

Smoking across the menopausal transition in a 10-year longitudinal sample: The role of sex hormones and depressive symptoms

MacKenzie R. Peltier, PhD*, José M. Flores, MPH, MD, PhD, Philip H. Smith, PhD,
Walter Roberts, PhD, Terril L. Verplaetse, PhD, Kelly E. Moore, PhD, Robyn Hacker, PhD,
Lindsay M. Oberleitner, PhD, Sherry A. McKee, PhD
Department of Psychiatry, Yale School of Medicine, New Haven, CT 06519

*Correspondence to: MacKenzie R. Peltier, PhD, 2 Church Street South, Suite 201, Yale School of Medicine, New Haven, CT 06519; Phone: 203.785.5153 Fax: 203.737.4243 Email: mackenzie.peltier@yale.edu

Funding: This work was supported by NIH grants P50DA033945 (SAM) and T32DA007238 (MRP).

Declaration of conflicting interests: All authors declare that they have no conflicts of interest.

ABSTRACT

Introduction: Current cigarette smoking rates among older women remain problematic, especially given that this population experiences increased smoking-related health consequences. Despite these increased health concerns, little research to date has explored smoking patterns across the menopausal transition (pre-, early peri-, late peri-, and postmenopausal) or the effect of unique factors such as sex hormones and depression during this transition. *Methods:* The present study used 10 yearly waves of data from the Study of Women's Health Across the Nation (SWAN), a longitudinal dataset. Data included 1,397 women endorsing ever smoking regularly at baseline. Random-effects logistic regression models were used to examine smoking transitions. *Results:* While there were not associations between menopausal transition stage and smoking behavior, increased estradiol was associated with an increased likelihood of quitting regular smoking (e.g., transitioning from regular smoking to non-regular/no smoking; Odds ratio [OR]=1.28), while increased testosterone was associated with an increased likelihood of relapsing to regular smoking (e.g., transitioning from former/non-regular smoking to regular smoking OR=2.56). Depression was associated with increased likelihood of continued smoking (OR=0.97) and relapse (OR=1.03). *Conclusions:* The results emphasize the need to develop interventions to target initiated or continued smoking among women across the menopausal transition and specifically highlight the importance of developing treatments that target depressive symptoms in this population. Additionally, while singular hormone measures were associated with smoking behavior, there is a need for future study of dynamic changes in hormones, as well as the impact of progesterone on smoking behaviors across the menopausal transition.

Keywords: cigarette smoking, menopause, smoking cessation, female, sex hormones, depression

Implications

To date, no studies have examined smoking behaviors across the menopausal transition. In the present study, while menopausal transition status was not significantly related to transitions in smoking behavior, important relationships between sex hormones and depression were observed. Increased estradiol was associated with an increased likelihood of quitting regular smoking, while increased testosterone was associated with an increased likelihood of relapsing to regular smoking behavior. Higher depression scores were related to continued smoking and relapse to regular smoking behavior. These results highlight the need to develop interventions to target smoking cessation among women across the menopausal transition.

Accepted Manuscript

INTRODUCTION

Current cigarette smoking rates among adults in the United States (US) have recently declined, with rates decreasing from 20.9% in 2005 to 15.5% in 2016¹. However, smoking among older females remains relatively common; among women 45-64 years old, 16.8% report current smoking¹. This is problematic given that cigarette smoking is the leading cause of preventable death and disease in the US and women experience a greater negative health burden when compared to men, with a greater risk of developing various cancers and cardiovascular diseases²⁻⁵. Additionally, women smokers suffer from sex-sensitive and sex-specific health risks, especially associated with menopause, including earlier menopausal transition, increased risk of osteoporosis, impaired respiratory function, and more severe menopausal symptoms^{2,6-8}. Despite these increased health risks, women overall have poorer rates of smoking cessation, indicating that increased efforts are needed to understand and improve cessation rates⁹, specifically among older females.

One potential explanation for the observed differences in cessation rates may be the hormonal milieu. During menopause, endogenous levels of estradiol and progesterone initially fluctuate during the menopausal transition, but gradually decrease to low/stable levels in postmenopause¹⁰. Follicular stimulating hormone (FSH) levels, typically an indicator utilized in categorizing menopausal stage, increase substantially over the menopausal transition and remain elevated until later in life, while testosterone levels remain relatively stable across the transition¹¹⁻¹³. The menopausal transition is typically divided into several stages based upon fluctuating hormone levels and menstrual cycle length. Premenopause, is generally a time describing a women's reproductive years, which is often characterized by regular menses and low levels of FSH; the duration of premenopause is highly variable and may be further broken

down into early, peak, and late reproductive stages^{10,14}. The menopausal transition, often called perimenopause, is divided into early and late-perimenopause based upon acyclicity. Early perimenopause stage criteria includes variable menstrual cycle length and FSH values; however the length of this stage is also highly variable based upon the individual. Late-perimenopause is characterized by periods of amenorrhea, lasting at least 60 days, as well as high levels of FSH (greater than 25 IU/L). Late perimenopause typically lasts 1-3 years. Finally postmenopause follows 1 year of amenorrhea, and may be further broken down into early (variable FSH levels) and late (stabilized FSH levels) stages^{10,14}. Of note, the duration of such reproductive stages is highly variable based upon a myriad of variables, such as overall health, socioeconomic status, body mass, race/ethnicity, and genetic factors¹⁰.

Among pre-menopausal women, there is evidence that progesterone is generally protective against smoking-related variables (e.g., decreased subjective reactivity, fewer puffs of cigarettes in laboratory settings), whereas estradiol is implicated in smoking behavior (e.g., relapse, continued smoking; for review see¹⁵). However, it is worth noting that there is mixed evidence regarding the hormonal milieu, menstrual cycle, and smoking^{15,16}. As such, some studies, including one meta-analysis, have reported greater symptoms of withdrawal and craving during the luteal phase, when progesterone levels are highest¹⁷.

Regarding testosterone, smoking is associated with higher testosterone levels; however, the specific association among women smokers remains unclear and is understudied¹⁸. Among the few studies that have examined the role of testosterone in female smoking behavior¹⁸, higher concentrations of testosterone have been found in pre-menopausal smokers relative to female former smokers and non-smokers¹⁹. This pattern holds true for post-menopausal smokers, with higher levels of testosterone in current versus never smokers, which was associated with the

number of cigarettes smoked per day²⁰. Additionally, high levels of testosterone were also observed among the postmenopausal former smokers included in one population-cohort study²⁰. Given the declining levels of endogenous estradiol and progesterone, as well as the stable levels of testosterone, postmenopause may be an advantageous time to make a cessation attempt. However, to date the majority of the literature has focused on the impact of sex hormones and smoking behavior among pre-menopausal women¹⁷. In fact, little information is available regarding the impact of these endogenous hormones and their fluctuations on smoking cessation attempts during or after the menopausal transition⁷.

An additional factor that may explain changes in smoking behavior among older women is negative affect, specifically depressive symptoms. Women are at an increased risk of developing depressive symptoms during the menopausal transition, with a recent study showing that 31% experienced a period of persistent/recurrent depression and 9% endorsed a single major depressive episode, across a 13-year period during the menopausal transition^{21, 22}. Such associations between the menopausal transition and depressive symptoms, may be associated with the fluctuating hormonal milieu across the transition^{7, 22}. This likely has a meaningful impact for female smokers, as it is well established that negative affect impedes smoking cessation attempts among smokers²³⁻²⁵. However, little information is known regarding how depressive symptomatology impacts smoking behavior across the menopausal transition.

The current scant literature regarding smoking behaviors in older women leaves several important gaps to address in order to improve cessation outcomes in this population. For instance, to our knowledge, there are no studies examining smoking outcomes across the menopausal transition (pre-, early peri-, late peri-, and postmenopausal stages) and the impact of endogenous sex hormones and depression on such outcomes. Additionally, there is a need to

focus on long-term smoking cessation outcomes, as no study has examined treatment outcomes beyond a one-year follow-up in postmenopausal females²⁵. This information may provide necessary insights to help develop targeted interventions for cessation among females during and after the menopausal transition.

The present study sought to investigate the effect of transitions across menopausal status (pre-, early peri-, late peri-, and postmenopausal stages) on the transition from regular smoking to non-regular/no smoking (i.e., quitting regular smoking behavior) as well as the reverse transition from non-regular/no smoking, among those endorsing ever smoking to regular smoking (i.e., relapse to regular smoking behavior). Additionally, we analyzed the impact of sex hormones, specifically, estradiol and testosterone, as well as depressive symptoms on these changes, while accounting for age.

The present study utilized data from the Study of Women's Health Across the Nation (SWAN). SWAN is a longitudinal, epidemiological study designed to capture the relevant biopsychosocial changes that impact females' health across the menopausal transition²⁶. This dataset allowed investigation of the effects of menopausal status and endogenous sex hormones, as well as depression, on smoking. It was hypothesized that late peri-menopausal and postmenopausal status would be associated with an increased likelihood of quitting regular smoking in women followed across the transition and decreased likelihood of women relapsing to regularly smoking. It was hypothesized that increased levels of estradiol and testosterone would be associated with a decreased likelihood of quitting regular smoking and an increased likelihood of relapsing to regular smoking. Additionally, it was hypothesized that higher scores of depressive symptoms would be associated with a decreased likelihood of quitting regular smoking, as well as an increased likelihood of relapsing to regular smoking.

METHODS

Data source

The data utilized in the present study are drawn from the publicly available SWAN datasets²⁶. The study enrolled 3,302 participants from seven research centers across the US between 1996-1997. SWAN enrolled women who were between 42-52 years old, reported being pre- or early-perimenopausal (defined as reporting a menstrual period within the past 3 months), did not take hormone medications in past three months and denied a total hysterectomy (participants reported an intact uterus and at least one ovary). These participants were then followed annually over ten years following the baseline visit with in-person examinations, which included biological measures (e.g., height, weight, blood draws), as well as and surveys assessing for various physical, biological, psychological and social changes. Additional information regarding the SWAN data and the specific variables it includes is available elsewhere²⁶.

Data analysis

Data were analyzed using Stata Statistical Software 16.1 (StataCorp. 2016. College Station, TX: StataCorp LP). Annual datasets were merged, and variables were matched based upon a source-identification variable.

Menopausal status stage was coded each year during annual surveys²⁶. Women were identified as *pre-menopausal* if they reported menses within the past 3 months with no change in menstruation patterns (e.g., no changes in regularity or menses occurring further or closer than previous menses). They were classified as *early peri-menopausal* if they experienced menses within the past 3 months, but identified decreased predictability between menses (e.g., changes in menses being further or closer apart; changes in variability or regularity of menses). *Late peri-*

menopausal women were classified as those who had reported no menses within the past 3-11 months. Finally, women reporting no menses for the past year were identified as *postmenopausal*.

Once categorized, women were not permitted to be categorized “backwards” in future visits²⁶. In the SWAN dataset, women who reported taking hormonal therapies who had a hysterectomy/ovaries removed were classified as “unknown due to [hormonal therapy] use,” or “unknown due to hysterectomy,” respectively²⁶. Accordingly, these women were not included in analyses for the years their menopausal status was marked “unknown.” Additionally, given the scope of this study, women who were currently pregnant/breastfeeding, were classified as such²⁶ and were excluded from the present analyses for the years they were pregnant/breastfeeding. It is important to note that the menopausal status definitions used in the SWAN study were based upon menopausal status definitions that were included in the Massachusetts Women’s Health Study^{27,28}; FSH levels were not used to categorize stages of the transitions for participants.

The present study included only participants who transitioned to postmenopausal status during the 10-year period. Smokers were identified from baseline data by responding yes to a query about smoking behavior at baseline (*Have you ever smoked cigarettes regularly?*; response, yes/no). Transitions in smoking behavior were derived from an annual assessment of smoking behavior (*Did you smoke regularly since last visit?*; response, yes/no), beginning at Visit 1. Data was not censored at quitting and/or relapse to regular smoking behavior, in order to best capture subsequent transitions (e.g., if a participant relapsed, then, stopped smoking regularly, then relapsed to regular smoking again, both instances were counted in the analyses).

Random-effects logistic regression models with robust standard errors were calculated using the Xtlogit command in Stata: the association between menopausal status and transition

from regularly smoking to non-regular/no smoking (e.g., quitting regular smoking) between any waves of data collection, as well as the association between menopausal status and transition from non-regular/no smoking to regularly smoking between any waves of data collection, among those identified as “*ever smokers*” (e.g., relapse to regular smoking). Baseline age, age of post-menopausal status, and length of transition from early peri- to post-menopausal status were included in all models. Annual measures of hormonal assays, including estradiol and testosterone were included in the second and third models. Estradiol and testosterone results did not have normal distributions, and thus natural log transformed values were used. This strategy has been utilized in other analyses of SWAN hormonal data (e.g.,^{29,30}). Of note, FSH was not included in current analyses, due to multicollinearity with the menopausal transition variable. Depression symptoms were also evaluated annually, with the Center for Epidemiological Studies-Depression (CES-D)³¹, and were included in the third model.

RESULTS

Baseline data identified 1,397 females as being ever regular smokers. Of the identified baseline, ever regular smokers, the majority were White/non-Hispanic (54.4%; Black/African American, 30.60%, Hispanic, 6.70%, Asian/Asian American, 8.3%). Mean age at baseline was 45.84 years (SD=2.67 years).

Transition from smoking regularly to quitting regular smoking

There were no significant associations between menopausal status and the transition from smoking regularly to not regularly/not smoking. However, increased estradiol levels were associated with an increased likelihood of quitting regular smoking. Testosterone levels were not significantly related to the transition to quitting regular smoking. Additionally, increased depressive symptoms (measured via CESD) decreased one’s likelihood of quitting regular smoking. See Table 1 for complete results.

Transition from former smoker/not smoking regularly to smoking regularly

Again, no significant association between menopausal status and the transition from non-regularly/no smoking, among former “*ever smokers*,” to regular smoking (e.g., relapse) were observed. Similarly, estradiol levels were not significantly related to transition to relapse to regular smoking. However, increased levels of testosterone and depression (measured via CESD) were associated with an increased likelihood of relapsing. See Table 2 for complete results.

DISCUSSION

Given the scant literature investigating the menopausal transition and smoking outcomes to date⁷, the present study sought to explore the effect of menopausal status on smoking behavior. While our results did not demonstrate an association between the transition through menopause stages and quitting/relapsing of regular smoking behavior, the present results did illustrate that it is likely that other unique factors related to the menopausal transition are related to changes in smoking behavior.

One of these unique factors related to smoking outcomes across the menopausal transition is likely the hormonal milieu, given the previous evidence that endogenous sex hormone levels impact smoking cessation in pre-menopausal women¹⁷. In the current investigation, testosterone was related to an increased likelihood of relapse to regular smoking, with no significant effect on the likelihood of quitting regularly smoking behaviors. This supports previous literature that both male and female smokers, relative to non-smokers or former smokers, have higher levels of testosterone¹⁸⁻²⁰. Thus, it is likely that smoking increased testosterone levels among those smoking regularly, although future research should explore potential casual relationships and measure serum testosterone at multiple timepoints to capture potential dynamic changes in relation to smoking behavior.

In the present study, increased levels of estradiol increased the likelihood of quitting regular smoking; however, it was unrelated to relapse. This was contrary to the hypothesis that increased estradiol, which is generally associated with increased cravings, would be related to poorer smoking outcomes (i.e., less likely to transition to non-regular/no smoking and more likely to relapse to regular smoking). Previous research has asserted that estrogen is related to accelerated nicotine metabolism among pre-menopausal females; however, “menopausal” or postmenopausal females’ nicotine metabolism does not differ from that of male smokers³². Thus, women across the menopausal transition may be less susceptible to the proposed effects of estradiol on smoking behavior.

However, additional investigation regarding ovarian hormones and smoking cessation is still warranted in this population, specifically with future studies collecting hormonal assays at multiple timepoints throughout the menopausal transition. There is emerging evidence that endogenous progesterone levels are related to smoking abstinence among pre-menopausal females³³. It may be that progesterone, which decreases across the menopausal transition, also impacts transitions in smoking behaviors during the menopausal transition. Unfortunately, progesterone levels were not included in the publicly available, annual hormonal assays of the SWAN study; thus, the effect of progesterone and its metabolites (e.g., allopregnanolone) on smoking transitions were unable to be explored through this dataset²⁶. Progesterone levels may also be needed to understand estrogen’s effects on smoking behavior, as previous research has shown that the ratio of progesterone to estradiol is a useful predictor of smoking behavior¹⁶.

An additional factor related to smoking outcomes among older females is depressive symptoms. Previous literature has established that negative affect and depression negatively impacts smoking cessation in postmenopausal women^{7,25}. The present study supported this

finding in that depressive symptomatology was significantly related to a decreased likelihood of quitting regular smoking, as well as an increased likelihood of relapsing to smoking regularly. Research has found that postmenopausal women with a history of depression are less likely to quit smoking, compared to those with no history of depression²⁵. Given the previous research and this present study's results that depressive symptoms are significantly related to the increased likelihood of continued regular smoking, further study of the mechanisms underlying negative affect management and smoking during the menopausal transition are warranted in order to develop cessation interventions that target depressive symptomatology in this population.

Overall, while the present results did not demonstrate that menopausal status is associated to transitions in smoking behavior; they do illustrate that women are making transitions in smoking behavior as they age. Previous research among older smokers has shown that older smokers who are motivated to quit, have at least as high of a chance of quitting as their younger counterparts, especially when using nicotine replacement therapies³⁴. This highlights the need to develop novel interventions to increase motivation to quit smoking and improve cessation outcomes among this population. Previous research has shown that menopausal symptom severity, including somatic menopausal symptoms (e.g., sweating/flush, cardiac complaints), was related to increased motivation to quit smoking³⁵; thus, evaluating one's health and menopausal symptomatology may increase motivation to quit smoking among postmenopausal women³⁵. In future work, it may be beneficial to incorporate health evaluation into motivational-based interventions with this population. Additionally, addressing other potential barriers to cessation, including psychosocial stress may be advantageous. These avenues may offer important insight into the development of novel treatments for tobacco cessation for this population.

Limitations

To our knowledge, the present study is the first study to explore transitions in smoking behavior across the menopausal transition and investigate the impact of sex hormones. However, there are limitations that warrant mention. First, although the sample is comprised of a racially/ethnically diverse sample, drawn from seven geographic locations across the US, results may not be generalizable to women in other countries. Second, data analysis was limited to variables collected at annual assessment visits, as well as the study's inclusion/exclusion criteria (including age restrictions). As such, there is limited information to help us further characterize and understand factors related to smoking transitions. For example, more detailed questions regarding past year smoking behavior and measures of nicotine dependence, were not available for the current study. Measures of depressive symptomatology were also only obtained annually, with a measure that surveys the such symptoms over the past week. Thus, this may reflect state affect, as opposed to representing affect, as well as fluctuations in mood, across the past year. Furthermore, menopausal status classification did not include a biological confirmation. Inclusion of these variables would improve future research on this topic.

Additionally, sex hormone measurements were taken at only one time point at each annual visit and thus may not accurately represent the role of fluctuating hormones across the menopausal transition in relation to smoking. Future studies should include more comprehensive hormone assay collection. Finally, smoking behavior was self-reported and no biological measures were collected, thus smoking behavior may be subject to biased reporting. Despite these limitations, given the limited literature available on smoking across the menopausal transition, the present data are a valuable contribution to the literature. Future investigations are needed to replicate and reproduce the current results.

Conclusions

To our knowledge, results from the present investigation are the first to demonstrate unique factors that impact transitions in smoking behavior among women across the menopausal transition. Estradiol levels were associated with an increased likelihood of quitting regular smoking; while testosterone levels were related to an increase in likelihood to relapse to regular smoking. Similar to previous research among other populations of smokers, depressive symptoms were related to a decreased likelihood to quit regular smoking, while such symptomatology was also related to an increase in likelihood to relapse to regular smoking among this population. These results emphasize the importance of developing interventions potentially targeting depressive symptoms to improve smoking cessation among women across the menopausal transition. Future research is needed to explore additional barriers to cessation among this population. Additionally, the examination of the impact of progesterone on cessation outcomes during the menopausal transition is warranted.

References

1. Jamal A, Phillips, E., Gentzke, A.S, et al. Current Cigarette Smoking Among Adults — United States, 2016. *MMWR*. 2018;67:53-59.
2. The United States Department of Health and Human Services (HSS). Women and Smoking: A report of the Surgeon General. *MMWR*. 2002;51(RR12):1-30.
3. Huxley RR, Woodward M. Cigarette smoking as a risk factor for coronary heart disease in women compared with men: a systematic review and meta-analysis of prospective cohort studies. *Lancet*. 2011;378(9799):1297-1305.
4. Kiyohara C, Ohno Y. Sex differences in lung cancer susceptibility: A review. *Gen Med*. 2010;7(5):381-401.
5. Freedman ND, Silverman DT, Hollenbeck AR, Schatzkin A, Abnet CC. Association between smoking and risk of bladder cancer among men and women. *JAMA*. 2011;306(7):737-745.
6. Hayatbakhsh MR, Najman JM, O'Callaghan MJ, Williams GM, Paydar A, Clavarino A. Association Between Smoking and Respiratory Function Before and After Menopause. *Lung*. 2011;189(1):65-71.
7. McVay MA, Copeland AL. Smoking cessation in peri- and postmenopausal women: A review. *Exp Clin Psychopharmacol*. 2011;19(3):192-202.
8. Bjarnason NH, Nielsen TF, Jørgensen HL, Christiansen C. The influence of smoking on bone loss and response to nasal estradiol. *Climacteric*. 2009;12(1):59-65.
9. Smith PH, Bessette AJ, Weinberger AH, Sheffer CE, McKee SA. Sex/gender differences in smoking cessation: A review. *Prev Med*. 2016;92:135-140.

10. Lobo RA. Menopause and Aging. In: Strauss JF, Barbieri, R.L., ed. *Yen and Jaffee's Reproductive Endocrinology: Physiology, Pathophysiology, and Clinical Management*. 6th ed. Philadelphia, PA: Saunders Elsevier; 2009:325-356.
11. Carmina E, Lobo RA. Evaluation of Hormonal Status. In: Strauss JF, Barbieri, R.L., ed. *Yen and Jaffe's Reproductive Endocrinology: Physiology, Pathophysiology, and Clinical Management*. 6th ed. Philadelphia, PA: Saunders Elsevier; 2009:801-824.
12. Yasui T, Matsui S, Tani A, Kunimi K, Yamamoto S, Irahara M. Androgen in postmenopausal women. *J Med Invest*. 2012;59(1,2):12-27.
13. Kim C, Harlow SD, Zheng H, McConnell DS, Randolph JF. Changes in androstenedione, dehydroepiandrosterone, testosterone, estradiol, and estrone over the menopausal transition. *Womens Midlife Health*. 2017;3:9.
14. 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. *Menopause*. 2012;19(4): 387-395.
15. Wetherill RR, Franklin TR, Allen, SS. Ovarian hormones, menstrual cycle phase, and smoking: a review with recommendations for future studies. *Curr Addict Rep*. 2016;3(1): 1-8.
16. Schiller CE, Saladin ME, Gray KM, Hartwell KJ, Carpenter MJ. The Association Between Ovarian Hormones and Smoking Behavior in Women. *Exp Clin Psychopharmacol*. 2012;20(4):251-257.
17. Weinberger AH, Smith PH, Allen SS, et al. Systematic and Meta-Analytic Review of Research Examining the Impact of Menstrual Cycle Phase and Ovarian Hormones on Smoking and Cessation. *Nicotine Tob Res*. 2015;17(4):407-421.

18. Zhao J, Leung JYY, Lin SL, Schooling CM. Cigarette smoking and testosterone in men and women: A systematic review and meta-analysis of observational studies. *Prev Med.* 2016;85: 1-10.
19. Sowers MF, Beebe JL, McConnell D, Randolph J, Jannausch M. Testosterone Concentrations in Women Aged 25–50 Years: Associations with Lifestyle, Body Composition, and Ovarian Status. *Am J Epidemiol.* 2001;153(3):256-264.
20. Manjer J, Johansson R, Lenner P. Smoking as a determinant for plasma levels of testosterone, androstenedione, and DHEAs in postmenopausal women. *Eur J Epidemiol.* 2005;20(4): 331-337.
21. Soares, CN. Depression and menopause: Current knowledge and clinical recommendations for a critical window. *Psychiatr Clin North Am.* 2017;40(2):239-254.
22. Bromberger, JT, Kravitz HM, Youk A, Schott LL, Joffe H. Patterns of depressive disorders across 13 years and their determinants among midlife women: SWAN mental health study. *J Affect Disord.* 2017;206:31-40.
23. Weinberger AH, Mazure CM, Morlett A, McKee SA. Two decades of smoking cessation treatment research on smokers with depression: 1990-2010. *Nicotine Tob Res.* 2013;15(6):1014-1031.
24. Weinberger AH, Pilver CE, Desai RA, Mazure CM, McKee SA. The relationship of dysthymia, minor depression, and gender to changes in smoking for current and former smokers: longitudinal evaluation in the U.S. population. *Drug Alcohol Depend.* 2013;127(1-3):170-176.

25. Oncken C, Cooney J, Feinn R, Lando H, Kranzler HR. Transdermal nicotine for smoking cessation in postmenopausal women. *Addict Behav.* 2007;32(2):296-309.
26. Sutton-Tyrrell K, Selzer F, Sowers M, et al. Study of Women's Health Across the Nation (SWAN), 1996-1997: Baseline Dataset. Inter-university Consortium for Political and Social Research [distributor]; 2014.
27. Johnston JM, Colvin A, Johnson BD, et al. Comparison of SWAN and WISE menopausal status classification algorithms. *J Womens Health.* 2006;15,(10):1184-94.
28. Brambilla DJ, McKinlay SM, Johannes CB. Defining the perimenopause for application in epidemiologic investigations. *Am J Epidemiol.* 1994;140(12):1091-5.
29. Lasley BL, Chen J, Stanczyk FZ, et al. Androstenediol complements estrogenic bioactivity during the menopausal transition. *Menopause.* 2012;19(6): 650-657.
30. Luetters C, Huang MH, Seeman T, et al. Menopause transition stage and endogenous estradiol and follicle-stimulating hormone levels are not related to cognitive performance: Cross-sectional results from the Study of Women's Health across the Nation (SWAN). *J Womens Health.* 2007;16(3):331-344.
31. Radloff LS. The CES-D Scale: A Self-Report Depression Scale for Research in the General Population. *Appl Psychol Meas.* 1977;1(3):385-401.
32. Benowitz NL, Lessov-Schlaggar CN, Swan GE, Jacob P. Female sex and oral contraceptive use accelerate nicotine metabolism. *Clin Pharmacol Ther.* 2006;79(5):480-488.

33. Saladin ME, McClure EA, Baker NL, et al. Increasing Progesterone Levels Are Associated With Smoking Abstinence Among Free-Cycling Women Smokers Who Receive Brief Pharmacotherapy. *Nicotine Tob Res.* 2015;17(4):398-406.
34. Scholz J, Santos PCJL, Buzo CG, et al. Effects of aging on the effectiveness of smoking cessation medication. *Oncotarget.* 2016;7(21):30032-30036.
35. Peltier MR, Roys MR, Waters AF, et al. Motivation and readiness for tobacco cessation among nicotine dependent postmenopausal females: A pilot study. *Exp Clin Psychopharmacol.* 2018;26(2):125-131.

Accepted Manuscript

Table 1. Association between menstrual status and transition from regular smoking to quitting

	Model 1		Model 2		Model 3	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Menopausal transition status						
Pre-menopausal	Reference		Reference		Reference	
Early peri-menopausal	2.29 (0.56, 9.46)	0.251	1.70 (0.29, 9.89)	0.553	1.92 (0.29, 12.84)	0.501
Late peri-menopausal	1.32 (0.13, 13.49)	0.817	0.91 (0.06, 13.85)	0.945	1.09 (0.06, 21.00)	0.952
Post-menopausal	2.46 (0.31, 19.87)	0.397	1.60 (0.11, 22.77)	0.728	1.85 (0.11, 30.29)	0.665
Age (years) ^a	0.95 (0.69, 1.30)	0.735	1.06 (0.74, 1.54)	0.740	1.06 (0.69, 1.62)	0.796
Age of post-menopause (years)	1.14 (0.84, 1.56)	0.403	1.07 (0.74, 1.55)	0.733	1.08 (0.69, 1.62)	0.745
Length of transition (years) ^b	1.00 (0.76, 1.31)	0.994	1.05 (0.76, 1.44)	0.786	1.05 (0.74, 1.48)	0.778
Estradiol (pg/mL) ^c			1.28 (1.09, 1.51)	0.003	1.28 (1.08, 1.50)	0.004
Testosterone (ng/dL) ^c			0.85 (0.56, 1.29)	0.446	0.80 (0.54, 1.19)	0.275
Depression (CES-D), total score					0.97 (0.94, 1.00)	0.022

Note. OR= odds ratio; CI= confidence interval; ^a= at baseline; ^b= years from early peri- to post-menopause; ^c= natural log transformed hormonal assay results; CES-D=Center for Epidemiological Studies- Depression Scale; bold font indicates significance.

Table 2. Association between menstrual status and transition to relapsing to regular smoking

	Model 1		Model 2		Model 3	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Menopausal transition status						
Pre-menopausal	Reference		Reference		Reference	
Early peri-menopausal	0.83 (0.13, 5.29)	0.844	0.72 (0.11, 4.53)	0.726	0.64 (0.09, 4.38)	0.649
Late peri-menopausal	0.92 (0.19, 4.50)	0.921	0.74 (0.16, 3.36)	0.693	0.68 (0.16, 3.12)	0.622
Post-menopausal	0.71 (0.11, 4.38)	0.712	0.59 (0.08, 4.29)	0.601	0.54 (0.07, 4.33)	0.563
Age (years) ^a	0.92 (0.70, 1.19)	0.515	0.96 (0.68, 1.34)	0.797	0.99 (0.68, 1.43)	0.958
Age of post-menopause (years)	0.88 (0.70, 1.09)	0.238	0.87 (0.66, 1.15)	0.323	0.84 (0.62, 1.43)	0.256
Length of transition (years) ^b	1.16 (0.87, 1.56)	0.310	1.21 (0.82, 1.77)	0.330	1.25 (0.82, 1.90)	0.309
Estradiol (pg/mL) ^c			1.09 (0.80, 1.48)	0.578	1.11 (0.82, 1.51)	0.483
Testosterone (ng/dL) ^c			2.77 (1.48, 5.17)	0.001	2.56 (1.02, 1.04)	0.007
Depression (CES-D), total score					1.03 (1.02, 1.04)	<0.001

Note. OR= odds ratio; CI= confidence interval; ^a= at baseline; ^b= years from early peri- to post-menopause; ^c= natural log transformed hormonal assay results; CES-D=Center for Epidemiological Studies- Depression Scale; bold font indicates significance.