMansoor KM. Mental health and its association with coping strategies and intolerance of uncertainty during the COVID-19 pandemic among the general population in Saudi Arabia: Cross-sectional study. BMC Psychiatry 2021;21:382.
19. Abu Tabar N, Al Qadire M, Thultheen I, Alshraideh J. Health-related quality of life, uncertainty, and anxiety among patients with chronic obstructive pulmonary disease [version 1; peer review: 2 approved]. F1000Res 2021;10:420. doi: 10.12688/f1000research. 51936.1.
20. Zhang D, Fan Z, Gao X, Huang W, Yang Q, Li Z, *et al.* Illness uncertainty, anxiety and depression in Chinese patients with glaucoma or cataract. Sci Rep 2018;8:11671. doi: 10.1038/s41598-018-29489-1.
21. Cui C, Li Y, Wang L. The association of illness uncertainty and hope with depression and anxiety symptoms in women with systemic lupus erythematosus: A cross-sectional study of psychological distress in systemic lupus erythematosus women. J Clin Rheumatol 2020. doi: 10.1097/RHU.0000000000001280.

22. Gamwell KL, Roberts CM, Espeleta HC, Baudino MN, Hommel KA, Grunow JE, *et al.* Perceived stigma, illness uncertainty, and depressive symptoms in youth with inflammatory bowel disease: The moderating effect of mindfulness. Psychol Health Med 2020;25:1037-48.
23. Churbaji D, Lindheimer N, Schilz L, Böge K, Abdelmagid S, Rayes D, *et al.* Entwicklung einer Kultursensiblen Version des Mini-International Neuropsychiatric Interview (MINI) in hocharabischer Sprache [Development of a Culturally Sensitive Version of the Mini-International Neuropsychiatric Interview (MINI) in Standard Arabic]. Fortschr Neurol Psychiatr 2020;88:95-104. [German].
24. Hong Y, Yoo S, Mreydem HW, Abou Ali BT, Saleh NO, Hammoudi SF, *et al.* Factorial validity of the Arabic version of the Stress and Anxiety to Viral Epidemics-6 Items (SAVE-6) scale among the general population in Lebanon. J Korean Med Sci 2021;36:e168. doi: 10.3346/jkms. 2021.36.e168.
25. Sawaya H, Atoui M, Hamadeh A, Zeinoun P, Nahas Z. Adaptation and initial validation of the Patient Health Questionnaire-9 (PHQ-9) and the Generalized Anxiety Disorder-7 Questionnaire (GAD-7) in an Arabic speaking Lebanese psychiatric outpatient sample. Psychiatry Res 2016;239:245-52.
26. Harkness K, Arthur RN, McKelvie R. The measurement of uncertainty in caregivers of patients with heart failure. J Nurs Measurement 2013;21:23-42.
27. Mishel MH. The measurement of uncertainty in illness. Nurs Res 1981;30:258-63.
28. Apóstolo JLA, Viveiros CSC Nunes HIR, Domingues HRF. Illness uncertainty and treatment motivation in type 2 diabetes patients. Rev Latino-Am Enfermagem 2007;15. doi: 10.1590/S0104-11692007000400009.
29. Hoff AL, Mullins LL, Chaney JM, Hartman VL, Domek D. Illness uncertainty, perceived control, and psychological distress among adolescents with type 1 diabetes. Res Theory Nurs Pract 2002;16:223-36.
30. Celik S, Kelleci M, Satman I. The factors associated with disease mismanagement in young patients with type 1 diabetes: A qualitative study. Int J Community Based Nurs Midwifery 2015;3:84-95.
31. Nishio I, Chujo M. Structure of resilience among Japanese adult patients with type 1 diabetes: A qualitative study. Yonago Acta Med 2017;60:1-8.
32. Ripoli C, Ricciardi MR, Zuncheddu E, Angelo MR, Pinna AP, Ripoli D. Emotional eating and disordered eating behaviors in children and adolescents with type 1 diabetes. Sci Rep 2022;12:21854. doi: 10.1038/s41598-022-26271-2.
33. Sumiyoshi K, Kawata C, Shikata K, Makino H. Influencing factors for dietary behaviors of patients with diabetic nephropathy. Acta Med Okayama 2010;64:39-47.
34. Lee Y, Chang SO. Diabetic foot ulcer patients' uncertainty regarding their prognosis. J Wound Ostomy Continence Nurs 2019;46:531-8.
35. Afzal A, Atta M, Malik NI. Relationship between general health concern and illness uncertainty in diabetic patients; role of self-regulation. J Postgrad Med Inst 2020;34:164-9.
36. Al-Mamun F, Hasan M, Quadros S, Kaggwa MM, Mubarak M, Sikder MT, *et al.* Depression among Bangladeshi diabetic patients: A cross-sectional, systematic review, and meta-analysis study. BMC Psychiatry 2023;23:369.
37. Alzahrani A, Alghamdi A, Alqarni T, Alshareef R, Alzahrani A. Prevalence and predictors of depression, anxiety, and stress symptoms among patients with type II diabetes attending primary healthcare centers in the western region of Saudi Arabia: A cross-sectional study. Int J Ment Health Syst 2019;13:48.
38. Aldossari B, Alhossan A, Ahmad A. The association between type-1 diabetes mellitus and risk of depression among Saudi patients: A cross-sectional study. J Pers Med 2023;13:654. doi: 10.3390/jpm13040654.
39. Akbarizadeh M, Naderi Far M, Ghaljaei F. Prevalence of depression and anxiety among children with type 1 and type 2 diabetes: A systematic review and meta-analysis. World J Pediatr 2022;18:16-26.
40. Pouwer F. Depression: A common and burdensome complication of diabetes that warrants the continued attention of clinicians, researchers and healthcare policy makers. Diabetologia 2017;60:30-4.
41. Birk JL, Kronish IM, Moise N, Falzon L, Yoon S, Davidson KW. Depression and multimorbidity: Considering temporal characteristics of the associations between depression and multiple chronic diseases. Health Psychol 2019;38:802-11.
42. Herder C, Schmitt A, Budden F, Reimer A, Kulzer B, Roden M, *et al.* Association between pro- and anti-inflammatory cytokines and depressive symptoms in patients with diabetes-potential differences by diabetes type and depression scores. Transl Psychiatry 2018;7:1. doi: 10.1038/s41398-017-0009-2.
43. Tittel SR, Dunstheimer D, Hilgard D, Knauth B, Fröhlich-Reiterer E, Galler A, *et al.* Coeliac disease is associated with depression in children and young adults with type 1 diabetes: Results from a multicentre diabetes registry. Acta Diabetol 2021;58:623-31.
44. Kiriella DA, Islam S, Oridota O, Sohler N, Dessenne C, de Beaufort C, *et al.* Unraveling the concepts of distress, burnout, and depression in type 1 diabetes: A scoping review. EClinicalMedicine 2021;40:101118. doi: 10.1016/j.eclinm. 2021.101118.
45. Wardian JL, Kanzler KE, True MW, Glotfelter MA, Sauerwein TJ. Is it distress, depression, or both? exploring differences in the diabetes distress scale and the patient health questionnaire in a diabetes specialty clinic. Clin Diabetes 2019;37:124-30.
46. Snoek FJ, Bremmer MA, Hermanns N. Constructs of depression and distress in diabetes: Time for an appraisal. Lancet Diabetes Endocrinol 2015;3:450-60.
47. Hessler DM, Fisher L, Polonsky WH, Masharani U, Strycker LA, Peters AL, *et al.* Diabetes distress is linked with worsening diabetes management over time in adults with Type 1 diabetes. Diabet Med 2017;34:1228-34.
48. Grulovic N, Rojnic Kuzman M, Baretic M. Prevalence and predictors of diabetes-related distress in adults with type 1 diabetes. Sci Rep 2022;12:15758. doi: 10.1038/s41598-022-19961-4.
49. Li S, Fang L, Lee A, Hayter M, Zhang L, Bi Y, *et al.* The association between diabetes-related distress and fear of hypoglycaemia in patients with type 2 diabetes mellitus: A cross-sectional descriptive study. Nurs Open 2021;8:1668-77.
50. Kwon OC, Kim Y, Chun J, Han K, Park MC, Kim R, *et al.* Association of immune-mediated inflammatory diseases with depression and anxiety in patients with type 2 diabetes: A nationwide population-based study. Front Med (Lausanne) 2023;10:1103911. doi: 10.3389/fmed. 2023.1103911.
51. McInerney AM, Lindekilde N, Nouwen A, Schmitz N, Deschênes SS. Diabetes distress, depressive symptoms, and anxiety symptoms in people with type 2 diabetes: A network

analysis approach to understanding comorbidity. Diabetes Care 2022;45:1715-23.

52. Déniz-García A, Díaz-Artiles A, Saavedra P, Alvarado-Martel D, Wägner AM, Boronat M. Impact of anxiety, depression and disease-related distress on long-term glycaemic variability among subjects with Type 1 diabetes mellitus. BMC Endocr Disord 2022;22:122.
53. Awan H, Mughal F, Kingstone T, Chew-Graham CA, Corp N. Emotional distress, anxiety, and depression in South Asians with long-term conditions: A qualitative systematic review. Br J Gen Pract 2022;72:e179-89.
54. McDade-Montez EA, Watson D. Examining the potential influence of diabetes on depression and anxiety symptoms via multiple sample confirmatory factor analysis. Ann Behav Med 2011;42:341-51.
55. Dimitraki G, Karademas EC. The association of type 2 diabetes patient and spouse illness representations with their well-being: A dyadic approach. Int J Behav Med 2014;21:230-9.
56. Thombs BD, Kwakkenbos L, Levis AW, Benedetti A. Addressing overestimation of the prevalence of depression based on self-report screening questionnaires. CMAJ 2018;190:E44-9.

Supplement File 1

Figure 1: Age and diabetes-related uncertainty

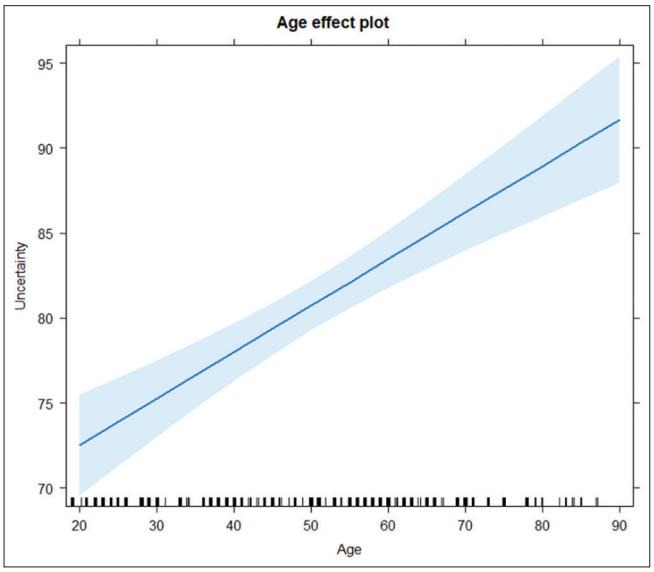

Figure 1 shows that age is positively correlating with diabetes-related uncertainty (μ = 50.0 years, SD = 17.1 years, r=0.2623, t = 6.2806, p < 0.00001)

Figure 2: Marital status and diabetes-related uncertainty

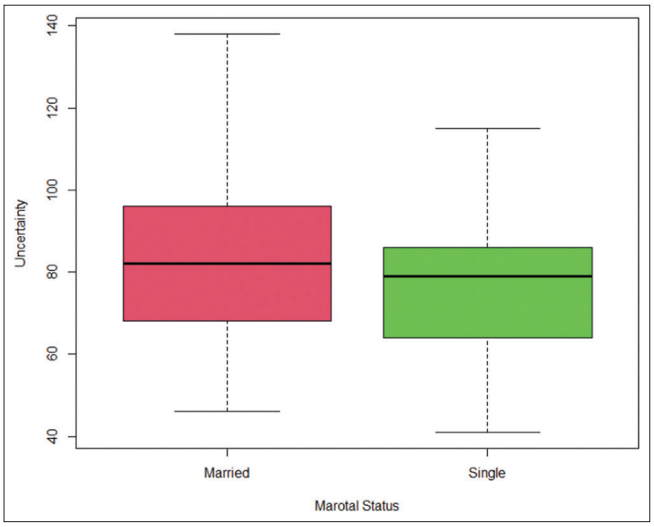

Figure 2 shows that among the participants, (n = 119, 22.2%) were single, and (n = 412, 76.9%) were married. The mean uncertainty score was higher among married patients (μ = 82.1 points) compared to single patients (μ = 76.5 points). The difference was statistically significant (t = 3.337, p = 0.0009937).

Figure 3: Children count and diabetes-related uncertainty

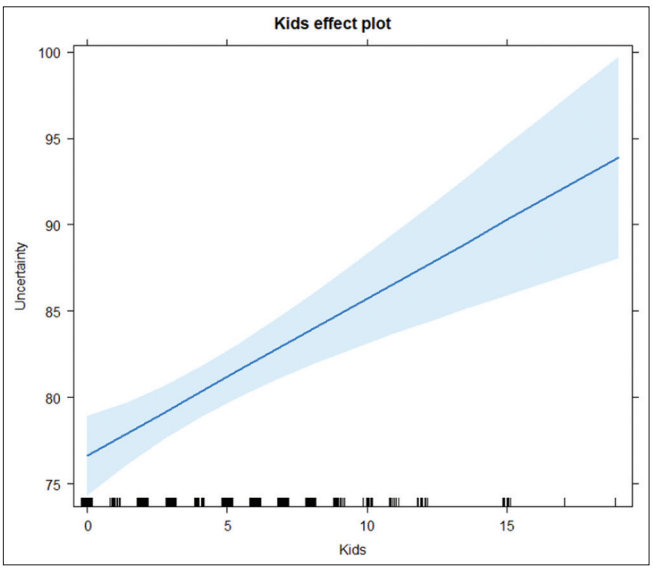

Figure 3 shows that the mean number of participants' children was 4.5 children (SD = 3.8 children) and the median children count was 5. Correlation was positive between kids' count and MIUS (correlation coefficient r = 0.195, p < 0.00001).

Figure 4: Interaction between age and diabetes duration effect on diabetes-related uncertainty

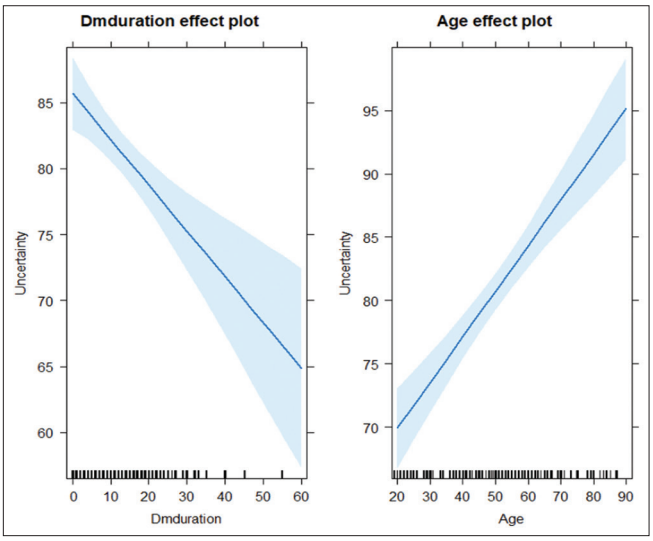

Figure 4 shows that adjusted for age, diabetes duration exerts a cooling effect on uncertainty, i.e. patients with longer diabetes duration reporting better certainty about their illness.

Figure 5: Nationality and diabetes-related uncertainty

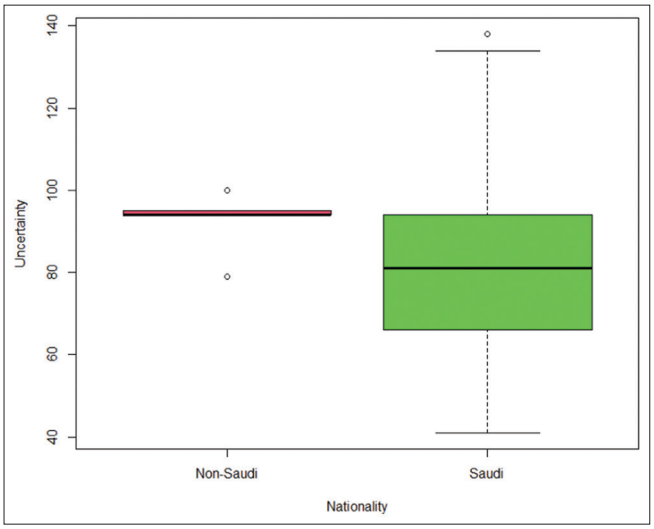

Figure 5 shows that the shear majority of participants were Saudi (n = 530, 98.9%), with only (n = 6, 1.1%) who were non-Saudis. It is difficult to infer statistical significance given the tangible discrepancy in number of non-Saudi individuals compared to Saudis.

Figure 6: Gender and diabetes-related uncertainty

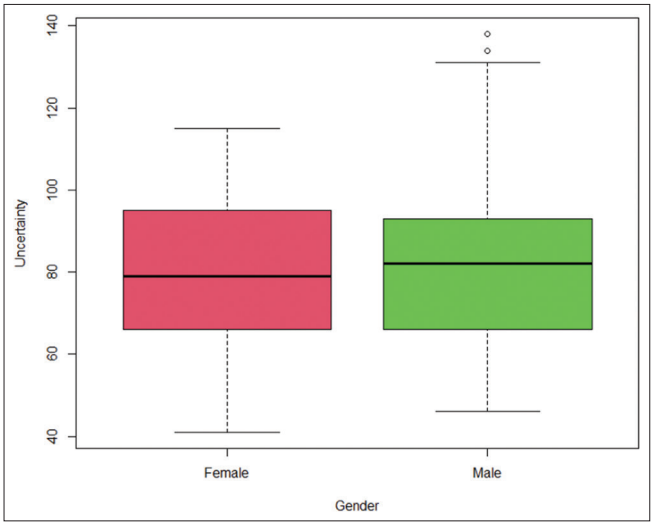

Figure 6 shows that men were (n = 315, 58.8%) whereas women were (n = 221, 41.2%). However, gender did not affect MIUS score (mean MUIS among male participants was 81.0 points compared to MIUS mean among females which was 80.4 points, t = 0.40923, p = 0.6825).

Figure 7: diabetes complications and diabetes-related uncertainty

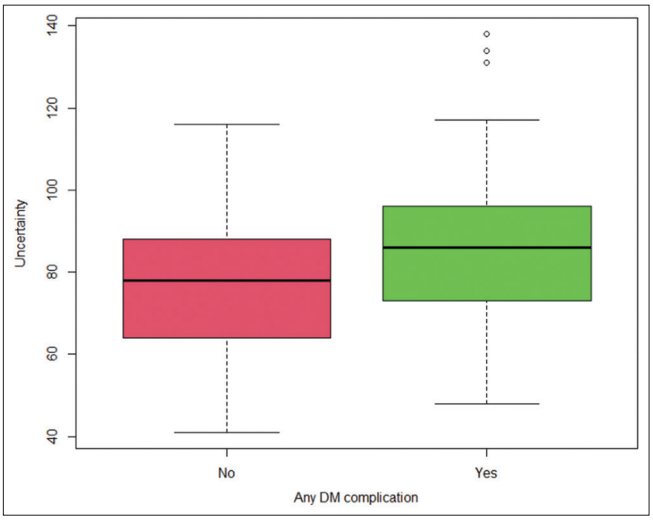

Figure 7 shows that some (n = 261, 48.7%) reported presence of diabetes complications whose mean MIUS score was 84.8 points. The rest (n = 275, 51.3%) reported no diabetes complications, with a mean MIUS score of 76.9 points. The difference was statistically significant (t = 5.257, p < 0.00001) indicating higher uncertainty levels among patients who developed diabetes complications.

Figure 8: Reported pain and diabetes related uncertainty

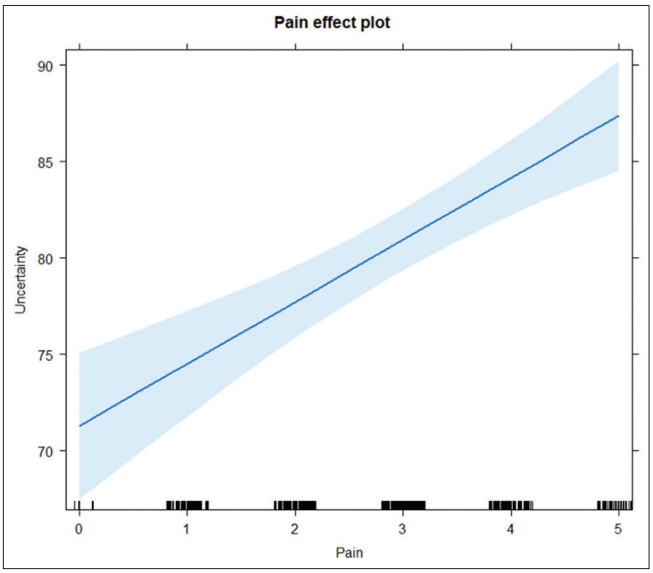

Figure 8 shows that the mean pain score was 2.94 points (Median = 3.0 points, SD = 1.24 points). Pain score correlated positively with MIUS score (r = 0.2247, p < 0.00001).

Figure 9: diabetes distress and diabetes-related uncertainty

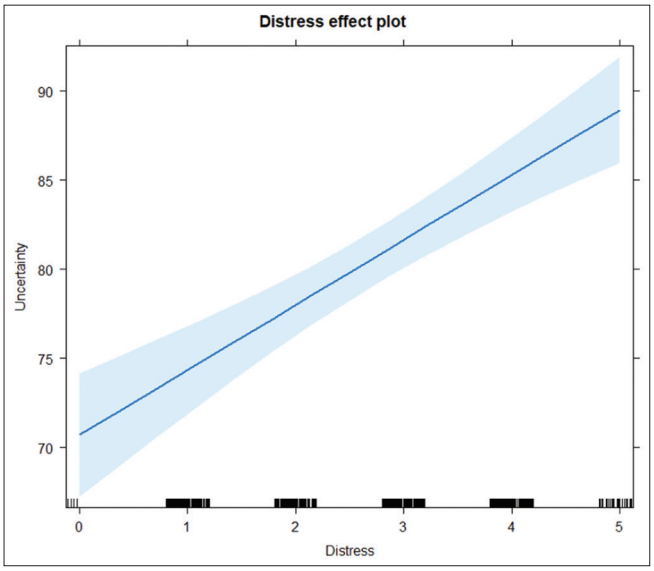

Figure 9 shows that the mean diabetes distress score was 2.7 points (SD = 1.29 points), ranging between 0 and 5 points. The median distress score was 3 points. Distress and MIUS scores were positively correlated (r = 0.2626, p < 0.00001).

Figure 10: Depression and diabetes-related uncertainty

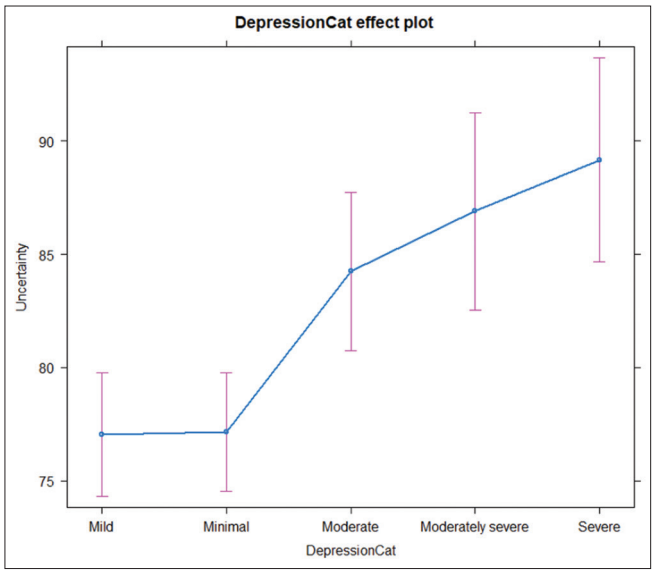

Figure 10 shows that we identified positive correlation between PHQ9 and MIUS score (r = 0.2484, p < 0.00001).

Figure 11: Anxiety and diabetes uncertainty

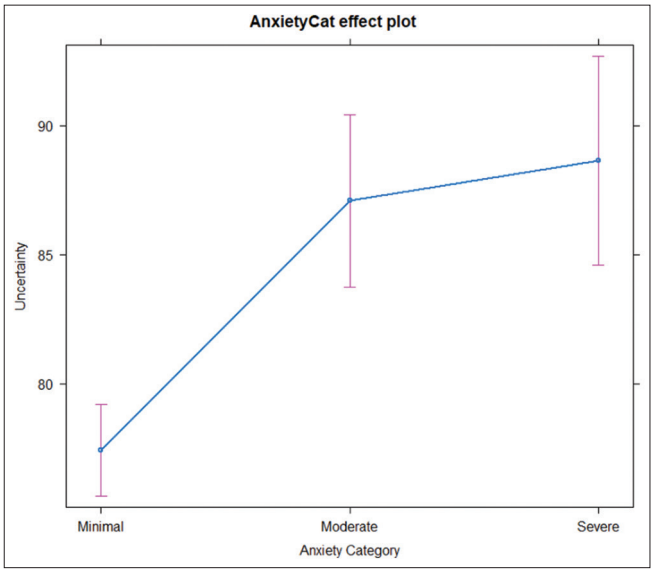

Figure 11 displays that the correlation between GAD7 and MIUS was significant statistically (r = 0.2548, p < 0.00001).

Figure 12: Moderating effect for diabetes-related ambiguity on anxiety and depressive symptoms

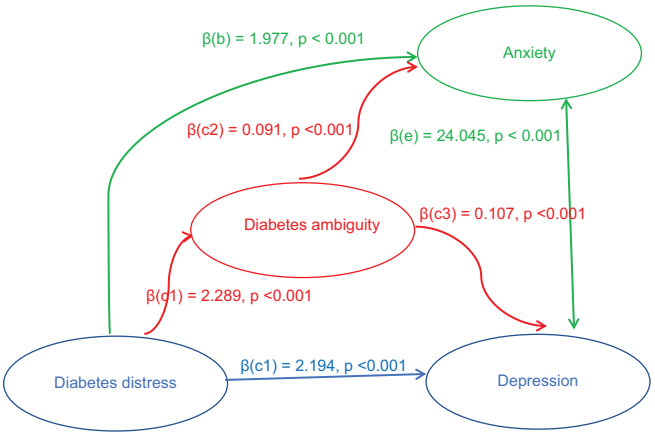

Figure 12 shows that a partial moderating effect were obtained for diabetes-related ambiguity in terms of depressive and anxiety symptoms.

Figure 13: Moderating effect for diabetes course unpredictability on anxiety and depression

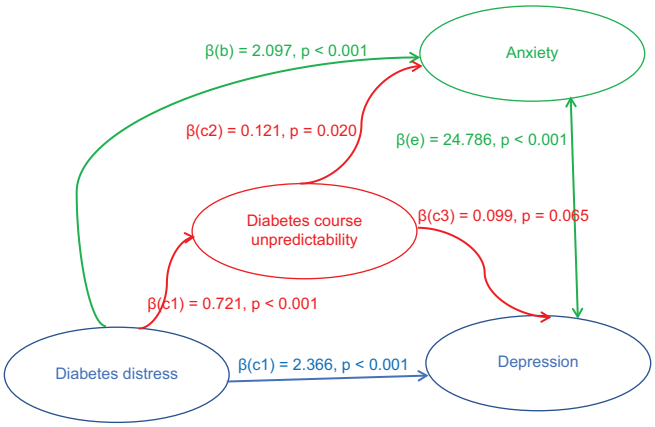

Figure 13 shows that diabetes-related course unpredictability, the moderating effect was significant for anxiety, but not so for depressive symptoms.

Figure 14: diabetes symptom unpredictability and moderating effect on anxiety and depressive symptoms

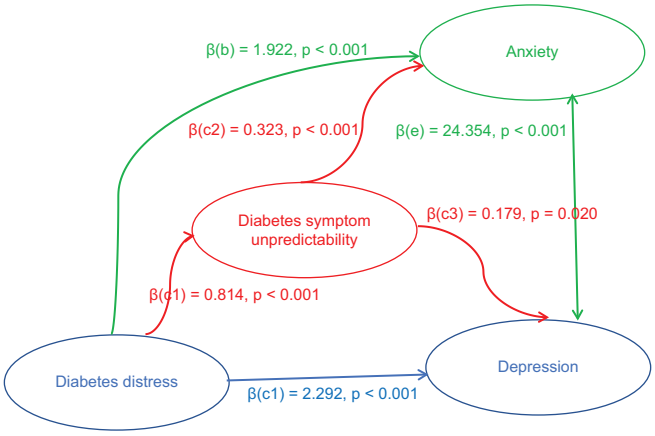

Figure 14 shows that diabetes-related symptom unpredictability exerted a significant partial moderating effect in terms of both depressive and anxiety symptoms.

Figure 15: Diabetes-related complexity and moderating effect on anxiety and depressive symptoms

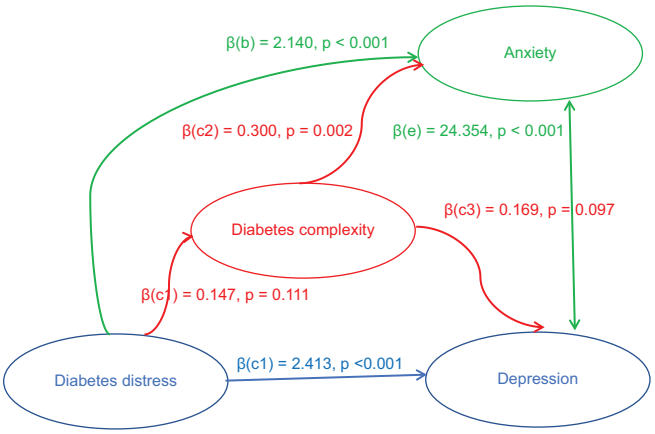

Figure 15 shows that diabetes-related complexity did not exert a significant moderating effect on neither depressive nor anxiety symptoms.