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Antidepressant use and circulating prolactin levels

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Abstract

Purpose—Whether antidepressants (AD), specifically selective serotonin reuptake inhibitors (SSRIs), are linked to elevated prolactin levels among the general population is unknown.

Methods—Circulating prolactin levels were available on 4593 healthy participants in the Nurses' Health Study (NHS) and NHS2, including 267 AD users. We fit generalized linear models to calculate and compare adjusted mean prolactin levels between AD users and non-users and further among SSRI users. Multivariable logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for “elevated” prolactin levels (>11 ng/mL) comparing AD users to non-users. We evaluated AD use and change in prolactin levels among 610 NHS participants with two measurements an average of 11 years apart.

Results—Adjusted geometric mean prolactin levels were similar among SSRI users (13.2 ng/mL, 95% CI 12.2–14.4), users of other classes of ADs (12.7 ng/mL, 95% CI 11.0–14.6), and non-users (13.1 ng/mL, 95% CI 12.8–13.4). Neither AD use (OR=1.17, 95% CI 0.89–1.53) nor SSRI use (OR=0.95, 95% CI 0.66–1.38) was associated with elevated prolactin levels. Change in prolactin levels was similar across women who started, stopped, consistently used, or never used ADs.

Conclusions—This study does not support the hypothesis that AD use would influence breast cancer risk via altered prolactin levels. These results provide some evidence that use of ADs to treat depression or other conditions may not substantially increase prolactin levels in the majority of women.

Keywords

Prolactin; antidepressants; selective serotonin reuptake inhibitors; women

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Introduction

Antidepressant (AD) use has quadrupled in the past two decades: ADs are now the top prescription drug taken by U.S. adults aged 18-44 years and the third most common pharmacological treatment used overall in this country [1]. Adult women are the most common consumers of these drugs, with recent NHANES data showing that 22.8% of American women aged 40-59 and 18.6% of those aged 60 and older self-reported use of AD medications, compared to 8.5% and 9.4% of similarly aged men, respectively [1]. Two of the most common classes of ADs are selective serotonin reuptake inhibitors (SSRI) and tricyclic antidepressants (TCA). SSRI prescriptions quickly outpaced other classes following their introduction in 1987 and have continued to increase in recent decades [2].

While these medications represent an important and effective treatment for depression and other medical conditions (e.g. anxiety disorders, eating disorders, premenstrual dysphoric disorder), concern has arisen that SSRIs in particular may increase circulating prolactin levels primarily via activation of the serotonergic pathway [3, 4]. Relations of SSRIs to increased prolactin have been illustrated in several small, clinical studies, while other classes of ADs had little or no effect on prolactin levels [5]. However, these associations have not been assessed in the general population.

Notably, prolactin levels are positively associated with breast cancer risk [6-12] and perhaps also ovarian cancer risk [13]. Prolactin is a hormone that may promote breast carcinogenesis by decreasing apoptosis and increasing cellular proliferation and estrogen responsiveness [10-12, 14, 15]. Strong evidence from the Nurses' Health Study (NHS) and Nurses' Health Study 2 (NHS2) links elevated circulating prolactin to an approximately 30% increased breast cancer risk, primarily for postmenopausal and estrogen-receptor-positive (ER+) disease [10-12]. A single prolactin measurement was predictive of risk over the short term (i.e. within 4-5 [6, 7, 9] or 10 years [8]) but not over the long term (>10 years) [8]. Cumulatively, prospective studies are more consistent for postmenopausal breast cancer than for premenopausal disease [7, 8]. Thus, the preponderance of evidence indicates an important role for prolactin in breast cancer.

We sought to evaluate if prolactin levels are significantly elevated among SSRI users as compared to users of other ADs and non-users in a population-based sample, and also if SSRI users are more likely to have prolactin levels in the range associated with increased breast cancer risk. Understanding whether SSRIs affect prolactin levels is important for clinicians when weighing the risks and benefits of prescribing ADs and monitoring their patients taking these medications. Therefore, we evaluated the association between AD use and circulating prolactin levels among participants in the NHS and NHS2. Additionally, in a subsample of NHS participants with two prolactin measurements an average of 11 years apart, we explored whether initiation of SSRI use was associated with increased circulating prolactin.

Materials and Methods

Study Population

The NHS (N=121,700, age 30-55 in 1976) and NHS2 (N=116,430, age 25-42 in 1989) are two ongoing prospective cohort studies of registered nurses. Follow-up on these cohorts continues through mailed biennial questionnaires.

As previously described [16], 32,826 NHS participants provided a blood sample between 1989 and 1990. Blood samples were shipped to the NHS laboratory via overnight courier with an icepack for processing. A subset of these women (N=18,743) provided a second blood sample from 2000-2002 using the same protocol. Similarly, 29,611 NHS2 participants provided a blood sample between 1996 and 1999 [12]. Prolactin levels were measured in prior nested breast cancer case-control studies within each cohort [8, 10-12]. We included all controls from the aforementioned breast cancer studies on whom both AD use and prolactin data were available. Control selection procedures were identical in both cohorts except that NHS2 cases and controls were additionally matched on luteal day for timed samples, which was not necessary among the postmenopausal NHS participants. Our final sample included 3,167 NHS participants, including 610 with two prolactin measurements, and 1,426 NHS2 participants.

Measurement of Antidepressant Use

Both NHS and NHS2 participants self-reported current AD use (yes, no) on a questionnaire submitted along with the blood sample. NHS participants self-reported AD use on the 1996 and 1998 questionnaires; starting with the 2000 questionnaire NHS participants separately reported use of Prozac, Zoloft, Paxil, Celexa (SSRIs), or use of “other” ADs (with given examples of Elavil, Tofranil, and Pamelor; TCAs). NHS2 participants self-reported use of SSRIs and TCAs beginning in 1993.

Among NHS participants, AD use at the first blood collection was obtained from the questionnaire accompanying the provided blood sample; therefore information on class of AD used was unavailable. AD use (yes, no) at the time of second blood sample also was assessed by the accompanying questionnaire, with information on AD class derived from the 2000 biennial questionnaire.

Among NHS2 participants, AD use was derived from the questionnaire coincident with the blood sample, with information on AD class derived from the nearest biennial questionnaire. “AD users” were women reporting AD use on both the blood questionnaire and matched biennial NHS2 questionnaire; “non-users” were women who did not report AD use on either questionnaire.

Depressive symptoms were assessed via MHI-5 scores on the NHS or NHS2 questionnaire closest to the blood draw, with scores ≥ 52 indicating severe depressive symptoms [17]. Because depressive symptoms were first assessed among NHS participants on the 1992 questionnaire, these data were used to retrospectively classify depressive symptoms at the time of the first blood draw in 1990.

Prolactin Measurement

Prolactin was measured by microparticle enzyme immunoassay, as described previously [10-12]. The laboratory was masked with respect to case-control status, and case-control sets were analyzed together with random ordering. The coefficient of variation from blinded replicate samples was <12% across all batches, though mean prolactin concentrations of quality control samples varied slightly by batch [8, 12]. We therefore statistically adjusted prolactin levels for assay batch using the methodology of Rosner et al [18, 19] and consistent with previous analyses within NHS and NHS2 [8].

Statistical Analysis

We compared AD users to non-AD users within each cohort on demographic and behavior characteristics potentially associated with AD use and/or prolactin levels: age, body mass index (BMI), race, marital status, educational level, parity, menopausal status/postmenopausal hormone (PMH) use, age at menopause, physical activity, alcohol intake, smoking status, steroid use, and thyroid medication use. We also compared natural log-transformed prolactin levels between these groups. Additionally, we defined women with “elevated” prolactin levels as those with prolactin levels associated with increased breast cancer risk in prior NHS and NHS2 studies (>11 ng/mL) [8]. Two sample t tests were used for continuous variables and chi square tests were used for categorical variables.

All further analyses were initially performed separately by cohort, with similar results within each cohort. Therefore, we pooled NHS and NHS2 data for analysis and report these results. We first examined whether any AD use compared to none was associated with prolactin levels, combining data from the first blood sample for NHS (1989-1990) and the NHS2 (1996-1999) data. We utilized generalized linear models to calculate and compare geometric mean prolactin levels across groups defined by AD use while adjusting for the aforementioned covariates, which were selected based on their association with AD use and/or prolactin levels within the study populations. Continuous covariates were centered on their mean values (combining NHS and NHS2 participants) to facilitate interpretation of results. We utilized multivariable logistic regression to estimate adjusted odds ratios (ORs) and 95% confidence intervals (CIs) associated with having “elevated” prolactin levels.

To examine whether SSRI use specifically was associated with prolactin, we combined data from the second blood draw (2000-2002) in NHS with data from NHS2. We utilized generalized linear models and logistic regression, as outlined above, to calculate adjusted geometric mean prolactin levels and ORs for elevated prolactin, respectively.

Among the subsample of NHS participants with prolactin levels measured at two timepoints, we defined AD use category as consistent non-users, started AD use, stopped AD use, or consistent users. We further classified women by SSRI use at the NHS second blood draw, when data on AD class were available. We used generalized linear models to calculate and compare adjusted geometric means of prolactin levels at the first blood draw, the second blood draw, their average, and the change in prolactin levels between the two timepoints.

We also assessed interactions between AD use and age (continuous), BMI (<25 kg/m², 25-30 kg/m², ≥30 kg/m²), menopausal status (premenopausal, postmenopausal without PMH

use, postmenopausal with PMH use, unknown), and parity (0, 1, 2, 3, 4+ children) in each model. We additionally repeated analyses in the subsample of participants without depressive symptoms as determined by MHI-5 score. All p values were two sided and statistical significance determined as $p < 0.05$. Analyses were conducted using SAS, version 9.3 (SAS Institute Inc., Cary, North Carolina).

Results

Within each cohort, AD users and non-users were of similar age, though AD users tended to be heavier, have lower levels of physical activity, and were more likely to be postmenopausal and using PMH, and to smoke (Table 1). The age-adjusted geometric mean prolactin levels were similar among AD non-users and users in both NHS (11.0 ng/mL at both first and second blood draws) and NHS2 (13.5 ng/mL), as was the percentage of women with “elevated” prolactin levels (NHS 1st blood draw 47% and 48%, respectively; NHS 2nd blood draw 45.8% and 44.1%, respectively; NHS2 65.9% and 67.5%, respectively). There was a statistically significant but weak inverse correlation between natural log-transformed prolactin levels and BMI ($r = -0.04$, $p = 0.02$).

In multivariable analyses, geometric mean prolactin levels were similar among AD users (12.0 ng/mL, 95% CI 11.3-12.7) and non-users (11.6 ng/mL, 95% CI 11.4-11.7), (Table 2). AD use also was not associated with prolactin levels >11 ng/mL (OR 1.17, 95% CI 0.89-1.53). However, we observed a statistically significant interaction with BMI ($p = 0.02$), such that prolactin levels were highest among obese women using ADs (13.2 ng/mL, 95% CI 11.7-15.0) compared to obese women not using ADs (11.0 ng/mL, 95% CI 10.5-11.4). Obese women with AD use had a two-fold increase in the odds of having prolactin levels >11 ng/mL (95% CI 1.11-3.58) compared to obese non-users. Prolactin levels were similar between AD users and non-users among the underweight/normal and overweight groups. There was no interaction between AD use and age, menopausal status, or parity (all p for interactions >0.60).

We combined data from the NHS2 and second blood draw within NHS to specifically evaluate associations between SSRI use and prolactin levels (Table 3). We found no association between SSRI use and geometric mean prolactin levels (SSRI users: 13.2 ng/mL, 95% CI 12.2-14.4; users of other classes of ADs: 12.7 ng/mL, 95% CI 11.0-14.6; non-users: 13.1 ng/mL, 95% CI 12.8-13.4). Likewise, SSRI use was not associated with prolactin levels >11 ng/mL (OR 0.95, 95% CI 0.66-1.38). We again observed a modest, but statistically significant, interaction with BMI ($p = 0.04$), with overweight non-SSRI AD users (16.8 ng/mL, 95% CI 12.8-22.0) and obese SSRI users (14.2 ng/mL, 95% CI 12.2-16.4) having higher prolactin levels than other groups defined by BMI and AD use (e.g. underweight/normal non-users: 13.3 ng/mL, 95% CI 12.9-13.8). SSRI use was not significantly associated with prolactin levels >11 ng/mL within any of the BMI categories. No statistically significant interactions were observed between SSRI use and age, menopausal status, or parity (all p for interactions >0.11).

For both AD use overall and SSRIs specifically, findings were similar when restricting to the subgroup of women without severe depressive symptoms (data not shown), though interaction with BMI category was not assessed due to small numbers.

A subset of NHS participants had two prolactin measurements an average of 11.1 (SD 0.5) years apart. Change in prolactin levels between these two times was similar among women who never used ADs, started AD use, stopped AD use, or used ADs at both times (Table 4). For example, prolactin levels increased by an average of 1.07 ng/mL (95% CI 0.93-1.23) among women who started AD use, which was similar to the observed increase of 1.01 ng/mL (95% CI 0.97-1.06) among non-users at both times. We likewise observed no difference in change in prolactin when further classifying women by their SSRI use at the second timepoint. The average of the two prolactin measurements did not vary by AD use status (data not shown). Interactions were not evaluated due to small numbers available for this analysis.

Discussion

We observed no significant association overall between AD use and circulating prolactin levels among this sample of pre- and postmenopausal women. Adjusted mean prolactin levels were similar among AD users and non-users. Concern about the effects of ADs on prolactin has focused largely on the SSRIs. However, overall, we found no evidence that this medication class was associated with prolactin levels in most women. Additionally, in the subgroup of participants with two measurements of prolactin available, initiating AD use, or SSRI use specifically, did not result in a significant increase in circulating prolactin levels over 11 years. Our findings did not vary by a woman's age, menopausal status, or parity. However, we did observe variation according to BMI, with elevated prolactin levels among obese women who were AD users, but not among normal weight or overweight women. Further, modestly higher prolactin levels were seen among obese SSRI users compared to obese users of other AD classes and obese non-users, though in overweight women non-SSRI users had suggestively higher prolactin levels compared to overweight non-users and SSRI users.

Prior clinical studies of some SSRIs, including fluoxetine, fluvoxamine, and paroxetine, have shown elevations in circulating prolactin levels among individuals initiating these medications [5]. Other AD classes, including TCAs, are reported to have a lesser effect, if any. One study [20] (N=41 women with major depressive disorder [MDD] being treated at a depression clinic in a major academic medical center) reported that fluoxetine treatment significantly increased prolactin levels from a mean of 7.7 ng/mL (SD 3.6) to 12.2 ng/mL (SD 8.8) after 12 weeks. Hyperprolactinemia (defined as prolactin levels ≥ 19.0 ng/mL) developed in 22% of women with normal baseline prolactin measurements [20]. A recent study observed hyperprolactinemia in 4 of 42 women using SSRIs on an outpatient basis to treat MDD for an average of 16 months [21]. Additional studies were small, ranging in size from 1 to 30 participants, and included healthy individuals [22-26], those with panic disorder [27], or other mental health conditions requiring hospitalization [28]. Clinical populations tend to have more severe depression, additional comorbidities, and may be using other drugs such as antipsychotics. Hyperprolactinemia is a well-established side effect of

antipsychotic medications [29, 30]. Some studies did not specifically exclude individuals using antipsychotics [23, 31, 32], while others only noted that participants were free of other medications for at least one week prior to and during the study [22, 24-28], though this does not necessarily exclude use of such drugs in the recent past. Thus, the effects of concordant or recent use of antipsychotic medications on prolactin levels cannot be excluded as an explanation for reported increases associated with SSRI use in some studies [22, 24-26, 28, 31, 32]. However, two studies reporting significant prolactin increases associated with SSRI use specifically excluded individuals using antipsychotic medications [20, 21]. Although data on antipsychotic medications are not available on NHS and NHS2 participants, pilot data within NHS2 indicates that antipsychotic use in the Nurses' cohorts is rare: only 9 out of 1,220 NHS2 pilot respondents (0.7%) reported use of antipsychotic medications (unpublished data). Thus, we believe that very few of our participants were using antipsychotic medications. The prevalence of AD use we observed in our populations, 4.4% for NHS at 1st blood draw in 1990 and approximately 10% for NHS2 in 1996-1999 and for NHS at the 2nd blood draw in 2000-2002, are only slightly lower than the observed prevalence of AD use among U.S. women age 45-64 during those periods, 7% in 1988-1994 and 13% in 1999-2000.[33] Thus we believe that the experience of AD use in our population is generally reflective of the broader population of U.S. women.

We observed higher prolactin levels among obese AD users, especially obese SSRI users, although the interaction effect we observed was only modest and could be due to chance. Our results suggest that obese women may be more likely to have slight elevations in prolactin levels with SSRI use. Though it is unclear why the prolactin response to ADs would differ by obesity status, decreased efficacy of ADs among the obese has been reported [34-38]. Given that obese postmenopausal women are already at increased breast cancer risk compared to normal weight postmenopausal women, this may represent a subgroup for whom prolactin levels following SSRI use should be carefully monitored. The elevated prolactin levels observed among overweight non-SSRI AD users is not consistent with our other findings or with the biological mechanism by which ADs are thought to affect prolactin, and may have occurred by chance. Previous investigations have not evaluated effects separately stratified by BMI category and have rarely reported the BMI distribution of their populations. Therefore, our results, while provocative, require confirmation in other cohorts.

The duration of AD use may be an important factor in understanding the potential effect of ADs on prolactin. Prior evidence that SSRIs could increase prolactin levels are largely from clinical trials of these drugs, often with a fairly short duration of use ranging from 1 to 12 weeks [20, 22-28, 31, 32] and only one study over one year [21]. We lacked detailed information on duration of AD and SSRI use, as NHS and NHS2 participants self-reported AD use every two years and at the time of blood draw. Thus, we do not have information on shorter vs. longer term use of ADs or SSRIs specifically. We observed that 57.5% of NHS SSRI users and 62.9% of NHS2 SSRI users had self-reported regular AD use across two or more consecutive biennial questionnaire cycles (data not shown). Continuous AD use was likely occurring in many of these participants, but the exact number is unknown. It is possible that SSRIs may have an acute effect on circulating prolactin levels, similar to reported short-term changes in prolactin associated with physical activity [39], but that these

effects are not sustained with long-term use, which represents the experience of the majority of SSRI users in NHS and NHS2. We were unable to evaluate this hypothesis in the present study, but additional research would be warranted to fully understand both the short- and long-term implications of SSRI use on prolactin levels. Also, we were unable to evaluate potential confounding by depression because data on depression diagnoses was not obtained prior to the blood draws.

These results should be considered in the context of a few potential limitations. First, AD use was self-reported, which may result in measurement error. We also lacked information on the dose and duration of AD and SSRI use. Additionally, information on AD class for the first blood sample in NHS was not available; these samples were taken at a time prior to SSRIs becoming the leading AD used in the U.S. Thus, the majority of AD use for the NHS first blood sample was likely non-SSRI medications, which could explain the lack of effect on prolactin levels. However, data on AD class were available for NHS2 and the second NHS blood sample, and no association between SSRI use and circulating prolactin levels was observed. Also, patients commonly switch between classes of ADs as they work with clinicians to manage their depression or other conditions. It is possible that some may have switched their AD between the blood draw and matched biennial questionnaire on which AD class was reported, which would cause non-differential exposure misclassification that would attenuate results. However, we expect the impact of such error to be minimal, and there was no indication of any effect of ADs overall, or SSRIs specifically, in this large study with appropriate power. Prolactin measurements exhibit moderate within-person variability, with a reported intra-class correlation coefficient of 0.45 over two to three years [11]; therefore non-differential exposure misclassification may have affected our results and obscured any true differences between AD users and non-users. Additionally, repeated prolactin measurements were made in separate batches; although we statistically corrected for batch effects, we cannot fully rule out laboratory draft as a source of error in our longitudinal analyses. Lastly, the NHS and NHS2 populations are quite homogeneous with respect to race/ethnicity and socioeconomic status, thus somewhat limiting the generalizability of our results. However, we are unaware of biologic differences in the serotonergic pathway across various racial/ethnic groups, therefore it is unlikely that biological pathways linking AD use to prolactin levels would vary substantially by race/ethnicity or socioeconomic status. Future studies replicating our results in more diverse populations would be useful.

Strengths of our study in comparison to previous work derive from the large established cohorts, which may better represent the experience of the general population of women than previous work. We also utilized extensive participant data from the NHS and NHS2 to adjust prolactin levels for potential confounders, such as age and menopausal status. Prolactin measurements were highly reliable and have previously been related to breast cancer risk in these cohorts. We also had sufficient numbers to evaluate interactions between AD use and a number of breast cancer risk factors, which prior studies have not considered. Additionally, we had the ability to look prospectively, albeit in a small sample, to evaluate whether initiation or cessation of AD use impacted prolactin levels over a long period; this question had not been addressed previously, but is an important factor to understand when considering the safety profile of ADs.

In conclusion, we found no evidence that AD use, SSRI or otherwise, is linked to elevated prolactin levels at the population-level, although prolactin levels may be affected by AD use in obese women. We also cannot exclude a modest within-woman increase, regardless of BMI. Furthermore, if AD use is separately related to breast cancer risk as has been hypothesized [40, 41], then these data do not support increased prolactin levels as the potential underlying mechanism. Future work in these cohorts will evaluate ADs as a risk factor for breast cancer to provide a more definitive answer. ADs represent an important and effective tool for treating depression, which is a highly prevalent condition and major source of morbidity among U.S. women. Although additional work is needed to confirm and extend these findings, especially the potential for increased prolactin levels observed among obese AD users, these results provide some evidence that use of ADs to treat depression or other conditions do not appear to substantially increase prolactin levels in the majority of women.

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Table 1

Age-standardized characteristics of the study population at time of initial blood sample by study cohort and antidepressant (AD) use status

	NHS 1 st Blood Sample		NHS 2 nd Blood Sample		NHS2	
	No AD use (n=3027)	AD use (n=140)	No AD use (n=543)	AD use (n=67)	No AD use (n=1278)	AD use (n=148)
Age, years ^a ; Mean (SD)	56.7 (7.0)	56.4 (7.4)	67.6 (6.7)	66.9 (7.3)	44.3 (4.4)	45.6 (4.2)
Body mass index, kg/m ² ; Mean (SD)	25.5 (4.5)	26.3 (3.4)	26.3 (5.0)	27.6 (3.2)	26.1 (4.3)	27.7 (3.9)
Caucasian race, %	98.7	99.4	99.5	100.0	98.4	99.0
Depressive symptoms ^b	4.7	21.4	3.2	48.8	2.1	13.2
Prolactin, ng/mL; Mean (SD)	11.0 (1.6)	11.0 (1.3)	11.0 (1.6)	11.0 (1.3)	13.5 (1.5)	13.5 (1.3)
Elevated prolactin level (>11 ng/mL) ^c , %	47.0	48.0	45.8	44.1	65.9	67.5
Parity						
No children, %	6.3	9.4	5.9	9.0	16.8	23.5
1 child, %	7.3	5.0	7.3	10.5	13.8	14.4
2 children, %	29.0	27.8	25.5	26.3	39.1	35.5
3 children, %	28.2	30.4	29.6	20.9	20.0	22.1
4+ children, %	29.2	27.4	31.6	33.3	10.4	4.5
Menopausal status/PMH use						
Premenopausal, %	35.4	23.6	1.2	0.0	85.8	81.4
Postmenopausal/No PMH, %	33.6	27.7	42.5	34.2	2.5	3.9
Postmenopausal/PMH use, %	19.4	28.6	55.8	64.7	11.7	14.7
Unknown, %	11.6	20.1	0.5	1.1	0.0	0.0
Age at menopause						
Premenopausal, %	37.1	26.0	1.2	0.0	85.8	81.4
<40, %	2.7	5.8	3.6	4.6	3.4	6.5
40-49, %	20.9	17.2	30.0	32.3	4.8	4.2
50-54, %	35.6	49.7	57.4	62.6	6.0	7.9
55, %	3.7	1.3	7.8	0.6	0.0	0.0
Total physical activity, METs/wk; Mean (SD)	15.8 (20.3)	11.7 (8.8)	20.7 (22.7)	17.2 (9.2)	20.2 (18.0)	12.8 (7.7)
Alcohol intake, g/d; Mean (SD)	5.1 (8.4)	3.1 (3.7)	5.5 (8.6)	4.2 (4.1)	4.4 (5.2)	4.2 (5.2)
Smoking status						
Never smoked, %	47.5	42.4	45.4	46.3	68.1	51.9
Past smoker, %	41.8	35.9	49.4	51.1	24.9	35.6
Current smoker, %	10.7	21.7	5.2	2.5	7.0	12.5
Current steroid use, %	1.6	11.8	1.4	0.0	0.6	0.4
Current thyroid hormone use, %	11.0	20.9	19.6	29.4	10.2	10.6

^aValue is not age adjusted

^bBased on MHI-5 score from nearest NHS/NHS2 questionnaire; for NHS 1st blood the questionnaire (1992) following the blood draw was used

^cElevated prolactin level (>11 ng/mL) based on levels previously associated with increased breast cancer risk in NHS/NHS2 analyses

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Table 2
Multivariable adjusted associations between AD use and prolactin levels for NHS 1st blood draw and NHS2

	N	Age-adjusted Geometric Mean Prolactin (95% CI), ng/mL	Multivariable Adjusted ^d Geometric Mean Prolactin (95% CI), ng/mL	P value	Multivariable Adjusted ^d OR for Elevated Prolactin Level (95% CI) ^b	P value
No AD use	4030	11.6 (11.4-11.7)	11.6 (11.4-11.7)	0.23	1 (reference)	0.26
AD use	267	12.1 (11.4-12.8)	12.0 (11.3-12.7)		1.17 (0.89-1.53)	
Underweight/Normal (<25 kg/m ²)				0.02 ^c		0.17 ^c
No AD use	2238	11.8 (11.5-12.0)	11.7 (11.5-12.0)		1 (reference)	
AD use	123	11.6 (10.7-12.7)	11.6 (10.6-12.7)		0.99 (0.67-1.46)	
Overweight (25-<30 kg/m ²)						
No AD use	1136	11.6 (11.2-11.9)	11.6 (11.3-11.9)		1 (reference)	
AD use	81	11.4 (10.2-12.7)	11.5 (10.3-12.8)		1.05 (0.65-1.71)	
Obese (≥ 30 kg/m ²)						
No AD use	656	10.9 (10.5-11.3)	11.0 (10.5-11.4)		1 (reference)	
AD use	63	13.7 (12.2-15.4)	13.2 (11.7-15.0)		1.99 (1.11-3.58)	

^a Adjusted for age (continuous), BMI (continuous), alcohol use (continuous), menopausal status/PMH use (premenopausal, postmenopausal without PMH use, postmenopausal with PMH use, unknown), parity (0, 1, 2, 3, 4+ children), smoking status (never, past, current), steroid use (no, yes)

^b Elevated prolactin level defined as > 11 ng/mL based on levels previously associated with increased breast cancer risk in NHS/NHS2

^c P value for interaction of AD use and BMI category

Table 3

Multivariable adjusted associations between AD use and prolactin levels for NHS 2nd blood draw and NHS2

	N	Age-adjusted Geometric Mean Prolactin (95% CI), ng/mL	Multivariable Adjusted ^a Geometric Mean Prolactin (95% CI), ng/mL	P value	Multivariable Adjusted ^a OR for Elevated Prolactin Level (95% CI) ^b	P value
No AD use	1779	13.1 (12.8-13.4)	13.1 (12.8-13.4)	0.88	1 (reference)	
SSRI use	140	13.2 (12.1-14.3)	13.2 (12.2-14.4)		0.95 (0.66-1.38)	0.80
non-SSRI AD use	47	12.7 (11.0-14.7)	12.7 (11.0-14.6)		0.77 (0.42-1.42)	0.40
Underweight/Normal (<25 kg/m ²)				0.04 ^c		0.69 ^c
No AD use	948	13.4 (13.0-13.8)	13.3 (12.9-13.8)		1 (reference)	
SSRI use	56	13.0 (11.4-14.8)	13.2 (11.6-15.0)		0.44 (0.11-1.74)	
non-SSRI AD use	21	11.4 (9.2-14.1)	10.9 (8.9-13.5)		0.40 (0.04-4.00)	
Overweight (25-30 kg/m ²)						
No AD use	491	13.0 (12.4-13.6)	13.1 (12.5-13.7)		1 (reference)	
SSRI use	41	12.1 (10.4-14.1)	12.1 (10.4-14.1)		0.46 (0.07-2.87)	
non-SSRI AD use	13	16.5 (12.6-21.8)	16.8 (12.8-22.0)		1.18 (0.27-5.20)	
Obese (>30 kg/m ²)						
No AD use	340	12.4 (11.8-13.1)	12.6 (11.9-13.3)		1 (reference)	
SSRI use	43	14.0 (12.1-16.2)	14.2 (12.2-16.4)		1.35 (0.38-4.86)	
non-SSRI AD use	13	11.8 (9.0-15.5)	12.0 (9.2-15.7)		1.41 (0.26-7.62)	

^a Adjusted for age (continuous), BMI (continuous), alcohol use (continuous), menopausal status/PMH use (premenopausal, postmenopausal without PMH use, postmenopausal with PMH use, unknown), parity (0, 1, 2, 3, 4+ children), smoking status (never, past, current), steroid use (no, yes)

^b Elevated prolactin level defined as >11 ng/mL based on levels previously associated with increased breast cancer risk in NHS/NHS2

^c P value for interaction of AD use and BMI

Table 4

Association between consistency of AD use and adjusted mean prolactin levels between 1st and 2nd blood draws in NHS^a

Prolactin level (ng/mL) Multivariable Adjusted Geometric Mean (95% CI)					
	N	1 st Blood Draw ^b	2 nd Blood Draw ^b	Change (2 nd -1 st) ^c	P value
AD use status					
No AD use	491	11.0 (10.5-11.5)	11.1 (10.6-11.6)	1.01 (0.97-1.06)	0.82
Started use	49	9.5 (8.2-11.0)	10.6 (9.2-12.2)	1.07 (0.93-1.23)	
Stopped use	8	10.3 (7.2-14.7)	9.9 (7.0-14.1)	0.95 (0.67-1.35)	
AD user	14	10.6 (8.1-13.9)	12.4 (9.5-16.3)	1.09 (0.84-1.42)	
AD use with SSRI status at 2 nd blood					
No AD use	491	11.0 (10.5-11.5)	11.1 (10.6-11.6)	1.01 (0.97-1.06)	0.81
Started non-SSRI	24	9.9 (8.0-12.1)	11.4 (9.3-14.0)	1.14 (0.93-1.39)	
Stopped AD use	8	10.3 (7.2-14.8)	9.9 (7.0-14.1)	0.95 (0.67-1.35)	
Non-SSRI user	10	10.0 (7.2-13.7)	12.0 (8.8-16.4)	1.17 (0.86-1.59)	
Started SSRI	25	9.2 (7.5-11.2)	9.8 (8.1-12.0)	1.00 (0.82-1.22)	
SSRI user	4	12.5 (7.5-20.8)	13.9 (7.9-24.5)	0.93 (0.57-1.53)	

^aMean time between blood draws 11.1 (SD 0.5) years

^bAdjusted for concurrent age (continuous), BMI (continuous), alcohol use (continuous), menopausal status/PMH use (premenopausal, postmenopausal without PMH use, postmenopausal with PMH use, unknown), parity (0, 1, 2, 3, 4+ children), smoking status (never, past, current), steroid use (no, yes)

^cAdjusted for baseline age (continuous), baseline prolactin (continuous), baseline BMI (continuous), change in BMI (continuous), baseline alcohol use (continuous), baseline menopausal status/PMH use (premenopausal, postmenopausal with PMH use, postmenopausal without PMH use, unknown), parity (0, 1, 2, 3, 4+ children), baseline smoking status (never, past, current), baseline steroid use (no, yes)