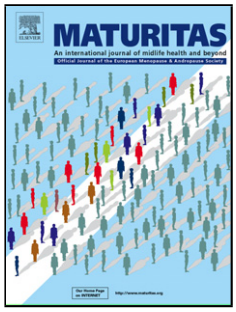


Title: Relationship between changes in vulvar-vaginal atrophy and changes in sexual functioning

Authors: JoAnn V. Pinkerton, Andrew G. Bushmakin, Barry S. Komm, Lucy Abraham

PII: S0378-5122(16)30352-8
DOI: http://dx.doi.org/doi:10.1016/j.maturitas.2017.03.315
Reference: MAT 6793

To appear in: *Maturitas*

Received date: 15-11-2016
Revised date: 10-3-2017
Accepted date: 20-3-2017

Please cite this article as: Pinkerton JoAnn V, Bushmakin Andrew G, Komm Barry S, Abraham Lucy.Relationship between changes in vulvar-vaginal atrophy and changes in sexual functioning.*Maturitas* http://dx.doi.org/10.1016/j.maturitas.2017.03.315

Relationship between changes in vulvar-vaginal atrophy and changes in sexual functioning

JoAnn V. Pinkerton, MD[a]; Andrew G. Bushmakin, MS[b]; Barry S. Komm, PhD[c]; Lucy Abraham, CPsychol[d]

[a]University of Virginia Health System, Charlottesville, VA
[b]Pfizer Inc, Groton, CT
[c]Pfizer Inc, Collegeville, PA
[d]Pfizer Ltd, Tadworth, Surrey, UK

Corresponding author:

Lucy Abraham
Director, Outcomes & Evidence, Global Health and Value
Pfizer Ltd
Walton Oaks, Dorking Road, Walton on the Hill
Tadworth, Kent, Surrey KT20 7NS, UK
Phone: 44(0)1737-332-154
E-mail: Lucy.Abraham@pfizer.com

This data were presented in a poster at the European Menopause and Andropause Society; May 20-22, 2015; Madrid, Spain.

Highlights

- Reducing pain with intercourse can improve sexual function in menopausal women
- Reducing vaginal itching and dryness also improves sexual function, albeit less so
- Large improvements in vaginal maturation index/pH minimally affect sexual function
- Clinicians should focus on improving symptoms rather than clinical parameters

ABSTRACT

Objective: Conjugated estrogens/bazedoxifene (CE/BZA) has demonstrated benefit in vulvar-vaginal atrophy (VVA, part of genitourinary syndrome of menopause) and the sexual function domain of the Menopause-Specific Quality of Life (MENQOL) questionnaire. The study's objective was to determine the relationship of VVA symptoms and clinical parameters with MENQOL sexual functioning in postmenopausal women receiving VVA treatment.

Study design: Post hoc analysis data were derived from the 12-week SMART-3 trial, which evaluated CE/BZA's effect on VVA in nonhysterectomized postmenopausal women (aged 40–65 years) experiencing one or more moderate-severe VVA symptoms (dryness, itching/irritation, pain with intercourse) and vaginal pH >5.0 (N=664).

Main outcome measures: Repeated measures models were used to determine relationships of VVA symptoms and clinical parameters (vaginal pH, parabasal/superficial cells) with sexual functioning; sensitivity analyses were performed to check assumptions of linearity.

Results: VVA symptoms showed an approximately linear relationship with sexual functioning. A one-point improvement in pain on intercourse (which has a large effect size [ES]=0.85) corresponded to medium improvement (ES=0.57) in MENQOL sexual functioning. Equivalent improvements (in terms of ES) in dryness and itching/irritation corresponded to small to medium (ES=0.35) and small (ES=0.27) improvements in sexual functioning, respectively. The same ES improvement in clinical parameters corresponded to small-trivial improvements in sexual functioning.

Conclusions: VVA symptoms have an approximately linear relationship with sexual functioning. Sexual functioning was most improved when pain on intercourse was reduced. Similar magnitudes of improvements in other VVA symptoms were linked with smaller, though potentially beneficial, improvements in sexual functioning. Changes in clinical parameters had only small or trivial associations with sexual functioning.

Trial registration number NCT00238732

Keywords: vulvovaginal atrophy, genitourinary syndrome of menopause, sexual function, conjugated estrogens/bazedoxifene, MENQOL, menopause

INTRODUCTION

Declining levels of estrogens after menopause can lead to genitourinary syndrome of menopause (GSM), a collection of symptoms resulting from changes to the internal and external genitalia and lower urinary tract [1]. Symptoms of GSM may include vulvar or vaginal dryness, burning, and irritation; inadequate lubrication; pain or discomfort during intercourse; postcoital bleeding; sexual impairment; urinary frequency/urgency; dysuria; and recurrent urinary tract infections [1]. Previously used terms such as vulvar-vaginal atrophy (VVA) or atrophic vaginitis are now considered individual components of the overall syndrome. Approximately 40% to 50% of postmenopausal women experience vulvar-vaginal symptoms related to GSM [2, 3], of whom about 60% report moderate or severe symptoms [3]. Subjective symptoms correlate with objective signs of VVA [4]. GSM can cause significant physical discomfort and sexual dysfunction, and can interfere with intimate personal relationships [2, 3]. One study estimated that postmenopausal women with sexual dysfunction are 3.84 times more likely to have VVA than women without sexual dysfunction [5].

As VVA is the result of estrogen deficiency postmenopause, treatment with oral or vaginal estrogen reverses these effects, resulting in improved vaginal superficial cell counts, pH, and lubrication [6]. Conjugated estrogens/bazedoxifene (CE/BZA) is a menopausal therapy indicated for treatment of moderate to severe vasomotor symptoms (eg, hot flushes) and prevention of postmenopausal osteoporosis [7]. Although not indicated for GSM, CE/BZA demonstrated benefit in improving vaginal signs and symptoms, as well as sexual functioning in women who had VVA at baseline

in the third phase 3 Selective estrogens, Menopause, And Response to Therapy (SMART-3) trial [8, 9]. The US Food and Drug Administration–approved dose of CE 0.45 mg/BZA 20 mg and a higher dose consisting of CE 0.625 mg/BZA 20 mg both significantly increased superficial cells, decreased parabasal cells, and decreased vaginal dryness compared with placebo [8]. The higher dose was also associated with significant reductions in vaginal pH and improvements in the women's self-reported most bothersome vaginal symptom, which could be dryness, itching or irritation, or pain with intercourse [8]. Compared with placebo, both doses were associated with statistically significantly higher rates of response, defined as more than one of the following: vaginal superficial cells >5%, vaginal pH <5, and/or improvement in their most bothersome vaginal symptom by at least one category from baseline [8]. In addition, both CE/BZA doses significantly improved Menopause-specific Quality of Life (MENQOL) sexual function domain scores, as well as vasomotor function and overall MENQOL scores [9]. Urinary symptoms of GSM were not evaluated in the CE/BZA phase 3 trials.

The extent to which changes in VVA are associated with change in MENQOL sexual functioning is currently unknown. The objective of this post hoc analysis was to examine the relationship of vulvar-vaginal symptoms and clinical parameters of VVA with sexual functioning as measured by MENQOL, using data from the CE/BZA SMART-3 trial [8, 9]. A better understanding of this relationship will help clinicians predict the magnitude of improvements in sexual functioning that can be expected based on a given treatment's effect on measures of VVA.

METHODS

SMART-3 Study Design and Population

SMART-3 (NCT00238732) [10] was a randomized, double-blind, placebo-controlled, 12-week study. Study design, methodology, and primary results were previously published [8]. Participants were nonhysterectomized postmenopausal women aged 40 to 65 years with a body mass index ≤34.0 kg/m^2, ≤5% vaginal superficial cells, vaginal pH >5, and at least 1 moderate to severe bothersome vulvar-vaginal symptom consisting of dryness, itching/irritation, or pain with intercourse. Women had to indicate on the symptom questionnaire that one of these 3 symptoms was their most bothersome symptom in order to participate. Key exclusion criteria included endometrial hyperplasia, estrogen-dependent neoplasia, undiagnosed vaginal bleeding, endometrial thickness >4 mm on transvaginal ultrasound, abnormal endometrial biopsy or cervical cytologic smear results, a history of breast or gynecologic cancer, and use of hormone-containing therapies within 1 to 6 months (depending on the formulation) prior to enrollment.

Participants were assigned to treatment with CE 0.45 mg/BZA 20 mg, CE 0.625 mg/BZA 20 mg, BZA 20 mg, or placebo. Participants were prohibited from using medications or alternative therapies known to treat vulvar-vaginal atrophy while participating in the study.

VVA and Sexual Function Outcomes

SMART-3 had 4 co-primary end points consisting of severity of most bothersome vulvar-vaginal symptom, vaginal pH, proportion of vaginal superficial cells, and proportion of vaginal parabasal cells. Symptoms of VVA were evaluated using a symptom questionnaire, on which participants rated vaginal symptoms (dryness, itching/irritation, pain with intercourse) as 0=none, 1=mild, 2=moderate, or 3=severe. Thus, these symptoms were rated with regard to presence and severity only, and were not specifically rated as to their impact on sexual functioning. Vaginal pH was assessed by applying a colormetric indicator strip to the vaginal wall, and the proportion of superficial and parabasal cells in vaginal epithelial samples was obtained from vaginal smears, performed at screening and weeks 4 and 12. Parabasal and superficial cell counts were represented by values from 0 to 100, corresponding to the proportion of the sample comprising each cell type. Vaginal pH >5, increased parabasal cells on vaginal maturation index, and decreased superficial cells on vaginal maturation index or wet mount are findings supportive of GSM diagnosis [1]; therefore, findings in the opposite directions were considered clinical improvements.

The MENQOL questionnaire [11] was administered at baseline and week 12 as one of the secondary efficacy end points in SMART-3. For the current analysis, scores from the sexual function domain of the MENQOL questionnaire were used as a measure of the patient's sexual function. (The MENQOL also includes vasomotor, psychosocial, and physical domains and an aggregate score [11]; however, this research centers only on the sexual function domain.) The sexual function domain contains 3 items: change in

sexual desire, vaginal dryness during intercourse, and avoiding intimacy. Responses for each of these items were converted to numerical scores ranging from 1=not experiencing symptom in previous month, 2=symptom was experienced but not at all bothersome, up to 8=symptom was present and extremely bothersome.

Statistical Analyses

For this analysis, we used all available data from baseline to week 12 from all 4 treatment arms combined. A repeated measures model was used to determine the relationship between vaginal symptoms and clinical parameters (superficial and parabasal cell counts, vaginal pH) with MENQOL sexual functioning. The MENQOL sexual functioning domain score was used as an outcome. Anchors for the model included symptoms and (separately) clinical parameters used as continuous predictors. This model imposes a linear relationship between the outcome and a predictor.

Sensitivity analyses were performed using vaginal symptoms and clinical parameter anchor scores as categorical predictors to check assumptions of linearity. This model does not impose any functional relationship between a predictor (symptoms or clinical parameters) and the outcome (MENQOL sexual functioning).

To facilitate a quantitative evaluation of the association between the VVA end points and MENQOL sexual functioning, we first estimated the improvement in the MENQOL sexual functioning domain score corresponding to an incremental change on the end point: a 1-point change in VVA symptom (pain with intercourse, dryness,

itching/irritation) or vaginal pH, a 10% increase in vaginal superficial cells, or a 10% decrease in vaginal parabasal cells. *P* values were calculated for the association between these VVA end points and MENQOL sexual function domain. Because each of these parameters uses a different measurement and scale thereby making it difficult to compare the findings, we then calculated effect sizes (ES) for each outcome to provide a standardized metric that would facilitate comparisons of the associations across all outcomes. ES, which here represents the magnitude of change, was calculated as mean change divided by the standard deviation (SD) at baseline. Lastly, we estimated the ES of the improvement in MENQOL sexual functioning that would correspond to a corresponding ES change in the VVA endpoints. A one-point change in pain with intercourse, divided by its SD at baseline (1.18), corresponded to a large ES of 0.85. For consistency, we then estimated the ES of the change in MENQOL sexual functioning score that corresponds to the same change of ES=0.85 in the other predictors (symptoms and clinical parameters). A standardized ES of about 0.1 was considered trivial, 0.2 was considered small, 0.5 medium, and 0.8 large [12, 13].

SAS version 9.4 (SAS Institute Inc, Cary, North Carolina, USA) was used to perform all analyses.

RESULTS

Participants and Observations

In the SMART-3 trial, 664 participants were randomly assigned to treatment, of whom 12 never received study medication; 601 completed the study [8]. Reasons for

discontinuation and baseline characteristics were previously published [8]. In brief, the mean age of the 652 participants who received study medication was approximately 56 years; on average the women were about 7 to 8 years postmenopausal; and more than 90% were white (Table 1) [8]. Adverse events were the most common reason for discontinuation across all treatment arms (n=31). As reported in the primary published data, adverse events that occurred in ≥5% of any treatment arm included pain, abdominal pain, back pain, headache, migraine, vasodilatation, abdominal distension, constipation, diarrhea, dyspepsia, nausea, arthralgia, leg cramps, myalgia, insomnia, infection, pharyngitis, vaginitis, and accidental injury.

Relationship of VVA Symptoms with MENQOL Sexual Functioning

All 3 studied symptoms of VVA (dryness, itching/irritation, pain with intercourse) had robust, approximately linear relationships with MENQOL sexual functioning (Fig.1A-C). Results were similar regardless of whether VVA symptom was modeled as a continuous or categorical predictor, confirming the linearity assumption of the main model (Fig.1A-C).

Our results showed that a 1-point improvement in vaginal symptoms of VVA (ie, a reduction in severity from severe to moderate, moderate to mild, or mild to none) was significantly associated (all $p<0.0001$) with changes in MENQOL sexual functioning (Table 2). A large change (ES 0.85) in pain with intercourse was associated with a medium change in sexual functioning (Fig.1A). The same large change (ES 0.85) in vaginal dryness was associated with a small to medium change in sexual functioning,

and the same magnitude of change in vulvar-vaginal itching/irritation was associated with a small change in sexual functioning.

Relationship of Clinical Parameters with MENQOL Sexual Functioning

Of the 3 clinical parameters, the relationship between pH and MENQOL sexual function can be characterized as the strongest (Fig. 2A). Although the relationship was significant (p<0.0001), large changes in vaginal pH (ie, a change corresponding to ES 0.85) were associated with only small changes in MENQOL sexual functioning (Table 1).

The relationship of superficial and parabasal cell counts with MENQOL sexual functioning was weak (Fig. 2B and 2C). The associations were significant (p<0.0001); however, large changes (ie, corresponding to 0.85 ES) in parabasal and superficial cell counts were associated with small or trivial changes in MENQOL sexual functioning, respectively (Table 2).

Modeling using each clinical parameter as a categorical predictor generally supported assumptions of linearity, although when superficial cell count was used as a predictor, a relationship was weak at best.

DISCUSSION

Results of this post hoc analysis indicate that by addressing vaginal symptoms of GSM, particularly pain with intercourse, clinicians can help improve menopause-specific quality of life related to sexual functioning. For example, a 1-point reduction in symptoms of pain with intercourse (ie, from severe to moderate, or moderate to mild) would be expected to improve MENQOL sexual function domain score by 1.20 points (on a scale ranging from 1 to 8); this degree of change in MENQOL sexual function corresponds to an ES of 0.57, which can be characterized as a medium effect. A medium effect (ES of about 0.5) represents a magnitude of difference that would be expected to be visible to the naked eye of an observer (eg, a difference of approximately 8 points on an IQ test with a mean score of 100 and standard deviation of 15) [13, 14].

Despite current focus on clinical parameters (vaginal pH and superficial and parabasal cell counts), these have only a trivial (or small at best) relationship with menopause-specific quality of life related to sexual functioning. For example, a large reduction in vaginal pH is expected to result in only minimal improvement in MENQOL sexual function domain score (ES=0.13). An effect of this size is considered small (ie, one that is a real effect but not readily observable without careful study). Testing vaginal pH is helpful to the clinician to confirm the diagnosis of VVA. It also allows the clinician to demonstrate the change visually to the patient by showing her the color of the pH paper before treatment and then the change in color after improvement in pH on therapy. However, a change in vaginal pH by itself does not lead to a significant improvement in

symptomatology. Therefore, to maximize benefit to patients, clinicians should focus more on addressing GSM symptoms, particularly improving painful intercourse, than on improving only clinical testing parameters such as vaginal pH or vaginal maturation indices.

This analysis utilized all available data from a phase 3 study of CE/BZA, and combined data from women treated with 2 doses of CE/BZA, BZA alone, or placebo. By including all available participants rather than limiting the analysis to those treated with CE 0.45 mg/BZA 20 mg or to those in the placebo group, the analysis has greater power such that the relationship between outcomes and predictors can be evaluated based on the magnitude and range of scores in the total population, irrespective of external factors. As a result, our findings with regard to the relationships between VVA signs/symptoms and MENQOL sexual functioning are not specific to CE/BZA or to any one dose of CE/BZA—rather, any intervention that results in improvements in VVA symptoms would be expected to produce corresponding improvements in MENQOL sexual functioning.

The standardized results shown in Table 2 are akin to the results of the standardized regression or standardized beta coefficient [15] with the exception that our analysis is done for longitudinal rather than cross-sectional data. Furthermore, slopes (beta coefficients) from standardized regression correspond to 1 standard deviation in predictor; however, here we used 0.85 as a reference to be consistent and more interpretable, as this value of 0.85 corresponds to a 1-point change in pain with intercourse.

To the best of our knowledge, our analysis is the first to directly link improvements in specific vaginal symptoms and clinical testing outcomes with the MENQOL sexual functioning domain and to quantify the magnitude of these effects. However, previous studies do provide further evidence that MENQOL sexual functioning scores are improved when vaginal symptoms or sexual dysfunction are treated with hormonal therapies. For example, in a randomized, double-blind, placebo-controlled study of postmenopausal women (N=40) with sexual dysfunction based on the Female Sexual Function Index (FSFI), a combination of CE 0.625 mg, micronized progesterone 100 mg, and methyl-testosterone 1.25 mg significantly (p<0.05) improved all MENQOL domains, including the sexual function domain (change of –2.3 vs –1.0 with placebo; p=0.04) [16]. In another double-blind, randomized, placebo-controlled trial, vaginal dehydroepiandrosterone 0.25%, 0.5%, or 1.0% significantly (p<0.01) decreased MENQOL sexual function domain scores by 54%, 43%, and 53%, respectively, compared with 32% for placebo in postmenopausal women with vulvar- vaginal atrophy (superficial cells ≤5%, pH >5) and moderate to severe vaginal symptoms (dryness, itching/irritation, or pain with intercourse) (N=216) [17].

Previous studies further support that treating pain with intercourse and other vaginal symptoms in postmenopausal women leads to improvement in other measures of sexual functioning as well. For example, significant (p<0.01) improvements in the FSFI overall score have been reported with ospemifene 60 mg daily (an estrogen agonist/antagonist approved for treatment of postmenopausal women with pain during

intercourse), as well as topical vaginal testosterone propionate cream (300 μg/application, applied 3 times per week for 12 weeks) or polyacrylic acid cream (3 g cream/application, applied 3 times per week for 12 weeks) compared with controls (oral placebo or vaginal lubricant) in postmenopausal women with vulvar-vaginal atrophy and related symptoms [18, 19]. Compared with placebo, oral CE 0.45 mg/medroxyprogesterone acetate 1.5 mg for six 28-day cycles, plus vaginal CE (0.625 mg/application) during the first 6 weeks, resulted in significant reductions in frequency and severity of pain with intercourse based on diary cards and the McCoy Female Sexuality Questionnaire (MFSQ). That regimen also improved sexual receptivity/initiation on the Brief Index of Sexual Functioning–Women scale and sexual interest, enjoyment of intercourse, and occurrence and pleasure of orgasm based on the MFSQ [20]. In a randomized, controlled trial of 75 postmenopausal women with urogenital atrophy and sexual dysfunction, scores on the Short Personal Experiences Questionnaire (an adaptation of the MFSQ) improved by 42% with vaginal CE cream (0.625 mg/application applied daily for 2 weeks and then twice weekly for 10 weeks) and 147% with a combination of vaginal CE and testosterone cream (CE 0.625 mg/application applied daily for 2 weeks and then CE 0.625 mg plus 1 mg testosterone applied twice weekly for 10 weeks) compared with 18% with a nonhormonal vaginal lubricant [21].

The current study has possible limitations that should be considered. For example, the population of the SMART-3 trial was primarily nonobese, mostly white (>90%), and restricted to women with ≤5% vaginal superficial cells, vaginal pH >5, and at least 1

moderate to severe bothersome vulvar-vaginal symptom consisting of dryness, itching/irritation, or pain with intercourse. It is unknown whether results of our analysis are generalizable to other ethnic populations or women with more or less severe VVA or other symptoms of GSM. In the Menopause Epidemiology Study, which analyzed MENQOL scores across a large population of postmenopausal women in the United States, overweight or obese women had higher sexual function scores (indicating more dysfunction) compared with normal weight women [22]. In that analysis, MENQOL vasomotor scores were higher in black, non-Hispanic women than other populations, but the other MENQOL domains, including sexual function, do not vary significantly by ethnicity or race [22]. Another limitation of our analysis is that SMART-3 was only 12 weeks in duration; therefore, our findings may not be extrapolated to long-term improvements in GSM on MENQOL sexual functioning. Because sexual symptoms can persist for many years after menopause [23], longer studies may be useful to confirm that the relationship between reduction in vaginal symptoms and improvements in MENQOL sexual functioning is maintained over longer durations of use.

This post hoc analysis relied on the MENQOL sexual functioning domain as a measure of menopause-related sexual functioning. The MENQOL sexual functioning domain provides information limited to the extent to which women are bothered by menopause-related change in sexual desire, vaginal dryness during intercourse, and avoiding intimacy. Future studies in this area should consider capturing other aspects of sexual functioning including sexual arousal, distress, sexual pleasure, and satisfaction. It should also be noted that sexual dysfunction (eg, dyspareunia, vaginal dryness) in

postmenopausal women may be influenced by factors other than menopause-related VVA and estrogen deficiency, including relationship and other psychosocial factors, lack of adequate sexual stimulation or arousal, cultural/religious restrictions, and medical/psychiatric conditions or treatments [24-27].

CONCLUSIONS

Estimating anticipated improvements in sexual functioning based on changes in vaginal symptoms will improve clinicians' ability to counsel women about possible benefits of treating GSM symptoms. Vaginal GSM symptoms (pain with intercourse, vaginal dryness, vaginal itching/irritation) had a robust and approximately linear relationship with sexual functioning. Of these 3 symptoms, pain with intercourse was the most strongly associated with MENQOL sexual functioning. A large improvement in pain with intercourse was associated with a medium improvement in sexual functioning. Similar magnitudes of improvement in vaginal dryness or vaginal itching/irritation corresponded to smaller, though potentially beneficial, improvements in sexual functioning. In contrast, large improvements in clinical parameters (vaginal maturation and vaginal pH) were associated with only small or trivial improvement in sexual functioning. Thus, addressing bothersome vaginal symptoms of GSM, especially pain with intercourse, is likely to have a greater impact on sexual functioning than focusing only on changes in clinical parameters such as vaginal pH or maturation index.

Contributors

The sponsor contributed to the design and conduct of the study; collection and analysis of data; and review of the manuscript. The authors were responsible for the review of the data, interpretation of the data and the clinical importance of the manuscript, all final content, and the decision to submit for publication.

Conflict of interest

L. Abraham and A.G. Bushmakin are employees and shareholders of Pfizer. B.S. Komm is a former employee of Pfizer. J.V. Pinkerton has served as a consultant (fees to the University of Virginia) for Pfizer Inc, received grants/research support (fees to the University of Virginia) from Therapeutics MD, received travel funds from Pfizer Inc and received editorial writing support from Pfizer Inc, TherapeuticsMD, Shionogi, and Noven Pharmaceuticals.

Funding

This analysis was sponsored by Pfizer Inc.

CONTRIBUTIONS

The sponsor contributed to the design and conduct of the study; collection and analysis of data; and review of the manuscript. The authors were responsible for the review of the data, interpretation of the data and the clinical importance of the manuscript, all final content, and the decision to submit for publication.

Ethical approval

This is a post-hoc analysis of a Phase 3 Selective estrogens, Menopause, And Response to Therapy (SMART-3) trial. Written informed consent was obtained from all participants during the original clinical trial (NCT00238732).

Provenance and peer review

This article has undergone peer review.

Acknowledgments

Medical writing support was provided by Lauren Cerruto and Diane M. Sloan, PharmD, at Peloton Advantage and was funded by Pfizer Inc.

REFERENCES

[1] Portman DJ, Gass ML. Genitourinary syndrome of menopause: New terminology for vulvovaginal atrophy from the International Society for the Study of Women's Sexual Health and The North American Menopause Society. Maturitas 2014;79:349-54.

[2] Kingsberg SA, Wysocki S, Magnus L, Krychman ML. Vulvar and vaginal atrophy in postmenopausal women: findings from the REVIVE (REal Women's VIews of Treatment Options for Menopausal Vaginal ChangEs) survey. J Sex Med 2013;10:1790-9.

[3] Simon JA, Kokot-Kierepa M, Goldstein J, Nappi RE. Vaginal health in the United States: results from the Vaginal Health: Insights, Views & Attitudes survey. Menopause 2013;20:1043-8.

[4] Palma F, Volpe A, Villa P, Cagnacci A. Vaginal atrophy of women in postmenopause. Results from a multicentric observational study: The AGATA study. Maturitas 2016;83:40-4.

[5] Levine KB, Williams RE, Hartmann KE. Vulvovaginal atrophy is strongly associated with female sexual dysfunction among sexually active postmenopausal women. Menopause 2008;15:661-6.

[6] Semmens JP, Tsai CC, Semmens EC, Loadholt CB. Effects of estrogen therapy on vaginal physiology during menopause. Obstet Gynecol 1985;66:15-8.

[7] Duavee [package insert], Wyeth Pharmaceuticals Inc, A subsidiary of Pfizer Inc., Philadelphia, PA, 2015.

[8] Kagan R, Williams RS, Pan K, Mirkin S, Pickar JH. A randomized, placebo- and active-controlled trial of bazedoxifene/conjugated estrogens for treatment of moderate

to severe vulvar/vaginal atrophy in postmenopausal women. Menopause 2010;17:281-9.

[9] Bachmann G, Bobula J, Mirkin S. Effects of bazedoxifene/conjugated estrogens on quality of life in postmenopausal women with symptoms of vulvar/vaginal atrophy. Climacteric 2010;13:132-40.

[10] Study evaluating bazedoxifene/conjugated estrogen combinations in vasomotor symptoms associated with menopause NCT00238732. <https://clinicaltrials.gov/ct2/show/NCT00238732>, 2007 (accessed May 2, 2016.).

[11] Hilditch JR, Lewis J, Peter A, van Maris B, Ross A, Franssen E, Guyatt GH, Norton PG, Dunn E. A menopause-specific quality of life questionnaire: development and psychometric properties. Maturitas 1996;24:161-75.

[12] Cappelleri JC, Zou KH, Bushmakin AG, Alvir JMJ, Alemayehu D, Symonds T, Patient-reported outcomes. Measurement, implementation and interpretation, CRC Press, Boca Raton, FL, 2014.

[13] Cohen J, The analysis of variance, in: J. Cohen (Ed.), Statistical Power Analysis for the Behavioral Sciences, Lawrence Erlbaum Associates, Hillsdale, NJ, 1988, pp. 273-406.

[14] Sullivan GM, Feinn R. Using Effect Size-or Why the P Value Is Not Enough. J Grad Med Educ 2012;4:279-82.

[15] Standardized Beta Coefficient: Definition & Example. <http://www.statisticshowto.com/standardized-beta-coefficient/>, 2016 (accessed February 7, 2017.).

[16] Blumel JE, Del PM, Aprikian D, Vallejo S, Sarra S, Castelo-Branco C. Effect of androgens combined with hormone therapy on quality of life in post-menopausal women with sexual dysfunction. Gynecol Endocrinol 2008;24:691-5.

[17] Labrie F, Archer D, Bouchard C, Fortier M, Cusan L, Gomez JL, Girard G, Baron M, Ayotte N, Moreau M, Dube R, Cote I, Labrie C, Lavoie L, Berger L, Gilbert L, Martel C, Balser J. Effect of intravaginal dehydroepiandrosterone (Prasterone) on libido and sexual dysfunction in postmenopausal women. Menopause 2009;16:923-31.

[18] Constantine G, Graham S, Portman DJ, Rosen RC, Kingsberg SA. Female sexual function improved with ospemifene in postmenopausal women with vulvar and vaginal atrophy: results of a randomized, placebo-controlled trial. Climacteric 2015;18:226-32.

[19] Fernandes T, Costa-Paiva LH, Pinto-Neto AM. Efficacy of vaginally applied estrogen, testosterone, or polyacrylic acid on sexual function in postmenopausal women: a randomized controlled trial. J Sex Med 2014;11:1262-70.

[20] Gast MJ, Freedman MA, Vieweg AJ, de Melo NR, Girao MJ, Zinaman MJ. A randomized study of low-dose conjugated estrogens on sexual function and quality of life in postmenopausal women. Menopause 2009;16:247-56.

[21] Raghunandan C, Agrawal S, Dubey P, Choudhury M, Jain A. A comparative study of the effects of local estrogen with or without local testosterone on vulvovaginal and sexual dysfunction in postmenopausal women. J Sex Med 2010;7:1284-90.

[22] Williams RE, Levine KB, Kalilani L, Lewis J, Clark RV. Menopause-specific questionnaire assessment in US population-based study shows negative impact on health-related quality of life. Maturitas 2009;62:153-9.

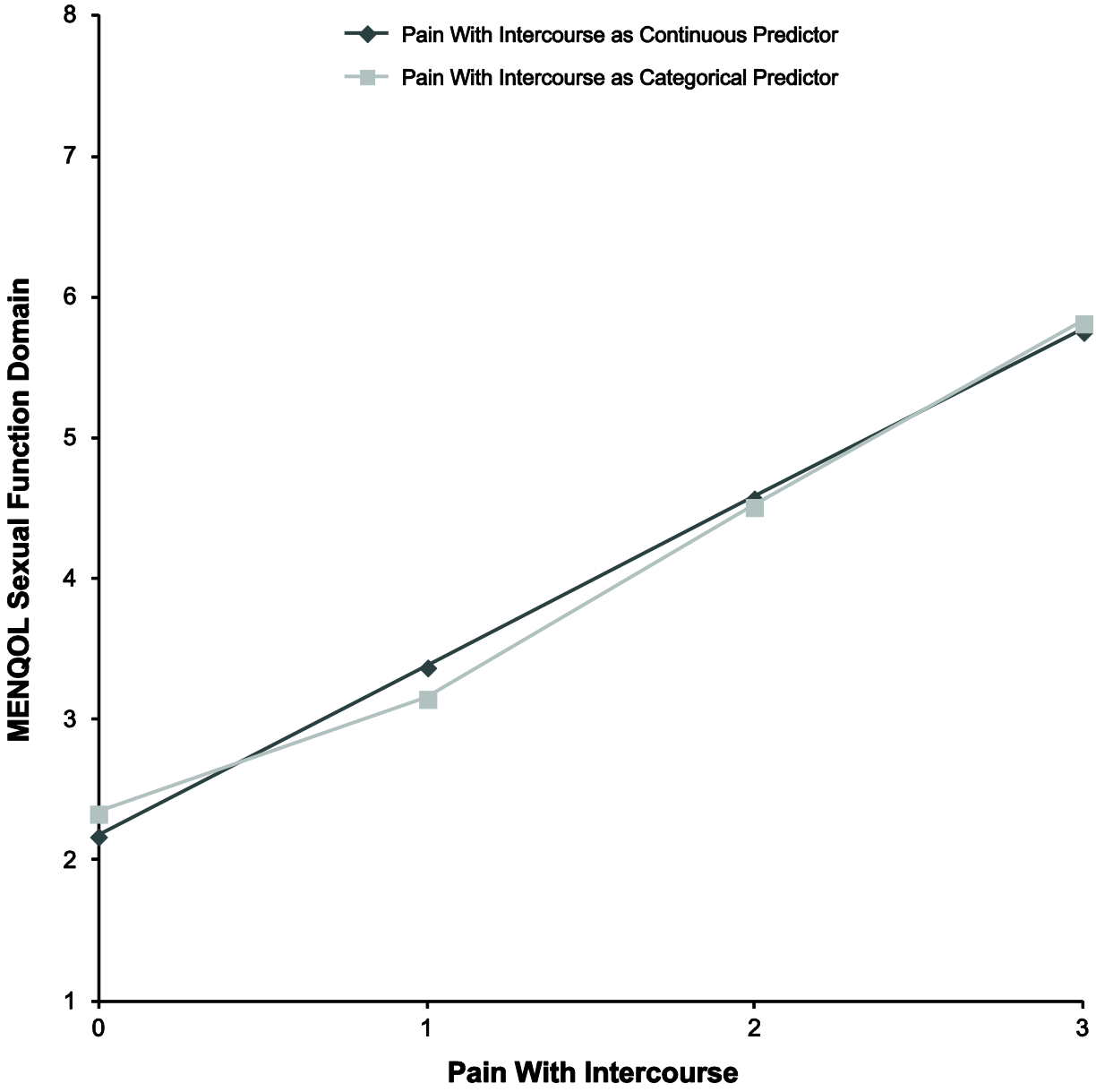
[23] Gartoulla P, Worsley R, Bell RJ, Davis SR. Moderate to severe vasomotor and sexual symptoms remain problematic for women aged 60 to 65 years. Menopause 2015;22:694-701.

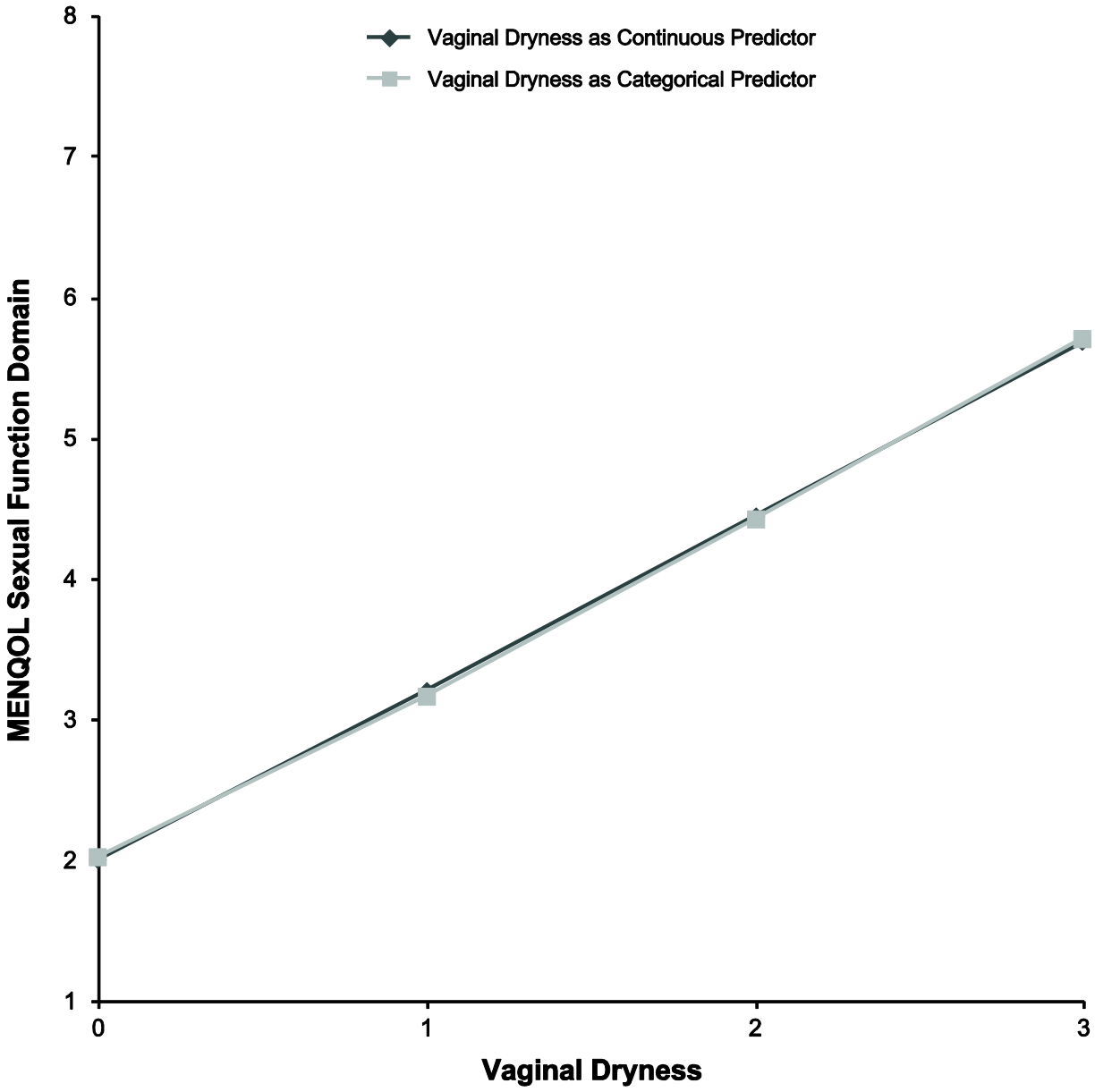
[24] Laan E, van Lunsen RH. Hormones and sexuality in postmenopausal women: a psychophysiological study. J Psychosom Obstet Gynaecol 1997;18:126-33.

[25] van Anders SM, Brotto L, Farrell J, Yule M. Associations among physiological and subjective sexual response, sexual desire, and salivary steroid hormones in healthy premenopausal women. J Sex Med 2009;6:739-51.

[26] van Lunsen RH, Laan E. Genital vascular responsiveness and sexual feelings in midlife women: psychophysiologic, brain, and genital imaging studies. Menopause 2004;11:741-8.

[27] Basson R, Leiblum S, Brotto L, Derogatis L, Fourcroy J, Fugl-Meyer K, Graziottin A, Heiman JR, Laan E, Meston C, Schover L, van LJ, Schultz WW. Definitions of women's sexual dysfunction reconsidered: advocating expansion and revision. J Psychosom Obstet Gynaecol 2003;24:221-9.





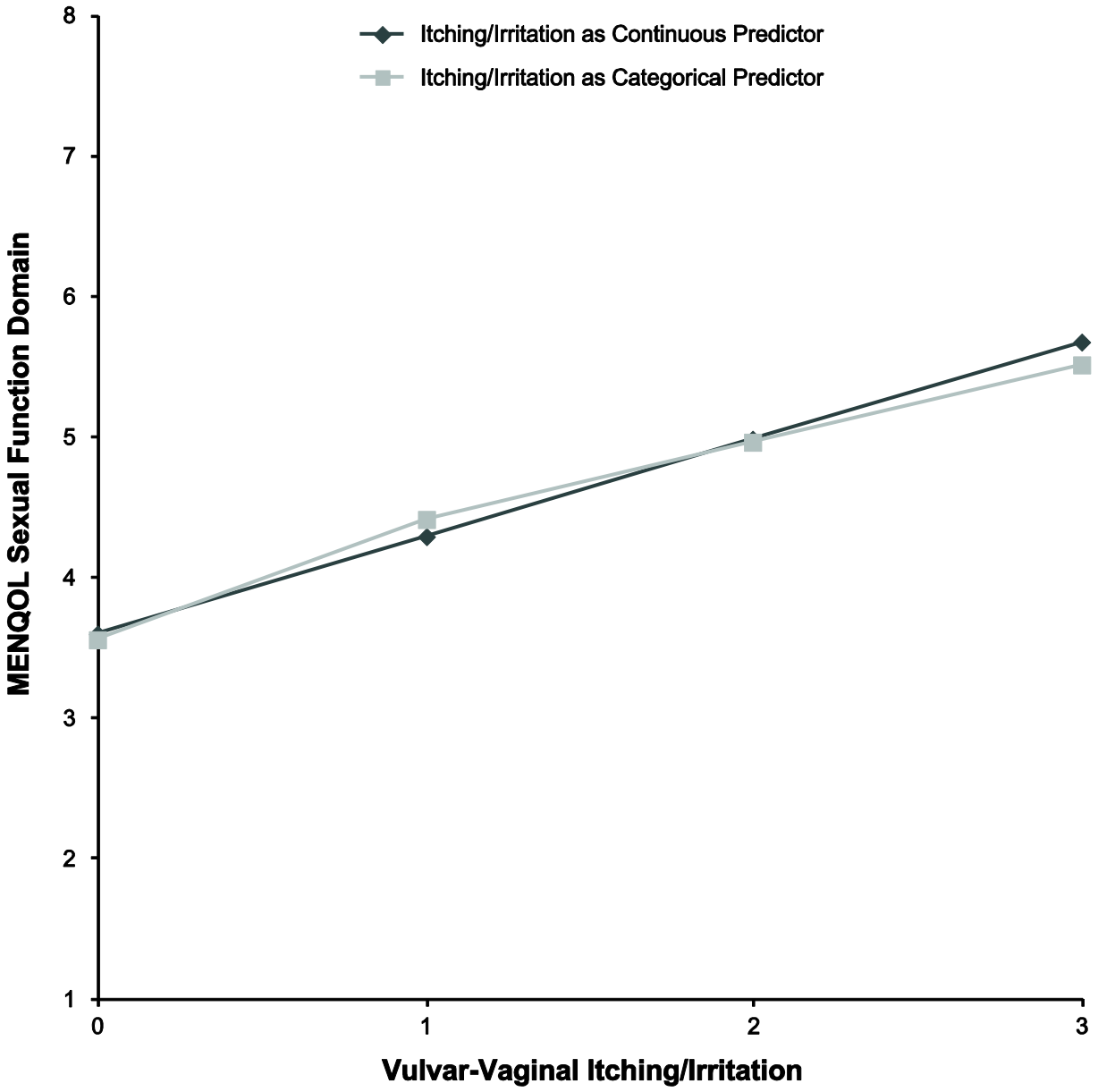
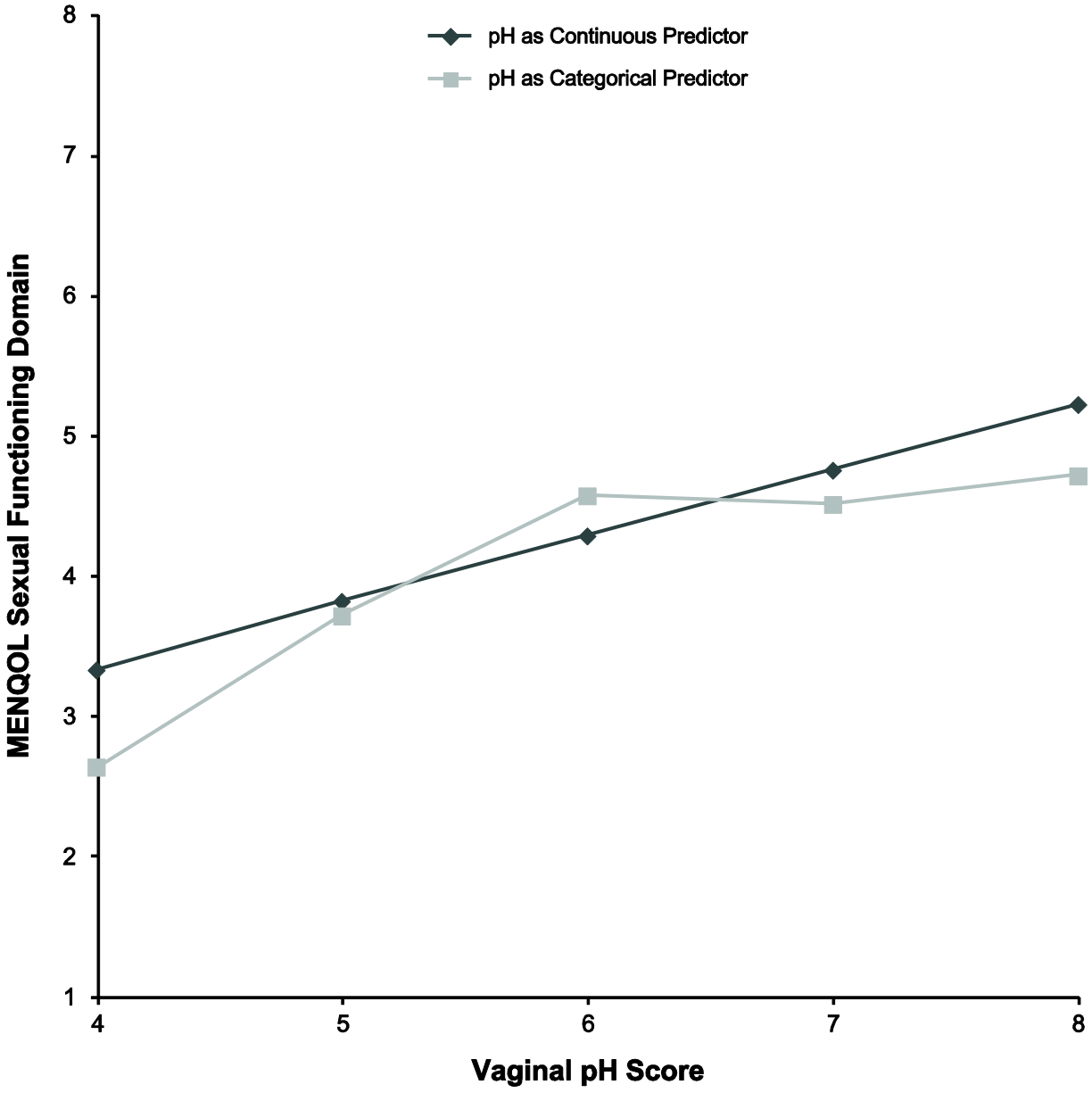
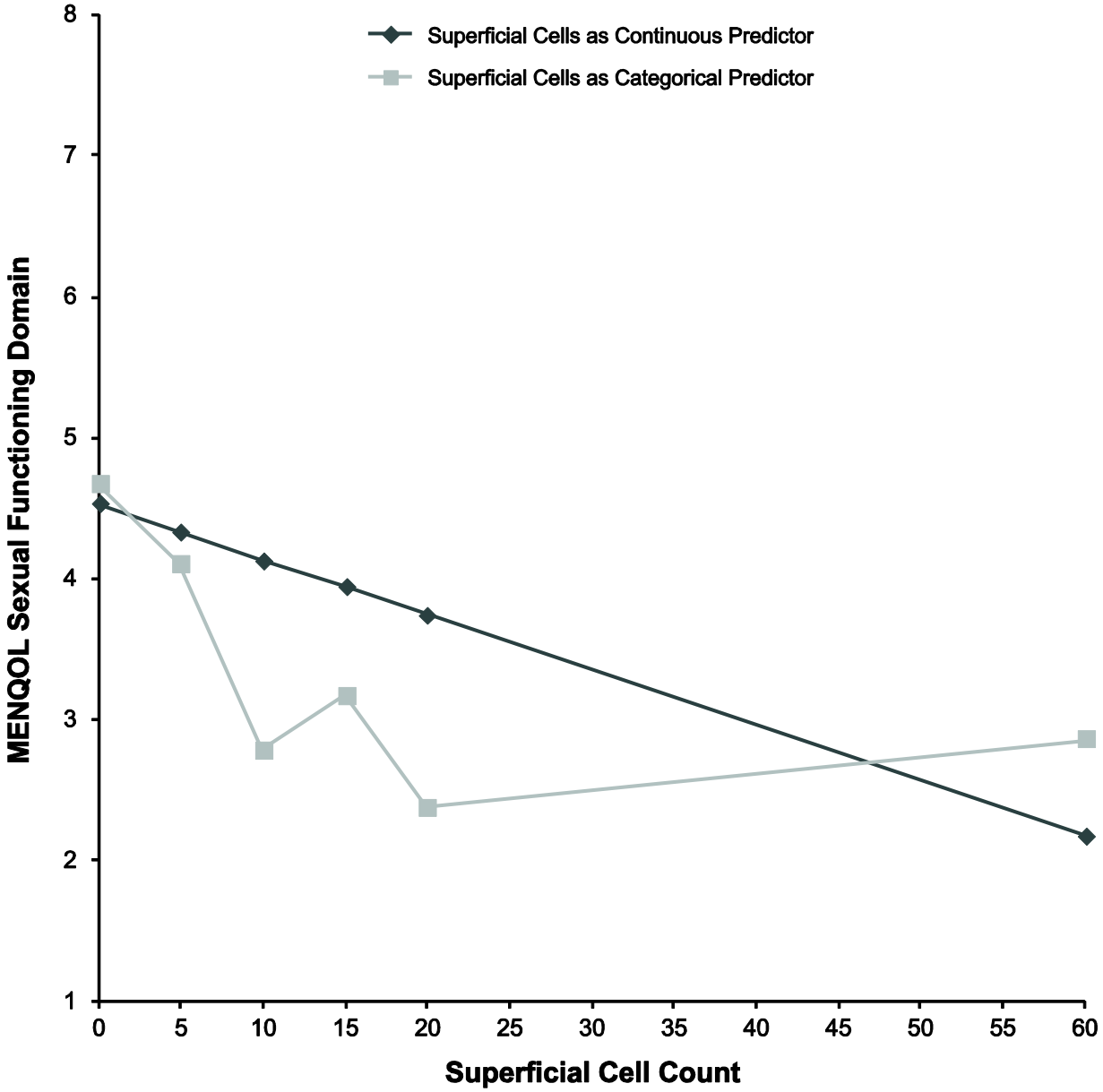


Fig. 1. VVA symptoms as continuous and categorical predictors vs the sexual function domain of the Menopause-specific Quality of Life (MENQOL) questionnaire as an outcome. (A) Pain with intercourse. (B) Vaginal dryness. (C) Vulvar-vaginal itching/irritation.





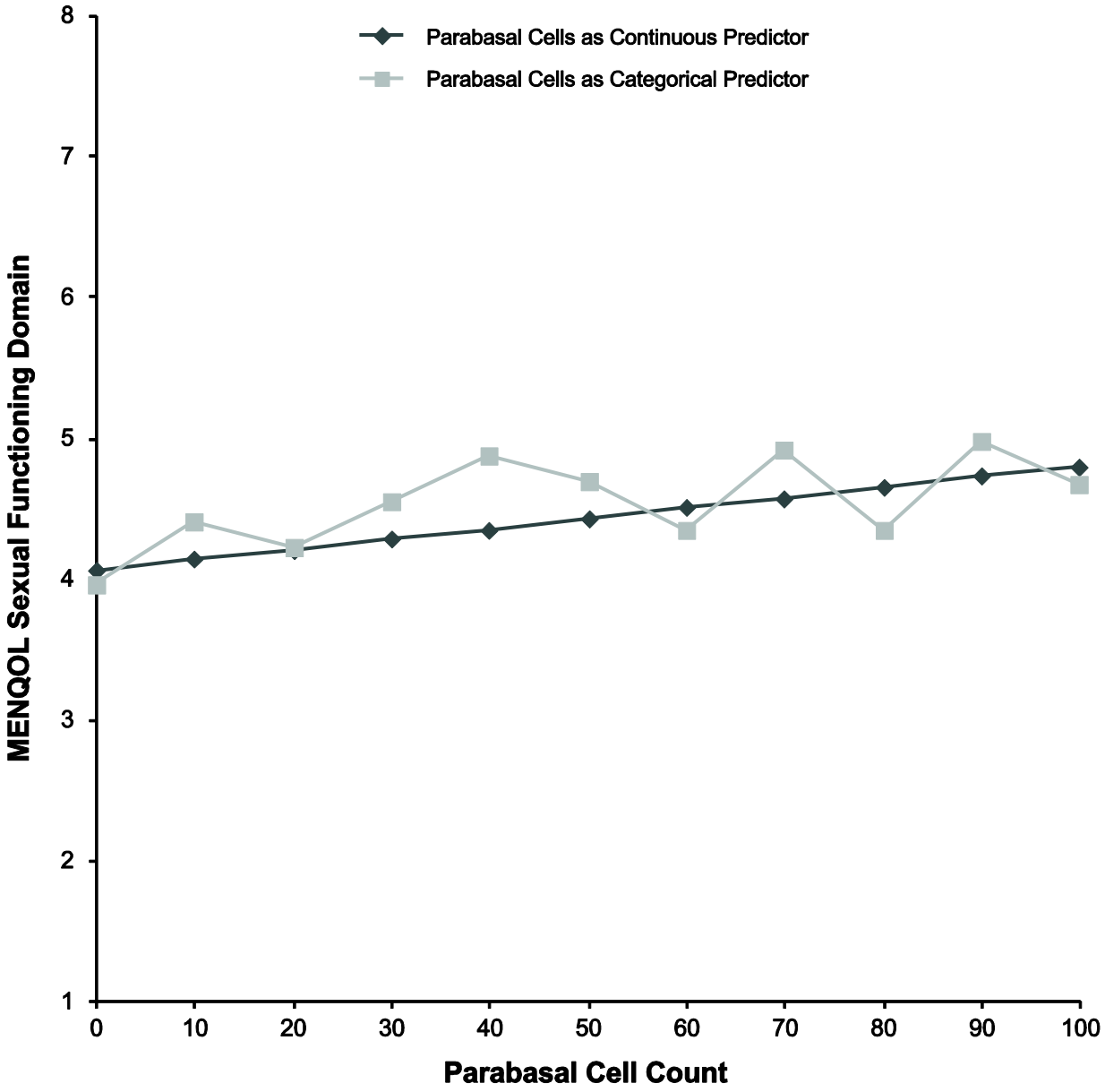


Fig. 2. Clinical parameters as continuous and categorical predictors vs the sexual function domain of the Menopause-Specific Quality of Life (MENQOL) questionnaire as an outcome. (A) Vaginal pH. (B) Superficial cell count.* (C) Parabasal Cell Count.

*Parabasal and superficial cell counts were represented by values of 0 to 100; however, most of the superficial cell counts ranged from 0 to 20. All observations with values >20

were pooled and represented by a value of 60 (the center value between 20 and 100) in the sensitivity analysis.

TABLES

Table 1. Baseline demographics

Characteristic	**Participants (N=652*)**
Age, mean (SD), years	56.3 (4.5)
Race, n (%)	
White	599 (91.9)
Black	23 (3.5)
Asian	10 (1.5)
Other	20 (3.1)
Ethnicity, n (%)	
Hispanic or Latino	37 (5.7)
Non-Hispanic and non-Latino	615 (94.3)
BMI, mean (SD), kg/m^2	25.4 (3.8)
Years since menopause, mean (SD)	7.5 (4.8)

*Subjects who received study medication.

Table 2. Relationships of VVA symptoms and clinical parameters to sexual function domain of the Menopause-Specific Quality of Life (MENQOL) questionnaire.

VVA end points (symptoms and clinical parameters)	Number of Subjects, Number of Observations	Absolute Changes (in Scale-Specific Units)		Standardized Measures of Change	
		Improvement in the VVA end point*	Improvement (95% CI) in sexual functioning MENQOL domain score* that corresponds to a 1-point or 10% change in VVA end point	Change in VVA end point that represents a large effect size of 0.85†	Effect size† of the change in sexual functioning MENQOL domain score that corresponds to a large change (ES=0.85) in VVA end point
Pain with intercourse	611, 1100	1 point reduction	1.20 (1.10–1.29)‡	1 point	0.57 (medium ES)
Dryness	650, 1274	1 point reduction	1.24 (1.14–1.34)‡	0.6 point	0.35 (small to medium ES)
Itching/irritation	650, 1273	1 point reduction	0.69 (0.56–0.82)‡	0.82 point	0.27 (small ES)
Superficial cell count	650, 1255	10% increase	0.39 (0.28–0.50)‡	2.2%	0.04 (trivial ES)
Parabasal cell count	650, 1255	10% decrease	0.07 (0.04–0.11)‡	35.5%	0.13 (small ES)
Vaginal pH	651, 1275	1 point decrease	0.47 (0.32–0.63)‡	0.56 point	0.13 (small ES)

ES, effect size (change/standard deviation); MENQOL, Menopause-specific Quality of Life; VVA, vulvar-vaginal atrophy.

*An improvement in MENQOL sexual function domain is a decrease in score.

†Effect Size (Cohen's *d*) interpretation: "trivial" corresponds to the effect size of about 0.1; "small" corresponds to the effect size of 0.2; "medium" is 0.5; and "large" is 0.8 [13].

‡$p<0.0001$ for association between VVA end point and MENQOL sexual function domain.