

**What is the relationship of stress to patients' kidney stone-related quality of life?**

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**Abstract**

**Introduction:** Health-related quality of life (HRQOL) is decreased in patients with kidney stones at all stages of stone disease, even when asymptomatic. Stress is thought to contribute to HRQOL, although there has been minimal investigation into the effect of stress on stone-related quality of life (QOL). We used the Wisconsin Stone Quality of Life Questionnaire (WISQOL) to assess the relationship of stress to stone-related QOL in kidney stone patients.

**Methods:** As part of the WISQOL Research Consortium, patients were approached in outpatient clinics and completed the WISQOL and the Perceived Stress Scale 10-item questionnaire (PSS-10). Patients with stones at enrollment were divided into those with symptoms and those without, while patients with no current stones formed another group. Questionnaire scores from each group were compared statistically and correlations between the groups were calculated.

**Results:** Patients (n=704) were enrolled from six centers. The WISQOL successfully discriminated between patients with current stones and those without ( $p<0.0001$ ), while the PSS-10 did not ( $p=0.0869$ ). The PSS-10 revealed patients with symptomatic kidney stones experienced higher levels of general stress than asymptomatic subjects ( $p<0.0001$ ). However, a Pearson correlation test comparing the responses from each instrument revealed no overall correlation between general stress and HRQOL ( $r=0.05$ ).

**Conclusions:** Symptomatic kidney stones increase general stress, as these patients demonstrate higher PSS-10 scores. Despite this, no correlation exists between general stress and stone-related

QOL in patients with stone disease regardless of their stone and symptom status. This implies the existence of other factors impacting QOL in these patients, which warrants further exploration.

## Introduction

Kidney stone disease affects nearly 1 in 11 people in the US<sup>1</sup> with the prevalence increasing over time.<sup>2</sup> Stone episodes, with resulting medical or surgical management, impact a patient's physical, emotional and psychological well-being. Despite treatment, stone recurrence occurs in over 30% of patients<sup>3</sup> which creates a significant burden on patients, their families and the healthcare system. The estimated costs associated with urolithiasis were over \$5.3 billion in 2005 and are expected to rise.<sup>4</sup>

Anxiety and depression<sup>5</sup> along with poor health related quality of life (HRQOL)<sup>6-13</sup> have been associated with urolithiasis. In addition, several studies have identified a correlation between stress and kidney stone disease<sup>14-18</sup> but no study has found a causative relationship between stress and stone formation.

The Wisconsin stone quality of life questionnaire (WISQOL) is a stone-specific HRQOL tool introduced in 2013 by Penniston and Nakada<sup>11</sup> and validated in 2017<sup>21</sup> in a diverse population across 8 North American sites. With a goal to accurately characterize stone specific decrements in HRQOL, WISQOL outperformed the validated, 36 item, Short Form General Health Survey (SF-36) in separating out patients with stones and symptoms from those without. The WISQOL questionnaire consists of 28 questions divided into four domains: 1 – social, 2 – emotional, 3 – stone related symptom impact and 4 – vitality. The Perceived Stress Scale (PSS-10) is a validated, widely utilized psychological tool to assess a person's perception of stress.<sup>22</sup> It is designed to measure general stress with easy to understand questions and has been widely used throughout a variety of medical fields.

The aim of our current multicenter study is to determine if a correlation between stress and HRQOL exists in kidney stone formers.

## Methods

### *Study design*

Data for this prospective observational study were collected from 6 sites (University of British Columbia, University of California San Francisco, Penn State University, University of California Irvine, University of Wisconsin-Madison and University of North Carolina) within the North American Stone Quality of Life Research Consortium. All sites obtained Institutional Review Board Ethics approval and the University of Wisconsin-Madison was the principal data coordination site.

***Site selection, subjects, and recruitment***

Participants with a history of kidney stones were approached in outpatient clinics at each site to fill out the WISQOL along with the PSS-10 at their initial visit. Eligibility criteria included a history of kidney stones, being 18 years of age or older and the ability to read English. Patients were recruited between June 2016 and April 2018 with approximately 80% participation. The questionnaires required, on average, 15 minutes to complete.

Patients were divided into three groups. Group 1 included those with a known kidney stone at the initial visit but without any current stone related symptoms. Patients in group 2 also had a recognized stone but were experiencing stone related symptoms. Group 3 consisted of patients with no known stone at the initial visit.

The principal investigator at each site was a urologist, providing medical and surgical stone management per local standard of care. Participation in this study did not alter clinical care in any way.

***Data collection***

Consent was obtained for each participant by a member of the study team at each site. The WISQOL, a 28-item, single page, double-sided questionnaire and the PSS-10, a single page questionnaire, were administered upon enrollment to each participant. Demographic information was collected along with medical and surgical data.

***Statistical analysis***

The primary study endpoints measured were subject scores on the WISQOL and PSS-10. Their correlation was assessed utilizing Pearson correlation coefficients. Patient demographics and baseline characteristics are summarized descriptively. Data was analyzed using Microsoft® Excel® and IBM® SPSS™ Statistics, version 23. Statistical significance was determined a priori at  $p < 0.05$ .

**Results**

Seven hundred and four (704) participants were included from 6 centers including 359 women and 345 men. The mean age was  $53.1 \pm 15.2$  years. Patients were recruited primarily from a urology or multidisciplinary clinic with 70% and 29% from each, respectively. The average BMI was  $29.7 \text{ kg/m}^2$  with 69% of participants being overweight or obese. The majority of participants were Caucasian ethnicity while Latino/Hispanic and Asian populations comprised 8% and 7%, respectively. Three hundred and twelve patients had no stone at the time of initial visit while 196 and 181 patients had a stone with and without symptoms, respectively. There were 15 patients with incomplete data who were not included in the comparisons.

When comparing participants with current stones present at the time of study enrollment to those without, the groups were similar but there were statistically significant differences in age at first stone episode, duration of stone history and number of stone related events ( $p < 0.05$ ) (TABLE 1). In patients with stones and symptoms compared to those with asymptomatic stones

differences were seen in age, BMI, age at first stone episode and number of prescriptions ( $p < 0.05$ ) (TABLE 2).

The WISQOL questionnaire identified lower quality of life in participants with stones compared to those without (FIGURE 1). These differences were observed in each of the four WISQOL domains in addition to the total score. Decreased scores for participants with stones compared to those without were seen in each of the 28 individual items compared.

Significant differences were also noted between participants with stones and symptoms and those with asymptomatic stones. (FIGURE 2) Comparing these two categories of participants, the WISQOL revealed higher quality of life for those with no symptoms, even though they had stones present (difference in total score was greater than 30%).

Unlike the WISQOL, the PSS-10 failed to show a difference in general stress between participants with and without stones. (FIGURE 3) On the other hand, the PSS-10 distinguished participants with symptomatic stones from those with stones but no symptoms. Participants with stones and symptoms had higher general stress levels than those with stones but no symptoms. In similar fashion the PSS-10 differentiated between patients with symptomatic stones and those with no stones ( $p < 0.001$ ).

When comparing the two questionnaires with Pearson's correlation coefficients, no correlation was seen between participants with stones and those without both in total scores and in each individual domain. (TABLE 3) Despite both questionnaires identifying differences in participants with stones and symptoms from those without, there was no correlation between WISQOL and PSS-10 for these groups.

## Discussion

This multicenter study shows that stress and HRQOL appear to be unrelated in kidney stone patients. While a possible relationship has been suggested in prior studies, our results indicate that general stress is not a driver of HRQOL in stone formers. A physiological link between stress and stones was posited by Walters in 1986.<sup>19</sup> His theory proposed that the stress response led to increased vasopressin levels, retention of free water and hypertonic urine. In addition, ACTH release in response to stress results in stimulation of the parathyroid glands and increased serum calcium.

Since that time, many other authors have investigated the link between stress and kidney stone formation. Diniz et al. found that patients presenting with an acute episode of renal colic had a nearly threefold risk of having undergone significantly stressful life events than controls.<sup>15</sup> Looking more closely at blood and urinary components of stone formation in relation to stress and HRQOL Arzoiz-Fabregas et al. found that chronic stress affects stone formers and may contribute to recurrent calcium oxalate stones.<sup>17</sup> However, in 2017 the same authors re-evaluated this data, using urinary marker ratios and quotients, and found no significant differences between the groups related to urinary risk factors.<sup>20</sup>

In recent years, medical research has placed an emphasis on investigating HRQOL. The relationship between stones and quality of life factors such as stress and depression have been studied. Early data were published on the impact of stress and kidney stone formation in 1997 by Najem et al.<sup>14</sup> They found, in a case control study, that multiple stress factors were higher in stone formers compared to controls. The most significant of these factors were low family income, stressful mortgage problems and emotional life issues. Angell et al. reported an increased risk of psychological distress in their cohort of stone formers compared to the general population.<sup>5</sup> Over 30% of their cohort reported significant psychological distress as opposed to only 16% of Americans in general. When assessing overall HRQOL in stone formers the SF-36 was utilized in early stone studies. Diniz<sup>7</sup>, Penniston<sup>6</sup> and Bensalah<sup>8</sup> and their groups all found decreased HRQOL in stone formers compared to controls.

In 2013 Penniston and Nakada developed the Wisconsin Stone Quality of Life Questionnaire (WISQOL), a novel tool to assess disease-specific HRQOL in kidney stone patients.<sup>11</sup> The WISQOL was then validated in a multi-national prospective study and delineated HRQOL decrements in patients with stones from those without.<sup>21</sup> The questionnaire was more sensitive than the SF-36 at detecting HRQOL changes. In addition, it detected HRQOL differences in patients with symptomatic stones from those with stones but no symptoms. In our study the WISQOL performed well at identifying HRQOL differences in participants with stones from those without along with those with stones and symptoms from those with stones but no symptoms. This further supports the use of the WISQOL in HRQOL research for kidney stone formers.

We hypothesized that stress would be negatively correlated with HRQOL. Using the WISQOL and PSS-10 tools, we discovered that no clear relationship exists between these two entities for kidney stone formers. While the PSS-10 discriminated between participants with symptomatic stones from those with asymptomatic stones, it was unable to differentiate participants with stones from those without. This was due to patients with stones and no symptoms having equivalent PSS-10 scores to patients without stones. Similar findings were seen in a study by Miyaoka et al. where symptomatic stones and frequent passage of stones were related to increased perceived stress using the PSS-10.<sup>16</sup> In that study it was noted that non-stone related characteristics such as female sex, employment status and recent traumatic events also impacted PSS-10 scores. Our findings expand on the suggestion that stone symptoms, as opposed to stone disease itself, cause an elevation in general stress. The PSS-10 appears to be capturing general stress as opposed to stress specifically related to stones. In contrast, the WISQOL filters out general stress and focuses in on HRQOL in stone disease.

We believe that this is the first study looking directly at the relationship between stress and HRQOL using validated questionnaires. Our hypothesis that increased stress leads to lower quality of life for stone formers was disproven. There does not appear to be a direct link between general stress and HRQOL suggesting that the PSS-10 measures stress unrelated to stone disease.

The study has a few limitations. First, the WISQOL is available only in English which excludes a portion of the population and reduces generalizability. Second, the study was performed only at academic centers and may not be applicable to the private practice or community setting. Third, most data were captured at outpatient appointments so may miss a relationship between stress and HRQOL that exists during an acute stone episode. Finally, this study looked at a single time point and may miss changes in stress and HRQOL over time.

**Conclusions**

General stress does not appear to be related to quality of life for kidney stone patients. Higher levels of stress in symptomatic patients, though, suggests that symptoms may add to stress levels. The WISQOL is more sensitive than the PSS -10 at identifying the adverse psychological effects of kidney stone disease. While the WISQOL revealed decrements in quality of life for patients with stones compared to those without, the PSS-10 was unable to differentiate between these groups. These findings would suggest that factors other than stress drive changes in HRQOL for stone formers.

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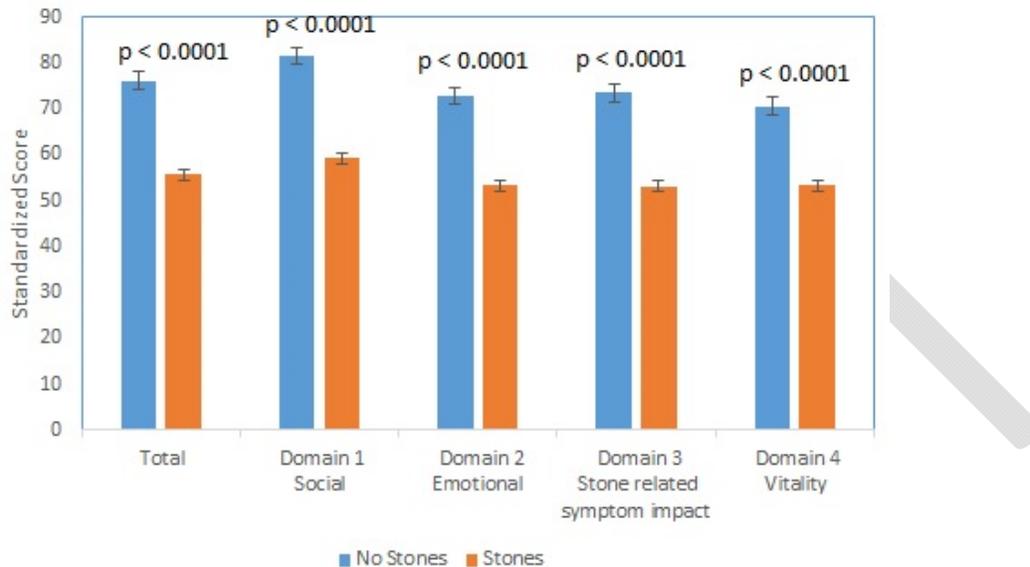
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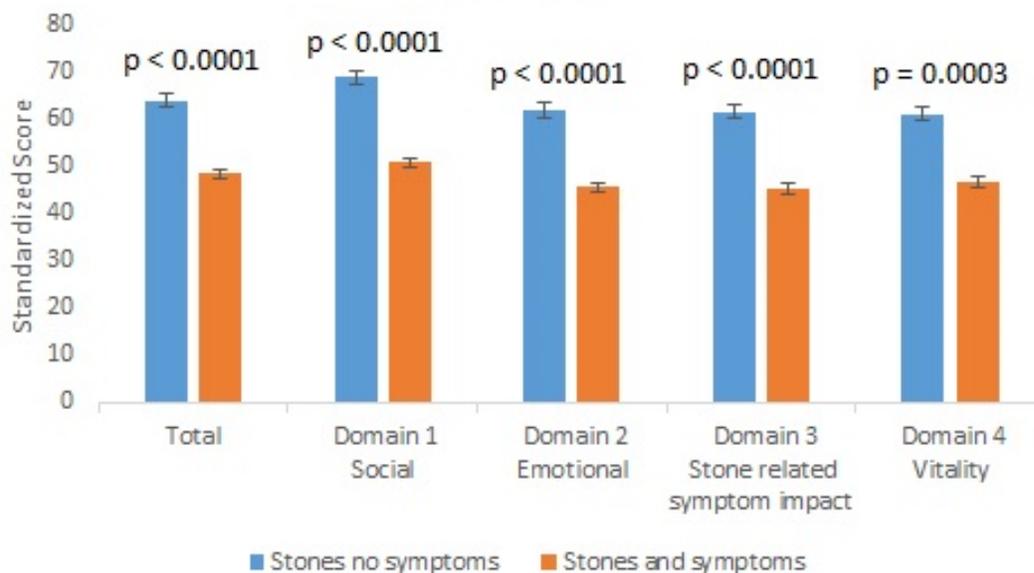
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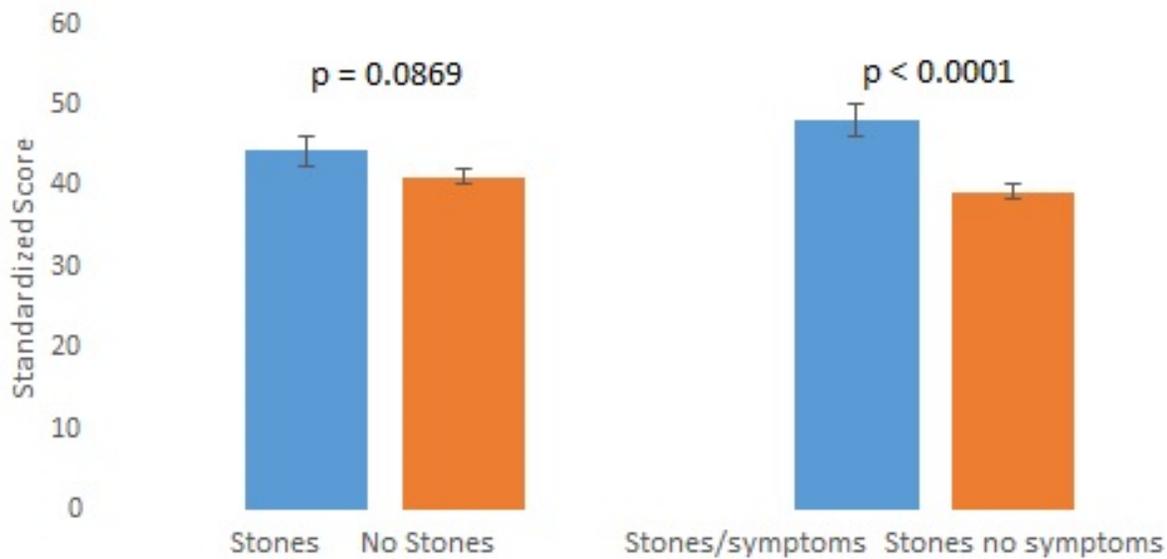
## Figures and Tables

**Fig. 1.** Comparison of Wisconsin Stone Quality of Life (WISQOL) scores between patients who reported having stones vs. those reporting no stones at the time they completed the WISQOL and the Perceived Stress Scale (PSS-10) questionnaire



**Fig. 2.** Comparison of Wisconsin Stone Quality of Life (WISQOL) questionnaire scores between patients who reported having stones and stone-related symptoms vs. those reporting stones but no symptoms at the time they completed the WISQOL and the Perceived Stress Scale (PSS-10).



**Fig. 3.** Comparison of Perceived Stress Scale (PSS-10) scores between groups.**Table 1. Baseline characteristics of patients who reported having stones vs. those reporting no stones at the time they completed the WISQOL and the PSS-10**

	Stones	No stones	p
Age (yrs)	52.2±15.0	54.5±15.4	0.091
BMI (kg/m <sup>2</sup> )	29.7±7.8	29.8±7.6	0.852
First stone episode (age in yrs)	39.7±16.6	44.4±17.2	0.003
Duration of stone disease (yrs)	13.1±13.6	10.5±12.6	0.040
Estimated number of events	8.9±16.6	4.8±10.8	0.005
Events per year	2.4±4.5	1.9±3.2	0.197
Number of comorbidities	1.8±1.8	2.0±1.9	0.108
Number of prescriptions	1.5±1.6	1.5±1.5	0.951
Percentage on diuretic therapy	14	15	0.739
Percentage on alkali therapy	17	20	0.367

Reported as mean ± standard deviation. BMI: body mass index; PSS-10: Perceived Stress Scale; WISQOL: Wisconsin Stone Quality of Life.

**Table 2. Baseline characteristics of patients who reported having stones and stone-related symptoms vs. those reporting stones but no symptoms at the time they completed the WISQOL and the PSS-10**

	Stones + symptoms	Stones with no symptoms	p
Age (yrs)	48.9±13.8	55.8±16.0	<0.001
BMI (kg/m <sup>2</sup> )	30.4±8.4	28.7±7.0	0.047
First stone episode (age in yrs)	37.4±15.2	42.1±14.25	0.011
Duration of stone disease (yrs)	11.7±11.9	14.3±14.6	0.085
Estimated number of events	10.3±18.9	7.0±12.0	0.071
Events per year	2.6±5.3	2.3±3.6	0.496
Number of comorbidities	1.6±1.7	2.0±1.8	0.051
Number of prescriptions	1.3±1.5	1.7±1.6	0.013
Percentage on diuretic therapy	12	14	0.276
Percentage on alkali therapy	16	20	0.139

Reported as mean ± standard deviation. BMI: body mass index; PSS-10: Perceived Stress Scale; WISQOL: Wisconsin Stone Quality of Life.

**Table 3. Correlation between WISQOL and PSS-10**

Correlation between WISQOL and PSS-10	Pearson's correlation coefficient (r)	p
Total	-0.05	0.621
Domain 1 (Social)	-0.001	0.571
Domain 2 (Emotional)	-0.061	0.605
Domain 3 (Stone-related symptom impact)	-0.074	0.188
Domain 4 (Vitality)	-0.121	0.050

PSS-10: Perceived Stress Scale; WISQOL: Wisconsin Stone Quality of Life.