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Association of Urinary Phytoestrogens with Pelvic Organ Prolapse and Fecal Incontinence Symptoms in Post-menopausal Women

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Abstract

OBJECTIVES: To investigate the association between urinary phytoestrogen levels with symptoms of pelvic organ prolapse (POP) and fecal incontinence (FI) in post-menopausal women.

METHODS: Cross-sectional study utilizing the National Health and Nutrition Examination Survey (NHANES) database from 2005-2010 including post-menopausal women defined age 40 years who either had both ovaries removed and/or no period in the past year due to hysterectomy and/or menopause. Urinary concentrations of six phytoestrogens were measured. POP symptoms were defined as a positive response to the question, "Do you see or feel a bulge in the vaginal area?" FI defined as leakage of mucus, liquid, or solid stool occurring at least monthly. Using appropriate sample weights, prevalence estimates and 95% confidence intervals (CIs) were calculated. Logistic regression was performed assessing associations between pelvic floor symptoms and log-transformed phytoestrogen levels adjusting for appropriate covariates.

RESULTS: Participants included 1,341 post-menopausal women with phytoestrogen data; 1,213 with or without POP symptoms and 1,221 with or without FI symptoms. Multivariable analysis

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revealed no association of urinary phytoestrogen levels with POP symptoms. Higher urinary O-Desmethylangolensin (O-DMA) level was associated with decreased odds of FI symptoms in post-menopausal women, adjusted OR (aOR) 0.92, 95% CI 0.86-0.99.

CONCLUSIONS: Increased urinary O-DMA level was associated with lower odds of FI. Future research may be warranted to further investigate the potential of specific phytoestrogens as mediators of FI, as well as the role of phytoestrogens on POP symptoms.

Keywords

NHANES; phytoestrogens; pelvic prolapse; fecal incontinence; post-menopausal women

Introduction:

Symptoms of pelvic floor disorders (PFDs) are common with 17.1% of women in the United States suffering from moderate-to-severe urinary incontinence (UI), 9.4% with fecal incontinence (FI), and 2.9% with pelvic organ prolapse (POP).[1] Additionally, the prevalence of PFDs increases with age and menopausal status reaching 39% to 50% among women 60 years and older.[2] Given the association between decreased circulating estrogen levels and increased prevalence of PFDs and the presence of estrogen receptors in the bladder, pelvic floor, and anal sphincter [9-13], estrogen has been explored as a mediator of these conditions with mixed clinical results.[3-8]

Less explored as a potential mediator of or a treatment option for PFDs have been phytoestrogens, also known as plant or dietary estrogens. Phytoestrogens are biochemically similar to estradiol and are present in foods such as nuts, flax seed oil, soy products, cereals, breads, and legumes.[14] There are three major classes of phytoestrogens: isoflavones (eg, daidzein, equol, genistein, O-Desmethylangolensin [O-DMA]), coumestans (eg, coumestrol), and lignans (eg, enterodiol and enterolactone).[15] A recent review showed that, although the literature is limited, most studies on phytoestrogens and PFDs support potential associations with pathophysiologic mechanisms, symptoms, and treatment for UI and POP, but no data were available reflecting associations with FI.[16]

Utilizing the National Health and Nutrition Examination Survey (NHANES), Kreydin et al demonstrated that increasing urine concentration of the phytoestrogen, enterodiol, was associated with decreased odds of urgency (odds ratio [OR], 0.92; 95% confidence interval [CI], 0.85-0.99), mixed (OR, 0.90, 95% CI, 0.82-0.98), and other (OR, 0.90, 95% CI, 0.81-0.99) UI in post-menopausal women. In addition, increasing urine concentration of the phytoestrogen, enterolactone, was associated with decreased odds of urgency (OR, 0.92; 95% CI, 0.86-0.99) and mixed (OR, 0.91; 95% CI, 0.84-0.99) UI in women.[17] To expand on information from previous studies, the objective of this study was to utilize NHANES data to investigate the associations between urinary phytoestrogen levels and symptoms of POP and FI in post-menopausal women.

Materials and Methods:

The NHANES 2005-2006, 2007-2008, and 2009-2010

The NHANES program consists of cross-sectional, national health surveys conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (<http://www.cdc.gov/nchs/nhanes.htm>). The NHANES provide estimates of the health status of the U.S. population by selecting a representative sample of the noninstitutionalized population using a complex, stratified, multi-stage, probability cluster design. The NHANES years 2005-2006, 2007-2008, and 2009-2010 were used for this study. The NHANES 2005-2006 oversampled individuals who were aged 60 years or older; black; Mexican American; and low-income, non-Hispanic white race to provide more reliable estimates for these groups. In the NHANES 2007-2008 and 2009-2010, all Hispanic groups were oversampled, not just Mexican Americans. The NCHS Ethics Review Board approved the protocol, and all participants provided written informed consent.

Procedures and Participants

Participants were interviewed in their homes and underwent standardized physical examination, including measured height and weight, and further questioning in a mobile examination center (MEC). Trained interviewers asked questions about FI among women aged 20 years and older in a private MEC interview. Women answered questions regarding POP symptoms along with questions on reproductive health. For this study, the sample was limited to post-menopausal women who were age 40 years who either had both ovaries removed and/or no period in the past year due to hysterectomy and/or menopause.

Fecal Incontinence and Pelvic Organ Prolapse Assessment

To define FI and POP, similar methodology from a previous publication using NHANES data from 2005-06 were utilized.[19] To evaluate for the occurrence of monthly FI, the Fecal Incontinence Severity Index (FISI), which asks about the frequency of leakage of gas, mucus, liquid, and/or solid stool leakage with the following categories: “never,” “two or more times per day,” “once per day,” “two or more times per week,” “once a week,” to “one to three times per month” was used.[20] FI was defined as leakage of mucus, liquid, or solid stool occurring at least monthly on the FISI. Women were asked about POP using the previously validated question, “Do you see or feel a bulge in the vaginal area.”[21] The responses were dichotomized, and POP defined as a positive response.

Urinary Phytoestrogen Assessment

Urinary concentrations of six phytoestrogens (isoflavones- daidzein, equol, genistein, O-desmethylangolensin (O-DMA); lignans- enterodiol and enterolactone) were measured either using high performance liquid chromatography-atmospheric pressure photoionization-tandem mass spectrometry (HPLC-APPI-MS/MS) or liquid chromatography electrospray ionization mass spectrometric (LC-ESI-MS/MS). Crossover studies comparing samples analyzed by LC-ESI-MS/MS and LC-APPI-MS/MS showed similar spectrometric readings. [18]

Associated Risk and Protective Factors

Women self-reported their race/ethnicity, which was then categorized as non-Hispanic white, non-Hispanic black, Hispanic (including Mexican American) and Asian. Age was categorized in 10-year increments from 40 years of age to age 79, with women 80 years and older in the same category. Education was categorized as at least some level of high school education (General Education Development or equivalent) or more than high school. Body mass index (BMI) was calculated as kg/m^2 and categorized as less than 25.0 (underweight/normal weight), 25.0 to 29.9 (overweight), and 30.0 or more (obese). Smoking status was based on the question, “Smoked at least 100 cigarettes in your lifetime?” with an affirmative response resulting in the designation as “smoker”.

Data on disease status were ascertained through the question “Has a doctor or other health professional told you that you had [disease]?” In addition to hypertension, disease types also examined and categorized as positive by self-report were: arthritis, cerebrovascular accident, chronic lower respiratory tract disease, coronary heart disease, congestive heart failure, liver disease, thyroid disease, cancer (other than skin), and diabetes mellitus.[22] Chronic lower respiratory tract disease included self-reported emphysema, chronic bronchitis, or asthma; coronary heart disease included coronary heart disease, angina, or a myocardial infarction. Diabetes included participants who also were taking insulin and/or oral medication for diabetes mellitus. The cumulative number of positive responses to these disease types were divided into 5 categories: 0, 1, 2, 3, and 4 or more. Women self-reported number of pregnancies, vaginal deliveries, cesarean deliveries, having had a hysterectomy with or without oophorectomy, and prior hormone use.

Depression was assessed in a private interview in the MECs using the validated Patient Health Questionnaire-9 (PHQ-9). The PHQ-9 yields scores from 0 to 27, and scores ≥ 10 are used to define major depression with a sensitivity of 88% and a specificity of 88%.[23]

Stool consistency was assessed using the Bristol Stool Form Scale (color picture card with pictures and written descriptors of the seven stool types) and the following written question: “Please look at this card and tell me the number that corresponds with your usual or most common stool type”.[24] Stool types vary from Type 1 (separate hard lumps, like nuts), Type 2 rating (sausage like, but lumpy), Type 3 (like a sausage, cracks), Type 4 (like a sausage, smooth), Type 5 (soft blobs with edges), Type 6 (mushy stool), and Type 7 (entirely liquid), as in other NHANES publications.[25]

Statistical Analysis

The NHANES 2005-06 (N=2,638), 2007-08 (N=2,718), and 2009-10 (N=2,941) data were combined to provide robust sample sizes for women with phytoestrogen data. Prevalence estimates and 95% confidence intervals (CIs) were calculated by using STATA 12.1 (STATA Corp. College Station, Texas), which incorporates the design effect, appropriate sample weights, and the stratification and clustering of the complex NHANES sample design. The sample weights were adjusted for unequal probabilities of selection and nonresponse. The Pearson’s χ^2 test was used to assess the association between having FI or POP and risk and protective factors. Multivariable logistic regression models were adjusted for age, race, BMI

30, parity, hysterectomy status, smoking status, diabetes, chronic lung disease, depression, and hormone use to assess the association between pelvic floor symptoms (POP, FI) and log-transformed phytoestrogen levels. Prevalence odds ratios (ORs) and 95% CIs were reported from the multivariable models, using the appropriate sampling weights, with the level of statistical significance set at $p < 0.05$.

Results:

Phytoestrogens and Pelvic Organ Prolapse Symptoms

Characteristics of women with POP symptoms are shown in Table 1. Among 8,270 women with phytoestrogen data, 1,341 (16.2%) were postmenopausal. Of these women, 1,213 reported data on the presence or absence of POP symptoms (90.5%). Overall, 5.4% of postmenopausal women had POP symptoms (95% CI 4.2%, 6.9%). Women with and without POP symptoms had a mean age ($\pm$ SD) of 63.5 ($\pm$ 11.3) years. No differences existed in POP symptoms by mean age ($p = 0.91$) or by racial/ethnic groups ($p = 0.45$): White (5.5%, 95% CI 4.1, 7.4) compared to Latina (6.2%, 95% CI 3.8, 10.0), Black (4.8%, 95% CI 2.9, 7.9) and Asian (0%, 95% CI 0, 0) women. Women with POP symptoms were more likely to have depressive symptoms compared to women without prolapse symptoms (18.8% vs 10.9%, $p = 0.05$). The results of the multivariable analysis (Table 2) revealed that there was no association of POP symptoms with urinary phytoestrogens.

Phytoestrogens and Fecal Incontinence Symptoms

Characteristics of women with FI symptoms are also included in Table 1. Among the 1,341 postmenopausal women with phytoestrogen data, 1,221 (91.1%) reported on FI symptoms. Overall, 15.9% (95% CI 14.2%, 17.7%) reported at least monthly FI symptoms. Postmenopausal women with and without FI symptoms had a mean age was 63.2 ($\pm$ 11.3) years without differences by mean age ($p = 0.18$) or among racial groups ($p = 0.23$). Compared to women without FI symptoms, women with FI symptoms were more likely to report diabetes (26.8% vs 18.5%, $p = 0.04$), chronic lung disease (28.9% vs 19.4%, $p = 0.001$), and more depressive symptoms (20.3% vs 9.5%, $p < 0.001$). Women with FI symptoms were also more likely to report using female hormones compared to women without FI symptoms (45.1% vs 34.7%, $p = 0.004$). The most common Bristol stool type was type 4 (normal; smooth and soft consistency; 41.9% (95% CI 34.9-49.2) in women with FI symptoms and 56.6% (95% CI 53.2-59.9) without FI symptoms, $p < 0.001$. After adjusting for potential confounding covariates including age, race, BMI 30, parity, hysterectomy status, smoking status, diabetes, chronic lung disease, depression, and hormone use, increased level of urinary O-DMA was associated with decreased odds of FI symptoms, aOR 0.92, 95% CI, 0.86-0.99 (Table 2).

Discussion:

Analysis of a U.S. population-based survey revealed that increased urinary phytoestrogen concentrations were not associated with POP symptoms, however, a higher level of O-DMA appeared to be associated with a protective effect for FI symptoms. The current data are similar to other NHANES data that reported decreased odds of urgency and mixed urinary

incontinence symptoms among post-menopausal women with increased specific urinary phytoestrogen levels (enterodiol, enterolactone).[17] Perhaps, women with increased exposure to certain phytoestrogens share similar protective effects regarding UI and FI symptoms.

The current exploratory analysis reveals that increased levels of ingested estrogen or estrogen-like compounds may share potentially similar mechanisms for decreased UI and FI symptoms in post-menopausal women. Aside from providing estrogen replacement in menopause, the biologic activities of ingested estrogens (phytoestrogens) and exogenous estrogens are complex. Prior to this study, there have been no previously published studies on phytoestrogens and FI. Although urinary levels of the phytoestrogen, enterolactone, was not associated with FI symptoms in this study, another study showed that enterolactone activates specific estrogen receptors (estrogen receptor alpha) in mouse uterus and vagina, while having little or no activity in bone.[26] Additionally, more estrogen receptor-alpha receptors are distributed throughout the female urinary tract, compared to the less consistent estrogen receptor-beta receptors present in the urethra and bladder.[26] Although estrogen receptors are present in the anal sphincter complex and have not been found in the rectal mucosa [10], less is known about the activation of the estrogen receptors in the external anal sphincter.[11] Interestingly, according to one study, lignans, such as enterolactone, preferentially bind to estrogen receptor-alpha receptors compared to isoflavones, such as O-DMA, that preferentially bind to estrogen receptor-beta receptors.[27] Unfortunately, none of these studies sufficiently explain the physiology as to why increased urinary levels of O-DMA (isoflavone) are associated with decreased FI symptoms in post-menopausal women and why there is no association between urinary levels of enterolactone (lignan) and FI symptoms in these women. Other studies evaluating the role of exogenous estrogen on FI symptoms have shown inconclusive results.[5, 6] More studies, especially in vitro and translational, are needed to further investigate the physiologic mechanism by which phytoestrogens may be protective regarding UI and FI symptom development in post-menopausal women.

In contrast, estrogen taken as part of menopausal replacement therapy (MRT) has been shown to be associated with increased FI symptoms in women.[4] In the Nurses' Health Study, the authors reported that women who had used MRT in the past had an increased hazard ratio for FI of 1.32 (95% CI, 1.20-1.45) compared to women who had never used MRT.[4] Women who took oral combined estrogen and progestin MRT also had an increased risk of FI (hazard ratio, 1.37; 95% CI, 1.10-1.70) compared to women who used estrogen-only MRT.[4] Of note, in the current study, women who reported FI symptoms reported higher rates of "ever" using hormones compared to women without FI symptoms.

Although the literature on the role of phytoestrogens in the prevention and treatment of PFDs is limited, a review article on phytoestrogens and their associations with PFDs presented evidence from in vitro studies on type I collagen production and oxytocin expression suggesting that phytoestrogens may have a role in POP development, which is not supported by this current study's finding.[16, 28, 29] Whether these in vitro studies translate to a decreased risk of the development of POP is unknown.[30] In another study, the phytoestrogen, puerarin, was associated with decreased POP symptoms in post-

menopausal women with stage II-IV prolapse as well as increased expression of elastin and collagen I/III.[31] In the current study, perhaps the amount of phytoestrogens ingested by the post-menopausal participants was too low to demonstrate positive clinical effects on their POP symptoms. Given the current paucity of data in the literature, more prospective studies are needed to further evaluate the role of phytoestrogens on POP symptoms.

The strengths of this study include the population-based study design and large sample size. Validated questions were used to assess both POP and FI symptoms. In addition, this is the first study to assess the association between phytoestrogens and FI symptoms in post-menopausal women. The limitations of this study include the cross-sectional nature of the NHANES dataset and therefore the inability to prove causality between phytoestrogens and FI symptoms. Given the definition of 'post-menopause' used in this analysis, the study sample may not reflect an accurate representation of the general post-menopausal population. Furthermore, while there is a significant association between urinary O-DMA and FI symptoms on multivariable analysis, the adjusted odds ratio is 0.92. Although controlling for potential confounding factors, there may be other confounding variables that influence this outcome, including the amount of time that the women may have ingested these compounds as well as other factors that may be involved in maintaining stool continence such as diet, stool consistency and pelvic floor innervation, vascularity and coordinated muscle function. Due to the study design, this study is unable to explain the physiologic mechanism as to how O-DMA may be protective against FI symptoms in post-menopausal women.

In conclusion, increased urinary O-DMA level was associated with decreased FI symptoms in post-menopausal women but were not associated with POP symptoms. Further investigation is warranted to explore the relationships between phytoestrogens and the development of pelvic floor disorders in post-menopausal women.

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References:

1. Wu JM, Vaughan CP, Goode PS, et al. Prevalence and trends of symptomatic pelvic floor disorders in U.S. women. *Obstet Gynecol*, 2014 123(1): p. 141–8. [PubMed: 24463674]
2. Wu JM, Hundley AF, Fulton RG, et al. Forecasting the prevalence of pelvic floor disorders in U.S. Women: 2010 to 2050. *Obstet Gynecol*, 2009 114(6): p. 1278–83. [PubMed: 19935030]
3. Cody JD, Jacobs ML, Richardson K, et al. Oestrogen therapy for urinary incontinence in post-menopausal women. *Cochrane Database Syst Rev*, 2012 10, Cd001405. doi: 10.1002/14651858.CD001405.pub3. [PubMed: 23076892]
4. Staller K, Townsend MK, Khalili H, et al. Menopausal Hormone Therapy Is Associated With Increased Risk of Fecal Incontinence in Women After Menopause. *Gastroenterology*, 2017 152(8), 1915–1921.e1911. doi:10.1053/j.gastro.2017.02.005. [PubMed: 28209529]
5. Donnelly V, O'Connell PR, and O'Herlihy C. The influence of oestrogen replacement on faecal incontinence in postmenopausal women. *Br J Obstet Gynaecol*, 1997 104(3), 311–315. [PubMed: 9091007]

6. Pinedo G, Garcia E, Zarate AJ, et al. Are topical oestrogens useful in faecal incontinence? Double-blind randomized trial. *Colorectal Dis*, 2009 11(4), 390–393. doi:10.1111/j.1463-1318.2008.01624.x. [PubMed: 18637100]
7. Cardenas-Trowers OO, Borgstrom M, and Addis I. Associations Between Type and Route of Hormone Use on Urinary Incontinence and Pelvic Organ Prolapse in Premenopausal and Postmenopausal Women. *Female Pelvic Med Reconstr Surg*, 2017 24(2): p. 100–04.
8. Rahn DD, Carberry C, Sanses TV, et al. Vaginal estrogen for genitourinary syndrome of menopause: a systematic review. *Obstet Gynecol*, 2014 124(6): p. 1147–56. [PubMed: 25415166]
9. Copas P, Bukovsky A, Asbury B, et al. Estrogen, progesterone, and androgen receptor expression in levator ani muscle and fascia. *J Womens Health Gend Based Med*, 2001 10(8): p. 785–95. [PubMed: 11703891]
10. Franz HB, Wendler D, and Oetting G. Immunohistochemical assessment of steroid hormone receptors in tissues of the anal canal. Implications for anal incontinence? *Acta Obstet Gynecol Scand*, 1996 75(10): p. 892–5. [PubMed: 9003088]
11. Haadem K, Ling L, Ferno M, et al. Estrogen receptors in the external anal sphincter. *Am J Obstet Gynecol*, 1991 164(2): p. 609–10. [PubMed: 1992711]
12. Iosif CS, Batra S, Ek A, et al. Estrogen receptors in the human female lower urinary tract. *Am J Obstet Gynecol*, 1981 141(7): p. 817–20. [PubMed: 7198384]
13. Oetting G and Franz HB. Mapping of androgen, estrogen and progesterone receptors in the anal continence organ. *Eur J Obstet Gynecol Reprod Biol*, 1998 77(2): p. 211–6. [PubMed: 9578281]
14. Thompson LU, Boucher BA, Liu Z, et al. Phytoestrogen content of foods consumed in Canada, including isoflavones, lignans, and coumestan. *Nutr Cancer*, 2006 54(2): p. 184–201. [PubMed: 16898863]
15. Gold EB, Leung K, Crawford SL, et al. Phytoestrogen and fiber intakes in relation to incident vasomotor symptoms: results from the Study of Women's Health Across the Nation. *Menopause*, 2013 20(3): p. 305–14. [PubMed: 23435028]
16. Cardenas-Trowers OO, Meyer I, Markland AD, et al. A Review of Phytoestrogens and Their Association With Pelvic Floor Conditions. *Female Pelvic Med Reconstr Surg*, 2018 24(3): p. 193–202. [PubMed: 29432329]
17. Kreydin EI, Kim MM, Barrisford GW, et al. Urinary Lignans Are Associated With Decreased Incontinence in Postmenopausal Women. *Urology*, 2015 86(4): p. 716–20. [PubMed: 26232691]
18. 2005 - 2006 Data documentation, codebook, and frequencies. Available at: http://wwwn.cdc.gov/nchs/nhanes/2005-2006/PHYTO_D.htm. Accessed April 21, 2018
19. Nygaard I, Barber MD, Burgio KL, et al. Prevalence of symptomatic pelvic floor disorders in US women. *Jama*, 2008 300(11): p. 1311–6. [PubMed: 18799443]
20. Rockwood TH, Church JM, Fleshman JW, et al. Patient and surgeon ranking of the severity of symptoms associated with fecal incontinence: the fecal incontinence severity index. *Dis Colon Rectum*, 1999 42(12): p. 1525–32. [PubMed: 10613469]
21. Hendrix SL, Clark A, Nygaard I, et al. Pelvic organ prolapse in the Women's Health Initiative: gravity and gravidity. *Am J Obstet Gynecol*, 2002 186(6): p. 1160–6. [PubMed: 12066091]
22. Weiss CO, Boyd CM, Yu Q, et al. Patterns of prevalent major chronic disease among older adults in the United States. *Jama*, 2007 298(10): p. 1160–2. [PubMed: 17848649]
23. Kroenke K, Spitzer RL, and Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*, 2001 16(9): p. 606–13. [PubMed: 11556941]
24. Heaton KW, Radvan J, Cripps H, et al. Defecation frequency and timing, and stool form in the general population: a prospective study. *Gut*, 1992 33(6): p. 818–24. [PubMed: 1624166]
25. Markland AD, Dunivan GC, Vaughan CP, et al. Anal Intercourse and Fecal Incontinence: Evidence from the 2009-2010 National Health and Nutrition Examination Survey. *Am J Gastroenterol*, 2016 111(2): p. 269–74. [PubMed: 26753893]
26. Penttinen P, Jaehrling J, Damdimopoulos AE, et al. Diet-derived polyphenol metabolite enterolactone is a tissue-specific estrogen receptor activator. *Endocrinology*, 2007 148(10): p. 4875–86. [PubMed: 17628008]

27. Mueller SO, Simon S, Chae K, et al. Phytoestrogens and their human metabolites show distinct agonistic and antagonistic properties on estrogen receptor alpha (ERalpha) and ERbeta in human cells. *Toxicol Sci*, 2004 80(1): p. 14–25. [PubMed: 15084758]
28. Tomaszewski J, Rechberger T, Bogusiewicz M, et al. Collagen type I biosynthesis in culture of pubocervical fascia fibroblast obtained from women suffering from stress urinary incontinence and pelvic organ prolapse. *International Urogynecology Journal and Pelvic Floor Dysfunction*, 2009 20(3): p. S336–S337.
29. Tomaszewski J, Adamiak-Godlewska A, Bogusiewicz M, et al. Oestrogen treatment and N-terminal propeptide of type I collagen concentration in culture media of human pubo-cervical fascia fibroblasts surrounding polypropylene mesh used in urogynaecological surgery procedures. *Przegląd Menopauzalny*, 2010 14(1): p. 5–12.
30. Iwanaga R, Branson ES, Orlicky DJ, et al. Phytoestrogen diet and estradiol rescue oxytocin receptor expression in uterosacral ligaments. *Female Pelvic Medicine and Reconstructive Surgery*, 2016 22(5): p. S7.
31. Jiang G, Zhu T, Zhou Y, et al. Effect of puerarin on vaginal connective tissue in patients with pelvic organ prolapse. *International Journal of Clinical and Experimental Medicine*, 2017 10(1): p. 732–738.

Table 1:

Characteristics of Postmenopausal Women with Phytoestrogen Levels from NHANES

Variable	Prolapse symptoms, N=1,213		P-value	Fecal incontinence symptoms, N=1,221		P-value
	No	Yes		No	Yes	
Age (years) % (CI), n			0.90			0.18
40-49	1.6% (1.0, 2.4), 18	1.5% (0.2, 10.3), 1		1.9% (1.3, 2.8), 20	0% (0), 0	
50-59	8.5% (6.9, 10.6), 98	4.6% (1.4, 14.4), 3		8.4% (6.6, 10.5), 86	7.7% (4.3, 13.6), 15	
60-69	27.3% (24.4, 30.3), 313	30.8% (19.7, 44.7), 20		28.0% (25.2, 31.1), 288	24.2% (18.6, 31.0), 47	
70-79	30.1% (27.3, 33.2), 346	30.8% (20.5, 43.3), 20		30.6% (27.6, 33.7), 314	30.4% (23.9, 37.9), 59	
80	32.2% (29.4, 35.2), 370	32.3% (21.1, 46.0), 21		30.8% (27.9, 33.8), 316	37.6% (31.5, 44.2), 73	
Race/ethnicity % (CI), n			0.45			0.29
Hispanic	93.8% (90.0, 96.2), 288	6.2% (3.8, 10.0), 19		87.3% (82.7, 90.9), 269	12.7% (9.1, 17.3), 39	
Non-Hispanic White	94.5% (92.6, 95.9), 586	5.5% (4.1, 7.4), 34		82.6% (80.0, 85.0), 519	17.4% (15.0, 20.1), 109	
Black	95.2% (92.1, 97.1), 238	4.8% (2.9, 7.9), 12		83.5% (77.8, 87.9), 212	16.5% (12.1, 22.2), 42	
Asian	100% (0), 36	0% (0), 0		87.1% (74.0, 94.1), 27	12.9% (5.9, 26.0), 4	
Education % (CI), n			0.34			0.45
<High school	30.9% (27.5, 34.4), 354	36.9% (24.7, 51.1), 24		30.8% (27.2, 34.7), 316	29.9% (22.3, 38.8), 58	
High school	26.1% (23.6, 28.7), 299	18.5% (11.3, 28.8), 12		26.3% (23.9, 28.9), 270	22.2% (16.3, 29.3), 43	
>High school	43.1% (39.8, 46.4), 494	44.6% (32.7, 57.1), 29		42.9% (39.6, 46.3), 440	47.9% (39.4, 56.6), 93	
BMI (kg/m²) % (CI), n			0.12			0.78
< 25.0	26.7% (24.1, 29.4), 304	13.9% (6.9, 25.9), 9		26.0% (23.2, 29.0), 265	24.4% (19.2, 30.4), 47	
25.0-29.9	31.6% (29.3, 34.0), 360	33.9% (21.4, 49.1), 2		31.2% (28.9, 33.7), 318	33.7% (26.5, 41.6), 65	
30.0	41.7% (38.5, 45.0), 475	52.3% (37.9, 66.3), 34		42.8% (39.4, 46.3), 436	42.0% (34.3, 50.1), 81	
Smoker % (CI), n			0.17			0.56
Yes	39.7% (36.4, 43.1), 455	30.8% (20.6, 43.2), 20		39.6% (36.3, 42.9), 406	41.8% (35.0, 48.8), 81	
Chronic lung disease % (CI), n			0.59			0.001
Yes	20.7% (18.2, 23.3), 237	23.1% (14.9, 33.9), 15		19.8% (17.2, 22.7), 203	28.4% (22.8, 34.7), 55	
Diabetes % (CI), n			0.71			0.04
Yes	20.4% (18.0, 23.0), 234	18.5% (10.6, 30.1), 12		18.5% (16.4, 20.8), 190	26.8% (18.9, 36.5), 52	
Pregnancies[^]	3.8 ± 3.2	4.0 ± 3.2	0.60	3.8 ± 0.1	4.0 ± 0.1	0.62
Vaginal delivery[^]	3.0 ± 0.1	3.0 ± 0.2	0.96	2.9 ± 0.1	3.1 ± 0.2	0.16

Variable	Prolapse symptoms, N=1,213		P-value	Fecal incontinence symptoms, N=1,221		P-value
	No	Yes		No	Yes	
Prior hysterectomy %(CI), n			0.31			0.14
Yes	44.7% (41.7, 47.8), 505	52.4% (38.7, 65.7), 33		44.7% (41.5, 48.0), 451	50.5% (44.0, 57.1), 97	
History of hormone use %(CI), n			0.60			0.004
Yes	35.9% (32.7, 39.3), 410	32.3% (20.6, 46.8), 21		34.7% (31.4, 38.1), 355	45.1% (38.3, 52.1), 87	
3 Chronic Diseases %(CI), n			0.50			0.83
Yes	10.3% (8.9, 11.8), 118	7.7% (3.2, 17.3), 5		10.2% (8.6, 12.1), 105	10.8% (6.9, 16.7), 21	
Major Depression %(CI), n			0.05			<0.001
Yes	10.9% (8.9, 13.1), 123	18.8% (11.0, 30.1), 12		9.5% (7.8, 11.5), 97	20.3% (15.1, 26.8), 39	
Common Stool Types %(CI), n						<0.001
1				3.1% (2.2, 4.3), 31	1.1% (0.3, 4.3), 2	
2				5.7% (4.3, 7.4), 57	4.7% (2.4, 8.9), 9	
3				18.4% (16.0, 21.0), 185	17.3% (12.6, 23.2), 33	
4				56.6% (53.2, 59.9), 569	41.9% (34.9, 49.2), 80	
5				8.0% (6.5, 10.0), 80	12.6% (8.5, 18.2), 24	
6				7.3% (5.9, 8.9), 73	16.8% (11.3, 24.2), 32	
7				1.1% (0.6, 2.1), 11	5.8% (3.2, 10.2), 11	

N= number, % percentage, CI= confidence interval, SE= standard error

Table 2:

Multivariable Association Between Urinary Phytoestrogen Levels and Symptoms of Pelvic Organ Prolapse and Fecal Incontinence in Post-Menopausal Women from NHANES

Phytoestrogens	Prolapse symptoms ^a aOR (95% CI) N= 1,092		Fecal incontinence symptoms ^b aOR (95% CI) N= 1,092	
Isoflavone Daidzein	0.95 (0.86-1.06)	p=0.37	0.95 (0.87-1.03)	p=0.20
O-DMA	0.99 (0.91-1.08)	p=0.40	0.92 (0.86-0.99)	p=0.02
Equol	0.95 (0.79-1.13)	p=0.43	0.95 (0.87-1.05)	p=0.30
Genistein	0.96 (0.88-1.05)	p=0.34	0.99 (0.92-1.06)	p=0.75
Lignan Enterodiol	0.85 (0.71-1.03)	p=0.31	1.00 (0.89-1.13)	p=1.00
Enterolactone	1.05 (0.88-1.25)	p=0.42	0.88 (0.77-1.01)	p=0.07

aOR= adjusted odds ratio; CI= confidence interval

^aModel adjusted for age, race, BMI > 30, parity, hysterectomy status, and smoking status

^bModel adjusted for age, race, BMI > 30, parity, hysterectomy status, smoking status, diabetes, chronic lung disease, depression, and hormone use