Original article:

Prevalence of Urinary Incontinence and Its Impact on the Quality of Life Among Women in Aseer region, Saudi Arabia

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Received on Mar 22, 2025, accepted for publication on May 4, 2025, dx.doi.org/10.5455/mjhs.2026.02.016

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Abstract:

Background and aim:
Urinary incontinence . It's affects millions of women worldwide . The objectives of this study were to measure the prevalence of urinary incontinence and the association with quality of life, physical, psychological, and social consequences of urinary incontinence Saudi women in Aseer region.

Methods:
A cross-sectional study was conducted from June to October 2024 in the Aseer region, Saudi Arabia. A total of 309 women participated in the study. Data were collected through a self-administered questionnaire, which included demographic information, the Urinary Incontinence Quality of Life Questionnaire (I-QOL), and health-related factors. Statistical analysis was performed using IBM SPSS Version 26.0, with chi-square tests and ANOVA used to identify associations between UI and various factors.

Results:
The study found that 47.2% of participants experienced some form of UI. The prevalence was highest among older women (89.7% in those aged 50+), married or widowed/divorced women (65.3% and 66.7%, respectively), and those with multiple pregnancies (71.4% for four or more pregnancies). Other significant risk factors included menopause (84.0%), obesity (57.9%), and chronic diseases (53.6%). Women with frequent UI reported lower QoL scores, particularly in psychosocial impact, avoidance behavior, and social embarrassment, with statistically significant differences ($p < 0.001$).

Conclusion:
UI is a prevalent issue among women in the Aseer region, significantly affecting their QoL. The findings highlight the need for targeted public health interventions, including awareness campaigns, early screening, and treatment strategies focused on high-risk groups. Addressing UI through lifestyle modifications, medical interventions, and community education can improve the well-being of affected women.

Keywords:
Urinary Incontinence, Women's Health, Urogynecology.

Introduction:

Urinary incontinence (UI) is the unintentional leakage of urine and is typically categorized into three primary types: stress urinary incontinence (SUI), urge urinary incontinence (UUI), and mixed urinary incontinence (MUI). SUI occurs when physical activities, like sneezing or coughing, exert pressure on the bladder, leading to urine leakage. UUI is marked by a sudden, intense urge to urinate, often followed by involuntary leakage. MUI is a combination of both SUI and UUI, with individuals experiencing symptoms of both urgency and exertion-induced leakage. Properly identifying these types is vital, as it allows healthcare providers to tailor treatment strategies to the specific needs of the patient[1,2]. The global prevalence of urinary incontinence (UI) in women varies considerably, affecting approximately 26% of women worldwide[3]. In the United States, data from NHANES (2015–2018) revealed that approximately 62% of women experience UI and around 22% experienced moderate to severe UI[4]. The prevalence rate of urinary incontinence for women aged 45 to 60 in Brazil was 23.6% . Conversely, the prevalence rates among adult women (over 18 years old) in Germany, Denmark, and Norway were 48.3%, 46.4% and 18.7%[5-7]. Studies from European and North American populations report frequencies ranging from 8.5% to 58%[8]. In the Middle East, prevalence rates range from 20% to 54%[9-10], with Saudi Arabia-specific studies indicating rates between 30% and 41.4%. Specifically, the prevalence of stress urinary incontinence (SUI) was found to be 31.7%, urge urinary incontinence (UUI) 22.9%, and mixed urinary incontinence (MUI) 18.4%. Several studies have identified a wide range of factors significantly associated with urinary incontinence (UI), including obesity, high parity, menopause, hysterectomy, current use of hormone replacement therapy (HRT), urinary tract infections, chronic obstructive pulmonary disease (COPD), respiratory system diseases, heart disease, a history of pelvic surgeries, and alcohol consumption. Additionally, diabetes, hypertension, and tobacco use have also been linked to an increased likelihood of developing UI[11-13]. The prevalence of UI tends to rise with age, as demonstrated in the United Kingdom, where an estimated six to seven million people experience this condition. Among those affected, approximately 39.9% are between the ages of 55 and 64, and 15% are between 75 and 80, underscoring the condition's growing impact on older adults[14]. While urinary incontinence (UI) is not typically classified as a severe physical disease or a direct threat to life, it influences women's QoL in several dimensions,

causing psycho-emotional changes and limitations such as physical, social, and sexual restrictions, as well as affecting daily activities. Researchers report that this impact is related to individual perceptions of the severity, type, and amount of urine leakage, as well as the cultural context in which women are situated[15-17]. The physical and social limitations stem from fear or shame of leaking urine in public, prompting women to avoid going out, attending parties, shopping, taking long trips, and participating in physical activities due to concerns about wet clothing, urine odor, or lack of nearby restrooms[18]. Many of these women only leave their homes when they know they will have easy access to facilities. According to the WHOQOL, 66% of affected women report QoL impairment, with UI having a greater impact on physical and social activities, trust, and self-perception[19]. Urinary incontinence. It's affects millions of women worldwide, including those in Aseer, Saudi Arabia. However, research on urinary incontinence has primarily focused on other countries, leaving a gap in understanding the experiences of women in Aseer. This study aims to address this gap by investigating the impact of urinary incontinence on the quality of life of women in the region. The objective of this research is to explore the physical, psychological, and social consequences of urinary incontinence on the quality of life of women in Aseer, Saudi Arabia. By understanding the unique challenges faced by these women, appropriate interventions can be developed to improve their quality of life and overall well-being.

Methodology:

Study population:

A cross-sectional descriptive study was conducted From June 1, 2024, to October 1, 2024, in Aseer region of southwestern SA. The study aimed at assessing the Prevalence of Urinary Incontinence and Its Impact on the Quality of Life. The target sample for this study comprises the female population of the Aseer Region.

Sample size:

The minimum required sample size to investigate the Prevalence of Urinary Incontinence and Its Impact on the Quality of Life Among Women in Aseer region was calculated using Epi-info software, version 7.2.2.6. With a confidence level (CI) of 95% and margin of error of 5%, and an expected frequency of 50%. The required sample size was determined to be 383 participants. We conducted a convenience sampling methodology to select our target population. Participants were recruited based on their availability, and efforts were made to include a diverse range of individuals to enhance the representativeness of the sample.

Data collection tool:

Data were collected through a self-administered anonymous questionnaire in Arabic created using Google Forms and distributed via various channels including social media platforms (Facebook and Twitter), messaging apps (email, WhatsApp, and Telegram), or through face-to-face. The questionnaire consists of three parts: The first part includes socio-demographic and personal data, including age, sex, residence (rural or urban), marital status (single, married, divorced, or widowed), working (employee or non-employee). Additionally, respondents were asked about any associated comorbidities and chronic diseases, including hypertension, thyroid issues, renal disease, liver disease, ischemic heart disease, chronic obstructive airway disease, cerebrovascular disease, and autoimmune diseases. The second part is the validated Arabic version of the Urinary Incontinence Quality of Life Questionnaire (I-QOL), which is a patient-reported outcome measure that specifically assesses the effects of urinary incontinence on various aspects of quality of life. The I-QOL comprises 22 items, each employing a five-point ordinal response scale where 1 = extremely, 2 = quite a bit, 3 = moderately, 4 = a little, and 5 = not at all. These items can be categorized into three sub-scales: Avoidance and Limiting Behavior (8 items), Psychosocial Impacts (9 items), and Social Embarrassment (5 items). To calculate the total I-QOL score and the scores for the three sub-scales, the unweighted item scores are summed and converted to a 100- point scale, with 0 indicating the most severe impact and 100 indicating no issues. This instrument has been extensively utilized and has been effectively validated for individuals experiencing urinary incontinence (UI).

Anthropometric measurements:

Waist circumference was measured by wrapping a measuring tape gently around the respondent's waist at the level of the top of the hip bone. Specific cutoff points of 102 cm for men and 88 cm for women were used to identify risk. The tape was

positioned parallel to the ground and formed a complete circle around the trunk. Body mass index (BMI) was calculated using the formula: BMI = weight (kg) / height (m^2). This involved dividing the body weight in kilograms by the square of the height in meters. BMI categories were defined as follows: a BMI below 18.5 classified as underweight, a BMI from 18.5 to less than 25 considered within the healthy weight range, a BMI between 25.0 and less than 30 indicating overweight, and a BMI of 30.0 or higher denoting obesity.

Data management and analysis plan:

The data collected from the study were analyzed using IBM SPSS Statistics

for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics, including frequencies and percentages, were used to summarize the demographic characteristics and responses of the participants. Chi-square tests were conducted to examine the associations between demographic factors (age, gender, marital status, educational level) and UI prevalence. The significance level was set at $p < 0.05$. One-way ANOVA was used to assess the impact of the frequency of urinary incontinence on quality of life domains, including Psychosocial Impact, Avoidance and Limiting Behavior, and Social Embarrassment. The mean scores and standard deviations for each quality of life domain were calculated and compared across different frequencies of urinary incontinence.

Ethics approval:

Participants were informed that their answers would be confidential and used only for scientific purposes. Ethical approval for the study was obtained from the relevant Ethics Research Committee prior to data collection, ensuring compliance with ethical standards. The research utilized validated instruments, including the King's Health Questionnaire (KHQ) and the Urinary Incontinence Quality of Life Questionnaire (I-QOL), both recognized for their effectiveness in assessing the impact of urinary incontinence on quality of life.

Results:

The study found that 47.2% of participants experienced urinary incontinence (UI). Of these, 19.4% had Stress UI, 28.8% had Urge UI, and 14.6% had Mixed UI.

Table 1 presents the bio-demographic characteristics of 309 women in the Aseer region, Saudi Arabia. The age distribution shows that nearly half of the participants are aged 18- 29 years, with 151 women (48.9%). This is followed by 68 women (22.0%) aged 30-39 years, 61 women (19.7%) aged 40-49 years, and 29 women (9.4%) aged 50 years and above. Regarding marital status, 135 women (43.7%) are single, 150 women (48.5%) are married, and 24 women (7.8%) are divorced or widowed. In terms of employment, a significant majority of participants are unemployed, with 223 women (72.2%), compared to 86 women (27.8%) who are employed. Looking at the number of pregnancies, 147 women (47.6%) have never been pregnant, 20 women (6.5%) have been pregnant once, 26 women (8.4%) have been pregnant twice, 32 women (10.4%) have been pregnant three times, and 84 women (27.2%) have been pregnant four or more times. Regarding normal vaginal deliveries, 20 women (12.3%) have never had a normal vaginal delivery, 92 women (56.8%) have had between 1-3 deliveries, 44 women (27.2%) have had 4-6 deliveries, and 6 women (3.7%) have had more than

6 deliveries. For menopause status, 25 women (8.1%) are menopausal, while 284 women (91.9%) are not. Smoking habits show that 14 women (4.5%) are smokers, while 295 women (95.5%) are non-smokers. About the chronic diseases among the women, 113 (36.6%) have no chronic diseases, 82 (26.5%) are obese, 45 (14.6%) have chronic constipation, 29 (9.4%) have diabetes mellitus, 28 (9.1%) have recurrent urinary tract infections, 28 (9.1%) have chronic respiratory diseases, 24 (7.8%) have experienced back trauma, 20 (6.5%) have chronic cough, 10 women (3.2%) have undergone urinary tract surgery, 6 (1.9%) have neurological disorders, 6 (1.9%) have thyroid disorders, and 6 (1.9%) have other conditions.

Table 1: Bio-demographic characteristics of study women in Aseer region, Saudi Arabia (n=309).

Bio-demographics	No	%
Age in years		
18-29	151	48.9%
30-39	68	22.0%
40-49	61	19.7%
50+	29	9.4%
Marital status		
Single	135	43.7%
Married	150	48.5%
Divorced / widow	24	7.8%
Employment		
Unemployed	223	72.2%
Employed	86	27.8%
Number of pregnancies		
Never	147	47.6%
1 time	20	6.5%
2 times	26	8.4%
3 times	32	10.4%
4 / more times	84	27.2%
Number of normal vaginal deliveries		
Never	20	12.3%
1-3	92	56.8%
4-6	44	27.2%
> 6	6	3.7%
Menopause		
Yes	25	8.1%
No	284	91.9%

Smoking		
Yes	14	4.5%
No	295	95.5%
Chronic diseases		
None	113	36.6%
Obesity	82	26.5%
Chronic constipation	45	14.6%
DM	29	9.4%
Recurrent UTI	28	9.1%
Chronic respiratory diseases	28	9.1%
Back Trauma	24	7.8%
Chronic cough	20	6.5%
Urinary tract surgery	10	3.2%
Neurological disorders	6	1.9%
Thyroid disorders	6	1.9%
Others	6	1.9%

Figure 1 illustrates the prevalence and frequency of urinary incontinence among women in the Aseer region, Saudi Arabia, over the past 12 months. The majority of respondents, 163 women (52.8%), reported never experiencing urinary incontinence. However, a significant portion of the population did experience incontinence to varying degrees: 63 women (20.4%) reported losing control of their urine once per month, and 48 women (15.5%) experienced it 2-3 times per month. Additionally, 23 women (7.4%) reported incontinence about once per week, and 12 women (3.9%) experienced it almost every day.

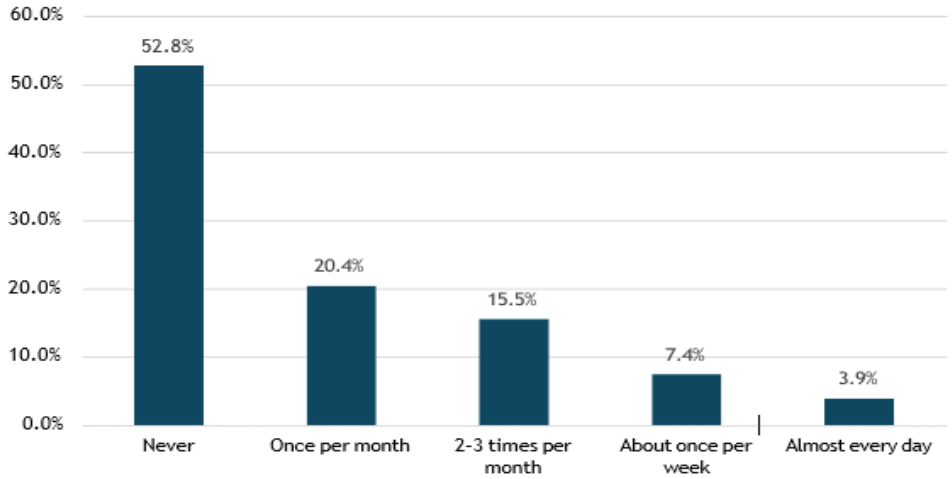


Figure 1: The prevalence and frequency of urinary incontinence among women in Aseer region, Saudi Arabia (n=309).

Table 2 presents the quality of life (QoL) scores among women in the Aseer region, Saudi Arabia. The Psychosocial Impact domain, which ranges from 1 to 5, has a mean score of 3.9 with a standard deviation of 1.0, representing 78.3% of the total possible score. The Avoidance and Limiting Behavior domain also ranges from 1 to 5 and has a mean score of 4.0 with a standard deviation of 1.1, accounting for 80.9% of the total score. The Social Embarrassment domain shows a mean score of 4.1 with a standard deviation of 1.1, covering 81.4% of the total score.

Table 2: Quality of life among study women, Aseer region, Saudi Arabia.

QoL domains	Range	Mean	SD	% of total
Psychosocial impact	1-5	3.9	1.0	78.3%
Avoidance and limiting behavior	1-5	4.0	1.1	80.9%
Social embarrassment	1-5	4.1	1.1	81.4%

Table 3 presents the factors associated with urinary incontinence among women in the Aseer region, Saudi Arabia. There is a significant association between age and urinary incontinence (p = 0.001). The prevalence of urinary incontinence increases with age: 25.8% of women aged 18-29, 66.2% of women aged 30-39, 59.0% of women aged 40-49, and 89.7% of women aged 50 and above reported experiencing urinary incontinence. Marital status also shows a significant association (p = 0.001). Urinary incontinence is more prevalent among married women (65.3%) and divorced/widowed women (66.7%) compared to single women (23.7%). Employment status is significantly associated with urinary incontinence (p = 0.002). A higher prevalence is observed among employed women (61.6%) compared to unemployed women (41.7%). There is a significant association between the number of pregnancies and urinary incontinence (p = 0.001). Women who have had multiple pregnancies show a higher prevalence: 55.0% for one pregnancy, 69.2% for two pregnancies, 62.5% for three pregnancies, and 71.4% for four or more pregnancies. In contrast, 25.2% of women who have never been pregnant reported urinary incontinence. Also, NVD is significantly associated with urinary incontinence (p = 0.018). The prevalence increases with the number of normal vaginal deliveries: 50.0% for those who have never had a normal vaginal delivery, 66.3% for 1-3 deliveries, and 81.8% for 4-6 deliveries. Interestingly, 33.3% of women with more than six normal vaginal deliveries reported incontinence. Menopause status shows a significant association with urinary incontinence (p = 0.001). A higher

prevalence is observed among menopausal women (84.0%) compared to non-menopausal women (44.0%). Body Mass Index (BMI) is significantly associated with urinary incontinence (p = 0.004). The prevalence of urinary incontinence is higher among overweight (58.3%) and obese women (57.9%) compared to those with normal weight (34.7%). Additionally, there is a significant association between chronic diseases and urinary incontinence (p = 0.003). Women with chronic diseases have a higher prevalence of urinary incontinence (53.6%) compared to those without chronic diseases (36.3%). On the other hand, smoking does not show a significant association with urinary incontinence (p = 0.376). The prevalence is 35.7% among smokers and 47.8% among non-smokers.

Table 3: Factors associated with urinary incontinence among women in Aseer region, Saudi Arabia.

Urinary incontinence					
Factors	**No**	**Yes**	**Factors**	**No**	**Yes**
No	**%**	**No**	**No**	**%**	**No**
Age in years					
18-29	112	74.2%	39	25.8%	*001.
30-39	23	33.8%	45	66.2%	
40-49	25	41.0%	36	59.0%	
+50	3	10.3%	26	89.7%	
Marital status					
Single	103	76.3%	32	23.7%	*001.
Married	52	34.7%	98	65.3%	
Divorced / widow	8	33.3%	16	66.7%	
Employment					
Unemployed	130	58.3%	93	41.7%	*002.
Employed	33	38.4%	53	61.6%	
Number of pregnancies					
Never	110	74.8%	37	25.2%	*001.
time 1	9	45.0%	11	55.0%	
times 2	8	30.8%	18	69.2%	
times 3	12	37.5%	20	62.5%	
more times / 4	24	28.6%	60	71.4%	
Number of normal vaginal deliveries					
Never	10	50.0%	10	50.0%	^*018.
1-3	31	33.7%	61	66.3%	
4-6	8	18.2%	36	81.8%	
6 <	4	66.7%	2	33.3%	

Number of cesarean sections					
Never	33	32.7%	68	67.3%	^068.
1-3	15	27.8%	39	72.2%	
+4	5	71.4%	2	28.6%	
Menopause					
Yes	4	16.0%	21	84.0%	*001.
No	159	56.0%	125	44.0%	
BMI					
Normal weight	62	65.3%	33	34.7%	*004.
Overweight	30	41.7%	42	58.3%	
Obese	16	42.1%	22	57.9%	
Chronic diseases					
No	72	63.7%	41	36.3%	*003.
Yes	91	46.4%	105	53.6%	
Smoking					
Yes	9	64.3%	5	35.7%	376.
No	154	52.2%	141	47.8%	

P: Pearson X2 test **^: Exact probability test**
***P < 0.05 (significant)**

Table 4 shows the impact of Urinary Incontinence Frequency on Quality of Life Domains among Women in the Aseer Region, Saudi Arabia. Women who never experience urinary incontinence report the highest quality of life scores, with mean scores of 4.5 (SD = 0.6) for Psychosocial Impact, 4.6 (SD = 0.6) for Avoidance and Limiting Behavior, and 4.7 (SD = 0.6) for Social Embarrassment (p = 0.001). However, as the frequency of UI increases to once per month, the mean scores drop to 3.8 (SD = 1.0) for Psychosocial Impact, 3.9 (SD = 1.1) for Avoidance and Limiting Behavior, and 3.9 (SD = 1.1) for Social Embarrassment (p = 0.001). Further, women who experience UI 2-3 times per month report even lower mean scores of 3.1 (SD = 0.9) for Psychosocial Impact, 3.1 (SD = 1.0) for Avoidance and Limiting Behavior, and 3.1 (SD = 1.1) for Social Embarrassment (p = 0.001). Those experiencing UI about once per week have mean scores of 2.7 (SD = 0.9) for Psychosocial Impact, 2.9 (SD = 1.0) for Avoidance and Limiting Behavior, and 2.8 (SD = 1.1) for Social Embarrassment (p = 0.001). Lastly, women who experience UI almost everyday report mean scores of 2.9 (SD = 0.8) for Psychosocial Impact, 2.9 (SD = 0.8) for Avoidance and Limiting Behavior, and 2.7 (SD = 0.9) for Social Embarrassment (p = 0.001).

UI	Psychosocial impact		Avoidance and limiting behavior		Social embarrassment	
	Mean	SD	Mean	SD	Mean	SD
Never	4.5	.6	4.6	.6	4.7	6.
Once per month	3.8	1.0	3.9	1.1	3.9	1.1
2–3 times per month	3.1	.9	3.1	1.0	3.1	1.1
About once per week	2.7	.9	2.9	1.0	2.8	1.1
Almost every day	2.9	.8	2.9	.8	2.7	9.
p-value	.001*		.001*		.001*	

P: One-Way ANOVA
***P < 0.05 (significant)**

Discussion:

The study focused on the prevalence and quality of life (QoL) impact of urinary incontinence (UI) among women in Aseer, Saudi Arabia. It found that nearly half (47.2%) of the participants experienced UI. The frequency of UI varied, with 20.4% having monthly episodes and 15.5% reporting 2–3 episodes per month. Age was a major factor, with 89.7% of women aged 50 and above affected. Marital status also played a role, with 65.3% of married and 66.7% of divorced/widowed women reporting UI. Other risk factors included multiple pregnancies (71.4% of women with four or more pregnancies) and menopause, which affected 84% of women.

Obesity was strongly linked to UI, with 57.9% of obese women affected. The study also highlighted the significant impact of UI on QoL, as women with frequent episodes reported lower scores in psychosocial impact, avoidance behavior, and social embarrassment.

As urinary incontinence (UI) frequency increased, women's quality of life (QoL) scores declined, reflecting emotional and social challenges. The study's UI prevalence of 47.2% aligns with previous research, including Almutairi et al. (2021), which reported a 41.7% prevalence among Saudi women, highlighting the significant impact of UI on QoL[20].While studies in Omani and Iranian populations reported rates of 32.8% and 46%[21-22], respectively . However, the prevalence was higher compared to certain Western populations, such as Mallorcan women, where the rate was 24% [23]. This difference may reflect regional variations in culture, healthcare, and lifestyle. The

study supports previous research, emphasizing age, parity, menopause, and obesity as key risk factors. Almutairi et al. (2021) and Iranian studies similarly highlighted older age, multiparity, and menopause[20,22]. Obesity's strong link to UI was consistent across studies, with prevalence reaching 88% in obese populations[24].

These findings reinforce the importance of targeted interventions addressing modifiable risk factors such as weight management. Regarding the impact on QoL, the current study aligns with global literature demonstrating that UI significantly reduces QoL, particularly in psychosocial and social domains. Studies by Steibliene et al. (2020) and Paes et al. (2016) also reported that women with UI experience higher levels of anxiety and depression, which negatively influence their overall well-being[25-26]. Additionally, the present study supports findings by Alshenqeti et al. (2022), which highlighted the emotional and social restrictions imposed by UI, especially in women reluctant to seek medical help due to stigma[27]. In the Middle Eastern context, Alquaiz et al. (2023) found a prevalence of 47.5% among Saudi women, with stress incontinence being the most common type. This matches the present study's findings, highlighting the shared burden across different Saudi populations [28]. Xie et al. (2021) similarly emphasized the significant impact of aging, BMI, and lifestyle factors on UI prevalence in Chinese women[29], which aligns with the role of these factors in the Aseer region . Moreover, studies on athletes and active populations, such as Hagovska et al. (2017), revealed that UI prevalence and QoL impact were substantial even in physically active groups, suggesting that UI affects diverse populations beyond the general public[30].

Lastly, Steibliene et al. (2020) identified a strong association between UI, depression, and anxiety, which is consistent with the psychosocial burden highlighted in this study[25]. However, a notable difference emerges when comparing this study's findings on help-seeking behavior. While the present study emphasizes a significant impact of UI on QoL, it does not explicitly address health- seeking behaviors, unlike Alshenqeti et al. (2022) and Al-Balushi (2020), who found low rates of medical consultation due to embarrassment and lack of awareness[27,31]. Future research should explore the barriers to seeking treatment for urinary incontinence (UI) in the region. This study focused on the prevalence and quality of life (QoL) impact of UI among women in Aseer, Saudi Arabia, confirming that UI is highly prevalent in the region and aligns with global patterns. The study highlighted the physical, psychological, and social consequences of UI. With a preva-

lence rate consistent with other Middle Eastern studies, the research emphasized UI's severe impact on daily life, particularly physical activity, social engagement, and emotional health. The findings validated the assertion that UI limits self-esteem and various life domains. The study underscores the need for tailored interventions, such as awareness campaigns, prevention programs, and accessible treatments, to address the specific needs of women in Aseer. Public health strategies should focus on risk factors like age, menopause, chronic conditions, and childbirth. This research contributes to both local and global knowledge on UI, offering valuable regional data.

Conclusions:

The study revealed that nearly half (47.2%) of the surveyed women in Aseer experienced some degree of UI, with prevalence increasing with age, as 89.7% of women aged 50 and above reported UI. Other significant risk factors included marital status, multiple pregnancies, menopause, obesity, and chronic diseases. The findings confirmed that UI negatively impacts QoL, particularly in psychosocial well-being, avoidance behaviors, and social embarrassment. Women with frequent UI episodes reported significantly lower QoL scores, highlighting the emotional and social burden of the condition. This study

underscores the high prevalence of UI among women in Aseer and its profound impact on QoL. Addressing UI requires a multifaceted approach, including public health initiatives, routine screening, and improved access to treatment . This study contributes region-specific insights to global UI literature and informs strategies to reduce its burden. Future research should address care barriers and evaluate intervention effectiveness.

Conflict of Interest: The authors declare no conflict of interest.

Financial Support: No external financial support was received for this research.

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