Climacteric status is associated with sexual dysfunction at the age of 46: a population-based study

Running title: Climacteric status and sexuality at mid-40s.

Authors: Susanna M. Savukoski, MD[1,2], Pekka A. Pinola, MD[1,2], Paula RO. Pesonen, MSc[3], Katri S. Puukka, PhD[2,4,5], Eila TJ. Suvanto, MD[1,2], and Maarit J. Niinimäki, MD[1,2]

[1]Department of Obstetrics and Gynaecology, PEDEGO Research Unit, Oulu University Hospital and University of Oulu, 90029 OYS, Finland [2]Medical Research Centre Oulu, Oulu University Hospital and University of Oulu, 90014 Oulu, Finland [3]Infrastructure for Population Studies, Faculty of Medicine, University of Oulu, 90014 Oulu, Finland [4]NordLab Oulu, Oulu University Hospital, 90029 Oulu, Finland [5]Department of Clinical Chemistry, University of Oulu, 90014 Oulu, Finland

FUNDING: Northern Finland Birth Cohort 1966 received financial support from University of Oulu Grant no. 24000692, Oulu University Hospital Grant no. 24301140, ERDF European Regional Development Fund Grant no. 539/2010 A31592. Pekka Pinola, Paula Pesonen, Katri Puukka, Eila Suvanto and Maarit Niinimäki received no financial support for the research, authorship, and/or publication of this article. Susanna Savukoski received a research grant from the Finnish Menopause Society, Juho Vainio Foundation, and Finnish Medical Foundation.

CONFLICTS OF INTERESTS: The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

The manuscript or abstract have not been presented/published previously.

Corresponding author: Susanna Savukoski (susanna.savukoski@oulu.fi). Address Kajaanintie 50, 90220 Oulu, Finland.

Reprint request: to Susanna Savukoski (susanna.savukoski@oulu.fi).

Abstract

Objective: Increasing age and menopausal transition increase the risk of sexual dysfunction. Sexual dysfunction is common in women experiencing menopause before the age of 40, while evidence on sexual function in women experiencing menopause in their mid-40s is scarce. We aimed to investigate sexual function in 46-year-old women in relation to their menopausal status.

Methods: This study cross-sectionally evaluated sexual function of women in a prospective population-based Northern Finland Birth Cohort 1966 (NFBC1966). A 46-year follow-up study of NFBC1966 included a broad questionnaire evaluating health, lifestyle, and life situation, as well as menstrual history and sexual function, and blood sampling analysis including follicle stimulating hormone (FSH) and free androgen index (FAI). The participants were divided into two groups by their menopausal status, defined by FSH and menstrual history. We performed logistic regression models in which parameters of sexual function were dependent factors and climacteric status, self-reported health, FAI, relationship status, smoking, and education level were independent variables.

Results: The study population included 2661 women. In regression models, more advanced climacteric status was associated with higher frequency and difficulty level of low sexual desire and vaginal dryness (Odds ratios with 95% confidence intervals 2.80[2.12–3.71], 3.22[2.43–4.27], 3.83[2.82–5.20], 3.75[2.75–5.12], respectively), lower frequency of sexual thoughts (1.34[1.02–1.75]), and higher frequency of problems with intercourse (2.35[1.51–3.66]). Lower FAI and poorer health were associated with impaired sexual function.

Conclusions: The current study suggests that women experiencing menopausal transition in their mid-40s are at risk of impaired sexual function.

Ethical Compliance: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Keywords: female sexual function/ sexual dysfunction / menopausal transition / climacteric phase / early menopause

Introduction

Menopausal transition is associated with impaired sexual function, independently of ageing [1]. Sex steroids -- estrogens and androgens -- play important roles in female sexual function, affecting the structure and function of both the central nervous system and genitals [2]. During menopausal transition, estrogen levels first fluctuate and then decline severely [3], whereas androgen levels in women decrease continuously after the age of 20 [3]. However, many non-hormonal factors, such as psychological, relationship-related, and cultural factors, as well as the overall health of women and their partners, have been reported to affect sexual function in middle-aged women even more than sex hormone levels [1,4]. Evidence suggests that the severity of menopause-related symptoms is inversely related to sexual function [5]. Hormone therapy (HT) may improve sexual function by relieving menopausal symptoms, though it does not appear to improve sexual function in postmenopausal women in general [6].

The median age at menopause is 50 years [7]. Premature ovarian insufficiency (POI), defined as declining ovarian function before the age of 40, has been associated with impaired sexual function in several studies [8–11]. Not only hormonal but also psychosocial issues are important factors that mediate sexual function in women with POI [12]. POI may have adverse psychological causes, as it increases the risk off depressive and anxiety symptoms as well as more negative self-image [13]. POI affects 1.1-3.7% of women, while 7.6-12% of women experience menopause between the ages of 40-44 (early menopause = EM) [7,14]. Evidence on sexual function and wellbeing in women experiencing menopause at an early age but not fulfilling the criteria for POI is scarce.

Smoking is associated with a higher risk of sexual dysfunction in women [15,16]. Lower levels of free androgens have been associated with a higher prevalence of sexual dysfunction in premenopausal women [17] as well as lower libido in both postmenopausal and premenopausal women [18,19]. Some socioeconomic factors, such as lower level of education, have been associated with a higher prevalence of sexual problems, as well as poor health [20]. Sexual function is related to general health [21].

As very few studies have focused on sexual function in women facing menopausal transition in their 40s, this prospective birth-cohort study aimed to investigate the association between menopausal status and sexual function in 46-year-old women. We used a wide range of parameters known to be associated with sexual function in our analyses. The primary aim was to study whether menopausal status is associated with sexual problems such as low sexual desire or vaginal dryness. Second, we aimed to describe which other parameters affected sexual function and the role of menopausal status among them.

Materials and methods

Study population and group division

To create The NFBC1966, all pregnant women living in northern Finland with an estimated date of delivery within 1966 were recruited. Originally, the NFBC1966 contained 12,231 children, and it comprised 96.3% of all births in Northern Finland in 1966. The cohort members have been followed-up with comprehensive follow-up studies since the antenatal period. This study was based on the most recent follow-up study, performed at 46 years of age. In this follow-up study, 10,331 cohort members, of whom 5123 were women, were sent a postal questionnaire. Participants living in Oulu or the capital area were also invited to participate in the clinical examination. [22,23]

The questionnaire evaluated life situation, health, lifestyle habits, and wellbeing. The questions related to this study concerned menstrual history, current use of medications (including contraceptive preparations), marital status, education level, smoking habits, and how the study participants estimated their current general health (very good, good, moderate, poor, and very poor). Concerning sexuality, the participants were asked how frequently they suffered from 1) low sexual desire and 2) vaginal dryness, on a scale of 1-5 (1= not at all, 5= very often) and how distressing they experienced these symptoms on a scale of 1-7 (1=not at all, 7= very

distressing). They were also asked whether they currently had difficulties having sexual intercourse (no/yes/I have no partner), how often they thought about sex (never, once a month, once a week, 2-3 times a week, daily), and how often they had sexual intercourse or masturbation (never, once a month, once a week, 2-3 times a week, daily).

The clinical examination included anthropometric measurements, such as weight and height, by which body mass index (BMI) was calculated. Blood samples was drawn from every participant to determinate several parameters, such as serum follicle stimulating hormone (FSH), testosterone, and sex hormone-binding globuline (SHBG). Serum FSH levels were determined using an immunochemiluminometric method (Advia Centaur XP, Siemens Healthcare Diagnostics, Tarrytown, NY, USA). Serum testosterone was assayed using an Agilent triple quadrupole 6410 LC/MS equipment (Agilent Technologies, Wilmington, DE, USA) and SHBG using a chemiluminometric immunoassay (Immulite 2000, Siemens Healthcare, Llanberis, UK). Therefore, SHBG values from age 31 were transformed to be comparable with the SHBG values analyzed at age 46 using a formula: 0,7615 x old method 31yr SHBG + 0,7088, and the results are reported according to this method. Free androgen index (FAI) was calculated using the formula: (testosterone/SHBG) *100 [24].

Female participants of the 46-year follow-up study were divided into two groups based on their menstrual history and FSH levels: climacteric and preclimacteric women (Figure 1). The group "climacteric women" included women who were, according to Straw +10 criteria for reproductive stages[25], in their late perimenopause or postmenopause, and the criteria were 1) FSH value > 25 IU/L and 2) amenorrhea ≥ 60 days before the study visit. The group "preclimacteric women" included premenopausal women and women in their early perimenopause, and the criteria were 1) FSH value ≤ 25 IU/L and having their last menstrual period < 60 days before the clinical examination. The women using systemic estrogen-containing hormone therapy (HT) were identified by the national medicine reimbursement register (if they had purchased HT during the one year prior to the 46-years study) and classified as "climacteric". The group division of women who were hysterectomized or who had progestin-only treatment (peroral, intrauterine device, or subdermal implant) was classified according to their FSH level, regardless of their menstrual history. Women who used combined estrogen-progestin hormonal contraceptive preparations (pills, rings, or patches) or tamoxifen were excluded from the study, as were women with missing or conflicting data.

Statistical methods

In comparing the background characteristics between the study groups, continuous variables with normal distribution were analyzed with an independent samples *t*-test and variables with skewed distribution were analyzed using the Mann-Whitney *U* test. Categorical background variables were compared using the Pearson's χ^2 test. Unadjusted and adjusted binary logistic regression models were used to investigate the association between climacteric status and sexuality-related variables. In the adjusted models, sexuality-related variables were dependent variables; climacteric status and other potential confounders—current smoking (yes/no), FAI, level of education (basic, secondary, tertiary), relationship status (living with a partner or not), and self-experienced general health (very good–good/moderate–very poor)—were independent variables. Confounders were chosen based on the findings of previous studies[15–21]. In subanalyses that included only climacteric women, we performed binary logistic regression models in which the use of HT, trouble with hot flashes, current smoking, FAI, level of education, relationship status, and general health were independent variables. A linear regression test was used to test multicollinearity, interpreting a variance inflation factor (VIF) >2.5 as multicollinearity between the variables. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 26 (IBM Corp. Armonk, NY, USA). Fig. 1 was drawn using Microsoft PowerPoint software, version 2204 (Microsoft Corporation, Redmond, Washington, USA) and Fig. 2 with GraphPad Prism version 8.0.1.244 (GraphPad Software, San Diego, California, USA).

Results

The study groups included 359 climacteric and 2302 preclimacteric women (flow chart of the study population is shown in Fig.1). The background characteristics of this study population are shown in Table 1. Climacteric women were more likely to be current smokers, slightly less educated, and experienced more severe hot flashes. Body mass index, self-reported general health, alcohol intake, FAI levels and marital status did not differ between groups.

The distribution of answers to the questions concerning sexual function (sexual desire and vaginal dryness) is presented in Table 2. Compared to preclimacteric women, climacteric women suffered more often from a low desire for sex as well as vaginal dryness and also reported having more trouble with these issues. They also thought less frequently about sex. Twenty-one (5.8%) climacteric and 130 (5.6%) preclimacteric women reported that they did not have a partner. Of the women who had a partner, climacteric women more often had problems with intercourse than did the preclimacteric women.

In binary logistic regression models, adjusted for confounding variables, being climacteric vs. preclimacteric was associated with all the investigated sexuality-related variables except frequency of intercourse/masturbation: higher frequency and more trouble from low desire for sex and vaginal dryness (odds ratios (ORs) with 95% confidence intervals (CIs): 2.80 [2.12–3.71], 3.22 [2.43–4.27], 3.83 [2.83–5.20] and 3.75 [2.75–5.12], respectively), thinking about sex less often (OR 1.34, 95% CI 1.02–1.75), and having more frequent problems with sexual intercourse (OR 2.35, 95% CI 1.51–3.66). Weaker self–reported health (moderate—very poor compared to good—very good) was associated with all the investigated variables: higher frequency and more trouble from low desire for sex and vaginal dryness (ORs with 95% CIs: 1.97 (1.55–2.51), 1.96 (1.52–2.51), 1,83 (1.38–2.43) and 2.07 (1.56–2.75), respectively), thinking about sex less often (OR 1.44, 95% CI (1.18–1.77) , having more problems with sexual intercourse (OR 2.52, 95% CI 1.71–3.70), and having sexual intercourse/masturbating less often (OR 1.44, 95% CI 1.18–1.74). In the models, lower FAI was associated with higher frequency of low sexual desire (OR 1.18, 95% CI 1.03–1.32) and vaginal dryness (OR 1.56, 95% CI 1.05–2.32), thinking about sex less often (OR 1.22, 95% CI 1.10–1.35), more often having problems with sexual intercourse (OR 1.39, 95% CI 1.11–1.72), and having sexual intercourse/masturbating less often (OR 1.12, 95% CI 1.03–1.23). Living with a partner was associated with higher frequency and more trouble with low desire for sex and vaginal dryness (ORs with 95% CIs 1.93 [1.40–2.67], 2.44 [1.71–3.50], 1.72 [1.18–2.52] and 2.41 [1.58–3.70], respectively), having more frequent problems with sexual intercourse (OR 2.52 (1.71–3.70), but having sexual intercourse/masturbating more often (OR 2.02, 95% CI 1.64–2.48). The results of the binary logistic regression models are shown in Fig. 2 and Table 3.
In the subanalyses, we investigated whether HT use and severity of hot flashes were associated with sexuality-related variables in climacteric women. In these analyses, having purchased HT during the last year was associated with higher frequency of vaginal dryness (OR 2.50, 95% CI 1.22–5.13) and having more trouble with low desire for sex (2.05, 95% CI 1.03–4.08). Having more severe hot flashes was associated with higher frequency of low desire for sex (OR 6.62, 95% CI 3.78–11.60) and vaginal dryness (OR 8.17, 95% CI 4.38–15.20), as well as experiencing more difficulty as a result of low desire for sex (OR 8.06 95% CI 4.54–14.31) and vaginal dryness (OR 9.59, 95% CI 5.03–18.25).

In the regression models, all VIF-values were < 2.5; hence, multicollinearity between the independent variables was not found.

Discussion

A more advanced climacteric status was associated with impaired sexual function at 46 years of age in the current study. In the logistic regression models, being climacteric was independently associated with a higher risk of impairment in all sexuality-related variables except the frequency of sexual intercourse/masturbation. Additionally, lower FAI, living with a partner, and weaker self-reported health were associated with impaired sexual function. In the subanalysis of climacteric women only, more disturbing hot flashes and having purchased HT during the last year were associated with impaired sexual function.

Sexual function and satisfaction in postmenopausal women play an important role in their general wellbeing. A study by Buczak-Stec et al. suggested that sexual satisfaction was positively associated with life satisfaction in adults over 40 [26]. In addition, Woloski-Wruble et al. reported that in postmenopausal women, sexual activity was positively correlated with sexual satisfaction and sexual satisfaction with life satisfaction [27]. Early age at menopause is a risk factor for sexual dysfunction through hormonal and psychological pathways, and it also exposes women to an increased risk of both physical and mental morbidities, which may also impair sexual function. [12,28] Women with POI have been described to have impaired sexual function in their 40s, compared to premenopausal women at the same age [11], and even compared to peri- and postmenopausal women aged 45-65 [8]. To the best of our knowledge, only a few studies have evaluated the effect of early menopause on sexual function.

In addition to more advanced menopausal status, weaker self-reported general health was associated with impaired sexual function in this study. Many physical and mental diseases as well as medications may affect sexual function [29]. As both the symptoms of the disease and the medications may increase the risk of impaired sexual function, we suggest that a participant's own experience of her general health is a representative marker of wellbeing. Living with a partner was negatively associated with several domains of sexual function, which we believe reflects the fact that having a relationship may make sexuality-related problems more prominent. Higher FAI levels were associated with better sexual function. Previous studies have consistently shown that FAI is inversely associated with sexual dysfunction in both premenopausal and postmenopausal women [17–19].

Of all the investigated sexuality-related variables, climacteric women had the highest odds ratio for having more frequent and distressing vaginal dryness. In a study by Cagnacci et al., vaginal dryness was independently correlated with several other domains of sexual function: desire, arousal, lubrication, orgasm, satisfaction, and dyspareunia [30]. Vaginal dryness is a common symptom that becomes more prevalent with advancing menopausal stage. A longitudinal Australian study of women aged 45-55 years, followed for seven years, reported that the prevalence of vaginal dryness was 4% in early perimenopause, 25% one year after last menstrual period, and 47% three years after last menstrual period [31]. A study of postmenopausal women by Kingsberg et al. reported that enjoyment of sex was negatively affected by vulvovaginal atrophy in 59% of the participants [32]. Local estrogen and estrogen-androgen therapies are very effective in improving sexual function in postmenopausal women suffering from urogenital atrophy [33]; non-hormonal local preparations such as lubricant and moisturizers also significantly relieve the symptoms of vulvovaginal atrophy [34]. Lack of knowledge of the treatment options and unwillingness to broach the topic of vaginal complaints with health care professionals, may prevent many women from receiving optimal treatment for vaginal dryness [32].

It has been reported that sexual dysfunction is very frequent in women attending menopause clinics; however, only a small proportion of women visiting gynecologists report sexual complaints spontaneously. [35]. Hence, it is important that clinicians ask about patients' sexual concerns. As in our analysis, living with a partner was associated with impaired sexual function; therefore, therapeutic methods for couples might be helpful for women concerned about their partnered sex life.

In the subanalysis of our study on climacteric women only, having more disturbing hot flashes and having purchased HT during the past year were associated with impaired sexual function. HT is effective in treating hot flashes [36], and it seems to have a small-to-moderate benefit in sexual function for women who have menopausal symptoms and/or are in early postmenopause, but not in unselected postmenopausal women [6]. Moreover, evidence suggests that transdermal HT may improve sexual function while oral HT seems to have no effect [37]. As the number of HT users in our study population was small and the details of the use (dose, duration of use, administration route, continuity, effectiveness on the menopausal symptoms) variable, further conclusions cannot be drawn. It is likely that women who purchase HT have been suffering from more prominent menopausal symptoms.

Our study has several strengths. This was a population-based birth cohort study that comprehensively evaluated lifestyle and health issues. The participants were not recruited from menopausal clinics; thus the findings reflect the situation in the general population. There is also evidence that several domains of sexual function in middle-aged women are affected by age [30,38] and ethnicity [39]. The women in this study population were born within approximately one year. The ethnicity of the women was highly homogenous. The questions evaluating sexual function were easy to understand and answer. We evaluated not only the frequency of vaginal dryness and low sexual desire, but also how disturbing the women found these symptoms, as we found this to be an important point of view in screening and treating sexual dysfunction. As the NFBC1966 data collection has been comprehensive, including linking to nationwide register data, versatile essential covariates were included into the regression models.

The weaknesses of this study include its cross-sectionality, as with many other studies evaluating sexual wellbeing. This study did not include validated questionnaires for measuring sexual function. Additionally, data on the duration of sexual dysfunction were not available. Sexual function is affected by several physical, mental, social, and environmental factors; hence it may vary significantly during even a short period of time. Furthermore, the participants' gender identity and sexual orientation were not evaluated in this study. Owing to the homogenous ethnicity and cultural background of the study subjects, it is unclear whether the study findings can be applied to other populations. Despite some drawbacks, we were able to comprehensively investigate sexual function in relation to menopausal status in middle-aged women who were several years younger than the average age at menopause.

Conclusion

In conclusion, the risk of impaired sexual function was increased in women who were in late perimenopause or postmenopause at the age of 46, compared to premenopausal women at the same age. In addition, this study showed that self-experienced health was strongly associated with sexual function. In health care, women facing menopausal transition at an early age should be asked about their sexuality-related concerns and counselled about possible solutions for improving their sex life. Health care professionals can help improve the sexual function of these women by opening the conversation about sexuality-related issues and offering adequate information about the multifactorial background and possible treatments of sexual dysfunction around menopause.

Acknowledgements

This work was supported by the Northern Ostrobothnia Hospital District, Oulu University Hospital, the University of Oulu, the Finnish Menopause Society, Juho Vainio Foundation, and the Finnish Medical Foundation. We thank all cohort members and researchers who participated in the 46-year study. We also wish to acknowledge the work of the NFBC project center.

References

1. Scavello I, Maseroli E, Di Stasi V, Vignozzi L. Sexual Health in Menopause. *Medicina (Kaunas)*2019;55(9):559. doi:10.3390/medicina55090559

2. Goldstein I, Traish A, Kim N, Munarriz R. The role of sex steroid hormones in female sexual function and dysfunction. *Clin Obstet Gynecol* 2004;47(2):471-484. doi:10.1097/00003081-200406000-00022

3. Burger HG, Hale GE, Robertson DM, Dennerstein L. A review of hormonal changes during the menopausal transition: focus on findings from the Melbourne Women's Midlife Health Project. *Hum Reprod Update* 2007;13(6):559-565. doi:10.1093/humupd/dmm020

4. Avis NE, Zhao X, Johannes CB, Ory M, Brockwell S, Greendale GA. Correlates of sexual function among multi-ethnic middle-aged women: results from the Study of Women's Health Across the Nation (SWAN). *Menopause* 2018;25(11):1244-1255. doi:10.1097/GME.0000000000001226

5. Nazarpour S, Simbar M, Tehrani FR, Majd HA. The relationship between menopausal symptoms and sexual function. *Women Health* 2018;58(10):1112-1123. doi:10.1080/03630242.2017.1414100

6. Nastri CO, Lara LA, Ferriani RA, Rosa-E-Silva ACJS, Figueiredo JBP, Martins WP. Hormone therapy for sexual function in perimenopausal and postmenopausal women. *Cochrane Database Syst Rev* 2013;(6):CD009672. doi:10.1002/14651858.CD009672.pub2

7. Mishra GD, Pandeya N, Dobson AJ, et al. Early menarche, nulliparity and the risk for premature and early natural menopause. *Hum Reprod* 2017;32(3):679-686. doi:10.1093/humrep/dew350

8. Mann E, Singer D, Pitkin J, Panay N, Hunter MS. Psychosocial adjustment in women with premature menopause: A cross-sectional survey. *Climacteric* 2012;15(5):481-489. doi:10.3109/13697137.2011.647841

9. Kalantaridou SN, Vanderhoof VH, Calis KA, Corrigan EC, Troendle JF, Nelson LM. Sexual function in young women with spontaneous 46,XX primary ovarian insufficiency. *Fertil Steril* 2008;90(5):1805-1811. doi:10.1016/j.fertnstert.2007.08.040

10. Van Der Stege JG, Groen H, Van Zadelhoff SJN, et al. Decreased androgen concentrations and diminished general and sexual well-being in women with premature ovarian failure. *Menopause* 2008;15(1):23-31. doi:10.1097/gme.0b013e3180f6108c

11. de Almeida DMB, Benetti-Pinto CL, Makuch MY. Sexual function of women with premature ovarian failure. *Menopause* 2011;18(3):262-266. doi:10.1097/gme.0b013e3181f4318d

12. Nappi RE, Cucinella L, Martini E, et al. Sexuality in premature ovarian insufficiency. *Climacteric* 2019;22(3):289-295. doi:10.1080/13697137.2019.1575356

13. Deeks AA, Gibson-Helm M, Teede H, Vincent A. Premature menopause: A comprehensive understanding of psychosocial aspects. *Climacteric* 2011;14(5):565-572. doi:10.3109/13697137.2011.566390

14. Golezar S, Ramezani Tehrani F, Khazaei S, Ebadi A, Keshavarz Z. The global prevalence of primary ovarian insufficiency and early menopause: a meta-analysis. *Climacteric* 2019;22(4):403-411. doi:10.1080/13697137.2019.1574738

15. Choi J, Shin DW, Lee S, et al. Dose-response relationship between cigarette smoking and female sexual dysfunction. *Obstet Gynecol Sci* 2015;58(4):302-308. doi:10.5468/ogs.2015.58.4.302

16. Ju R, Ruan X, Xu X, et al. Importance of active and passive smoking as one of the risk factors for female sexual dysfunction in Chinese women. *Gynecol Endocrinol* 2021;37(6):541-545. doi:10.1080/09513590.2021.1913115

17. Vale FBC, Coimbra BB, Lopes GP, Geber S. Sexual dysfunction in premenopausal women could be related to hormonal profile. *Gynecol Endocrinol* 2017;33(2):145-147. doi:10.1080/09513590.2016.1226793

18. Turna B, Apaydin E, Semerci B, Altay B, Cikili N, Nazli O. Women with low libido: correlation of decreased androgen levels with female sexual function index. *Int J Impot Res* 2005;17(2):148-153. doi:10.1038/sj.ijir.3901294

19. Wåhlin-Jacobsen S, Kristensen E, Pedersen AT, et al. Androgens and Psychosocial Factors Related to Sexual Dysfunctions in Premenopausal Women(∗): (∗)2016 ISSM Female Sexual Dysfunction Prize.

J Sex Med 2017;14(3):366-379. doi:10.1016/j.jsxm.2016.12.237

20. Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. *JAMA* 1999;281(6):537-544. doi:10.1001/jama.281.6.537

21. Lewis RW, Fugl-Meyer KS, Bosch R, et al. Epidemiology/risk factors of sexual dysfunction. *J Sex Med* 2004;1(1):35-39. doi:10.1111/j.1743-6109.2004.10106.x

22. University of Oulu: Northern Finland Birth Cohort 1966. University of Oulu. https://www.oulu.fi/nfbc/node/44315.

23. Nordström T, Miettunen J, Auvinen J, et al. Cohort Profile: 46 years of follow-up of the Northern Finland Birth Cohort 1966 (NFBC1966). *Int J Epidemiol* 2022;50(6):1786-1787j. doi:10.1093/ije/dyab109

24. Bui HN, Sluss PM, Hayes FJ, et al. Testosterone, free testosterone, and free androgen index in women: Reference intervals, biological variation, and diagnostic value in polycystic ovary syndrome. *Clin Chim Acta* 2015;450:227-232. doi:10.1016/j.cca.2015.08.019

25. Harlow SD, Gass M, Hall JE, et al. Executive summary of the stages of reproductive aging workshop + 10: Addressing the unfinished agenda of staging reproductive aging. *J Clin Endocrinol Metab* 2012;97(4):1159-1168. doi:10.1210/jc.2011-3362

26. Buczak-Stec E, König HH, Hajek A. The link between sexual satisfaction and subjective well-being: a longitudinal perspective based on the German Ageing Survey. *Qual Life Res* 2019;28(11):3025-3035. doi:10.1007/s11136-019-02235-4

27. Woloski-Wruble AC, Oliel Y, Leefsma M, Hochner-Celnikier D. Sexual activities, sexual and life satisfaction, and successful aging in women. *J Sex Med* 2010;7(7):2401-2410. doi:10.1111/j.1743-6109.2010.01747.x

28. Faubion SS, Kuhle CL, Shuster LT, Rocca WA. Long-term health consequences of premature or early menopause and considerations for management. *Climacteric* 2015;18(4):483–491. doi:10.3109/13697137.2015.1020484

29. McCabe MP, Sharlip ID, Lewis R, et al. Risk Factors for Sexual Dysfunction Among Women and Men: A Consensus Statement From the Fourth International Consultation on Sexual Medicine 2015. *J Sex Med* 2016;13(2):153-167. doi:10.1016/j.jsxm.2015.12.015

30. Cagnacci A, Venier M, Xholli A, Paglietti C, Caruso S. Female sexuality and vaginal health across the menopausal age. *Menopause* 2020;27(1):14-19. doi:10.1097/GME.0000000000001427

31. Dennerstein L, Dudley EC, Hopper JL, Guthrie JR, Burger HG. A prospective population-based study of menopausal symptoms. *Obstet Gynecol* 2000;96(3):351-358. doi:10.1097/00006250-200009000-00007

32. 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(7):1790-1799. doi:10.1111/jsm.12190

33. 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(3):1284-1290. doi:10.1111/j.1743-6109.2009.01667.x

34. Potter N, Panay N. Vaginal lubricants and moisturizers: a review into use, efficacy, and safety. *Climacteric* 2021;24(1):19-24. doi:10.1080/13697137.2020.1820478

35. Cuerva MJ, Gonzalez D, Canals M, et al. The sexual health approach in postmenopause: The five-minutes study. *Maturitas* 2018;108:31-36. doi:10.1016/j.maturitas.2017.11.009

36. Kaunitz AM, Manson JE. Management of Menopausal Symptoms. *Obstet Gynecol* 2015;126(4):859-

876. doi:10.1097/AOG.0000000000001058

37. Taylor HS, Tal A, Pal L, et al. Effects of oral vs transdermal estrogen therapy on sexual function in early postmenopause: Ancillary study of the Kronos Early Estrogen Prevention Study (KEEPS). *JAMA Intern Med* 2017;177(10):1471-1479. doi:10.1001/jamainternmed.2017.3877

38. Chedraui P, Perez-Lopez FR, San Miguel G, Avila C. Assessment of sexuality among middle-aged women using the Female Sexual Function Index. *Climacteric* 2009;12(3):213-221. doi:10.1080/13697130802607727

39. Huang AJ, Subak LL, Thom DH, et al. Sexual function and aging in racially and ethnically diverse women. *J Am Geriatr Soc* 2009;57(8):1362-1368. doi:10.1111/j.1532-5415.2009.02353.x

Figure and Table legends

FIG 1: Flow chart of the study population.

The study participants were members of the prospective Northern Finland Birth Cohort 1966 (NFBC1966), who participated in a 46-year follow-up study of NFBC1966. FSH, follicle stimulating hormone; HT, systemic hormone therapy with estrogen; CHC, combined hormonal contraception. *The women receiving progestin-only treatment or who were hysterectomized were classified according to their FSH levels.

TABLE 1. Background characteristics of the study participants.

The study participants were women of the Northern Finland Birth Cohort 1966, who attended a 46-year follow-up study of the cohort and were divided into two groups according to their climacteric status at the age of 46 years. Distributions of categorical variables were compared using Pearson's χ^2 test. Continuous variables were compared using independent samples *t*-test[(a)] or Mann-Whitney *U* test[(b)]. BMI, body mass index; SD, standard deviation; IQR, interquartile range; FAI, free androgen index.

TABLE 2. Climacteric status at the age of 46 and variables evaluating sexual desire and vaginal dryness.

The study participants were women of the Northern Finland Birth Cohort 1966, who attended a 46-year follow-up study of the cohor and were divided into two groups according to their climacteric status at the age of 46 years. The analyses were performed with Pearson's χ^2 test. [a] The women who reported not having a partner were excluded from the analysis.

FIG 2. Forest plot of climacteric status and sexual dysfunction at the age of 46.

The forest plot presents the results (odds ratios with 95% confidence intervals) from binary logistic regression models, in which climacteric status, self-reported health, free androgen index (FAI), smoking, living with a partner or not, and level of education were independent variables. Level of education was not associated with any of the variables and is not shown in the figure.

Table 3. Climacteric status and sexual dysfunction at the age of 46, the unadjusted and adjusted results (the odds ratios with 95% confidence intervals) from binary logistic regression models.

The study participants were women of the Northern Finland Birth Cohort 1966, who attended a 46-year follow-up study of the cohort and were divided into two groups according to their climacteric status at the age of 46 years. The table shows the odds rations with 95% confidence intervals from unadjusted ([a]) and adjusted ([b]) binary logistic regression models. The independent variables in the adjusted models were climacteric status, self-reported health, free androgen index (FAI), smoking, living with a partner or not, and level of education were independent variables. Level of education was not associated with any of the variables and is not shown in the table. [c] Scale 1 (not at all) to 7 (very much); [d]continuous variable; FAI, free androgen index.

Table 1

Variable	Climacteric (n=359)	Preclimacteric (n=2302)	*P*-value
BMI (mean, SD)[a]	26.3 (5.2)	26.6 (5.3)	0.408
Level of education (n,%)			0.040
Basic	26 (7.3)	112 (5.0)	
Secondary	236 (66.7)	1424 (63.7)	
Tertiary	92 (26.0)	701 (31.3)	
Smoking (n,%)			0.003
No	266 (76.9)	1849 (83.3)	
Yes	80 (23.1)	370 (16.7)	
Self-reported general health (n,%)			0.230
Good–very good	232 (66.3)	1539 (69.5)	
Moderate–poor	118 (33.7)	676 (30.5)	
Disturbance from hot flashes (Scale 1 (not at all)-7 (very much) (n, %)			<0.001
1–2	227 (64.5)	1973 (89.1)	
3–7	125 (35.5)	241 (10.9)	
Alcohol intake (grams/day) (median, IQR)[b]	3.0 (7.1)	2.9 (7.2)	0.506
FAI (median, IQR)[b]	1.5 (1.2)	1.6 (1.1)	0.313
Marital status (n, %)			0.734
Married/domestic partnership	284 (80.2)	1742 (78.0)	
Unmarried	34 (9.6)	219 (9.8)	
Divorced	34 (9.6)	259 (11.6)	
Widow	2 (0.6)	12 (0.5)	

Table 2

Variables of sexual desire and vaginal dryness	Climacteric (n=359) n(%)	Preclimacteric (n=2302) n(%)	*P*-value
How often do you suffer from low desire for sex?			<0.001
Not at all or rarely	245 (70.2)	1958 (87.9)	
Sometimes, quite often, or very often	104 (29.8)	270 (12.1)	
How often do you suffer from vaginal dryness?			<0.001
Not at all or rarely	261 (74.8)	2054 (92.1)	
Sometimes, quite often, or very often	88 (25.2)	175 (7.9)	
How much difficulty do you experience as a result of a low desire for sex? (Scale 1 (not at all)–7 (very much)			<0.001
1–2	242 (69.3)	1960 (88.8)	
3–7	107 (30.7)	248 (11.2)	
How much difficulty do you experience as a result of vaginal dryness? (Scale 1 (not at all)–7 (very much)			<0.001
1–2	262 (75.3)	2041 (92.3)	
3–7	86 (24.7)	171 (7.7)	
How often do you think about sex?			0.019
Once a month or less	96 (27.6)	482 (21.9)	
At least once a week	252 (72.4)	1719 (78.1)	
How often do you have sexual intercourse/masturbate			0.806
Often than once a month or less	99 (28.9)	618 (28.2)	
At least once a week	244 (71.1)	1572 (71.8)	
Do you have problems with sexual intercourse at the moment?[a]			<0.001
No	292 (90.4)	1936 (95.6)	
Yes	31 (9.6)	89 (4.4)	

Table 3

	Being climacteric[a] OR (95% CI)	Being climacteric[b] OR (95% CI)	FAI[b,d] OR (95% CI)	Being a smoker[b] OR (95% CI)	Living with partner[b] OR (95% CI)	Weaker general health (moderate–very week compared to good–very good)[b] OR (95% CI)
Higher frequency of low sexual desire (sometimes, quite often or very often compared to not at all to rarely)	3.08 (2.37–4.00)	2.80 (2.12–3.71	0.85 (0.76–0.97)	1.08 (0.79–1.46)	1.93 (1.40–2.67)	1.97 (1.55–2.51)
Higher frequency of vaginal dryness (sometimes, quite often or very often compared to not at all to rarely)	3.96 (2.97–5.27)	3.83 (2.82–5.20)	0.83 (0.71–0.96)	0.64 (0.43–0.95)	1.72 (1.18–2.52)	1.83 (1.38–2.43)
Experiencing more difficulty as a result of low sexual desire in scale 1 to 7[c] (3–7 compared to 1–2)	3.49 (2.69–4.55)	3.22 (2.43–4.27)	0.89 (0.79–1.01)	1.12 (0.82–1.53)	2.44 (1.71–3.50)	1.96 (1.52–2.51)
Experiencing more difficulty as a result of vaginal dryness in scale 1 to 7[c] (3–7 compared to 1–2)	3.92 (2.93–5.23)	3.75 (2.75–5.12)	0.88 (0.76–1.02)	0,68 (0.46–1.01)	2,41 (1.58–3.70)	2.07 (1.56–2.75)
Thinking about sex less often (not more than once a month compared to at least once a week)	1.36 (1.05–1.76)	1.34 (1.02–1.75)	0.82(0.74–0.91)	1.08 (0.84–1.39)	0.81 (0.65–1.02)	1.44 (1.18–1.77)
Having intercourse/masturbating less frequently (not more than once a month compared to at least once a week)	1.03 (0.80–1.33)	1.08 (0.83–1.41)	0.89 (0.81–0.98)	1,09 (0.86–1.38)	0.50 (0.40–0.61)	1.44 (1.18–1.74)
Having problems with sexual intercourse (yes compared to no) excluding women having no partner	2.31 (1.51–3.54)	2.35 (1.51–3.66)	0.72 (0.58–0.90)	1.29 (0.81–2.08)	2,05 (1.05–4.00)	2.52 (1.71–3.70)

Figure 1

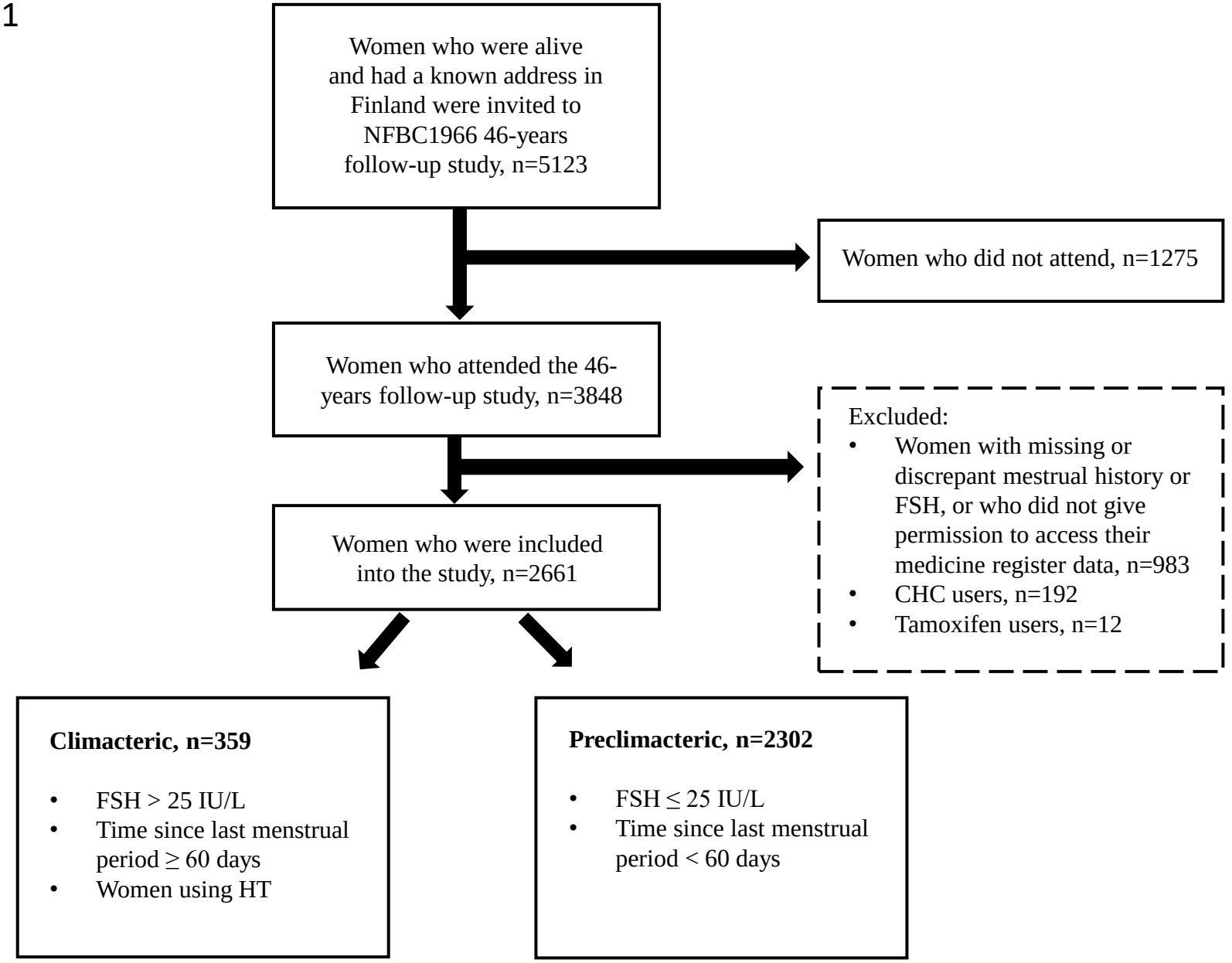
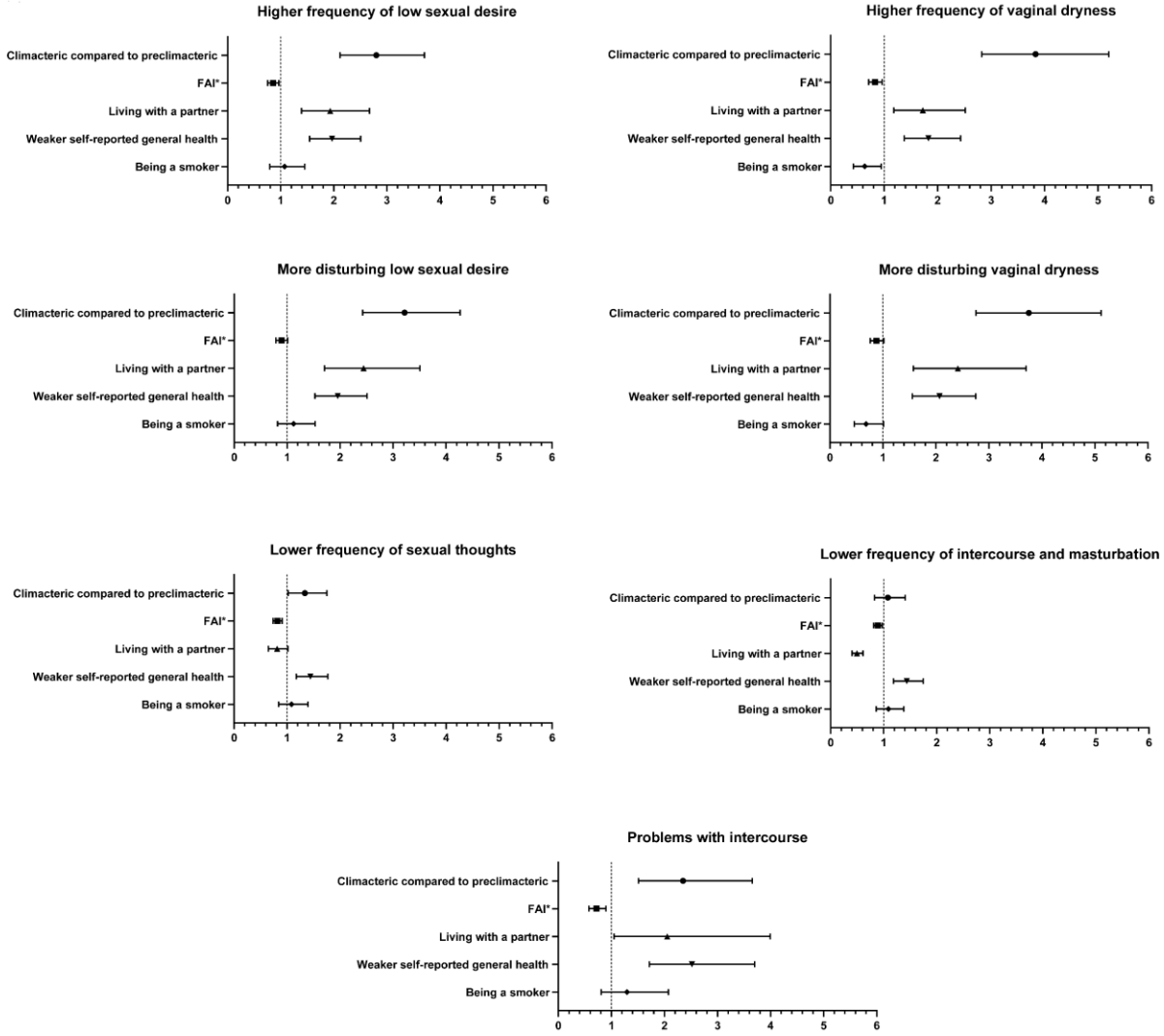

Women who were alive and had a known address in Finland were invited to NFBC1966 46-years follow-up study, n=5123
Women who did not attend, n=1275
Women who attended the 46-years follow-up study, n=3848
Excluded:
• Women with missing or discrepant mestrual history or FSH, or who did not give permission to access their medicine register data, n=983
• CHC users, n=192
• Tamoxifen users, n=12
Women who were included into the study, n=2661
Climacteric, n=359
• FSH > 25 IU/L
• Time since last menstrual period ≥ 60 days
• Women using HT
Preclimacteric, n=2302
• FSH ≤ 25 IU/L
• Time since last menstrual period < 60 days

Figure 2


Higher frequency of low sexual desire
Higher frequency of vaginal dryness
More disturbing low sexual desire
More disturbing vaginal dryness
Lower frequency of sexual thoughts
Lower frequency of intercourse and masturbation
Problems with intercourse
Climacteric compared to preclimacteric
FAI*
Living with a partner
Weaker self-reported general health
Being a smoker
0
1
2
3
4
5
6