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Alcohol, cigarette smoking, and ovarian reserve in reproductive-age African-American women

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Abstract

Background—While alcohol consumption and cigarette smoking are common behaviors in reproductive-age women, little is known about the impact of consumption patterns on ovarian reserve. Even less is known about the effects of smoking and alcohol use in reproductive age African-American women.

Objective—To examine the impact of patterns of alcohol intake and cigarette smoking on anti-Müllerian hormone levels as a marker of ovarian reserve in African-American women.

Study Design—Cross-sectional analysis from the baseline clinical visit and data collection of the Study of Environment, Lifestyle and Fibroids performed by the National Institute of Environmental Health Sciences. A total of 1,654 volunteers, aged 23–34 years, recruited from the Detroit, Michigan community completed questionnaires on alcohol intake and cigarette smoking and provided serum for anti-Müllerian hormone measurement. Multivariable linear and logistic regression were used as appropriate to estimate the effect of a range of exposure patterns on anti-Müllerian hormone levels while adjusting for potential confounders including age, body mass index and hormonal contraception.

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These findings were presented as an oral presentation at the 71st Annual Meeting of the American Society for Reproductive Medicine in Baltimore, Maryland, October 17-21, 2015 (alcohol consumption variables) and as an oral presentation at the 63rd Annual Meeting of the Society for Reproductive Investigation in Montreal, Canada (Quebec Province), March 16-19, 2016 (cigarette smoking variables).

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Results—Most participants were alcohol drinkers (74%). Of those, the majority (74%) engaged in binge drinking at least once in the last year. Women who reported binge drinking twice weekly or more had 26% lower anti-Müllerian hormone levels compared to current drinkers who never binged (CI: -44, -2, $P < 0.04$). Other alcohol consumption patterns (both past and current) were unrelated to anti-Müllerian hormone. The minority of participants currently (19%) or formerly (7%) smoked and only 4% of current smokers used a pack a day or more. Neither smoking status nor secondhand smoke exposure in utero, childhood or adulthood was associated with anti-Müllerian hormone levels.

Conclusion—Results suggest that current, frequent binge drinking may adversely impact ovarian reserve. Other drinking and smoking exposures were not associated with anti-Müllerian hormone in this cohort of healthy, young African-American women. Longitudinal study of how these common lifestyle behaviors impact variability in age-adjusted anti-Müllerian hormone levels is merited.

Keywords

alcohol; anti-Müllerian hormone; cigarette smoking; ovarian reserve; secondhand smoke

Introduction

Anti-Müllerian hormone (AMH) is a marker of ovarian reserve widely used in clinical practice^{1–3} and increasingly used as a tool in epidemiologic studies of potential ovarian toxicants.^{4–6} Despite educational campaigns on associated health risks, excessive alcohol consumption and cigarette smoking remain frequent behaviors in the U.S.⁷ Heavy alcohol consumption is increasingly common in reproductive-age women⁸, even those seeking conception⁹, and has been associated with decreased in vitro fertilization (IVF) cycle success.¹⁰ Cigarette smoking has established adverse effects on short and long-term fertility^{11–13} yet remains a common practice in the U.S., where 1 in 5 women smoke.¹⁴ Accordingly, whether alcohol intake and smoking behaviors influence fertility is a question of significant public health concern.^{9, 10}

Existing literature on alcohol intake and AMH levels is limited and suggests a possible differential impact of alcohol on AMH levels by ethnicity. Studies failed to identify a relationship with drinking and AMH levels¹⁵ or antral follicle count (AFC) in predominantly Caucasian cohorts¹⁶ but suggest worse ovarian reserve testing among black South African women¹⁷ and Japanese women¹⁸ who drink. Disparate results may be attributable to racial differences in AMH¹⁹, cultural differences in alcohol consumption not reflected by the exposure variables ascertained, or methodological differences in characterizing the exposure.²⁰

Evaluation of the impact of cigarette smoking on AMH levels has also produced discordant findings suggesting a differential impact by age. Among perimenopausal women, current smoking was associated with lower AMH levels.^{21, 22} While one large study identified an inverse, dose-dependent association of smoking with AMH levels¹⁵, other investigations failed to reproduce an association between current smoking and AMH levels.^{16, 23, 24} The influence of passive smoke exposure on AMH has been sparsely studied but one

investigation demonstrated lower AMH levels among healthy black South African women who reported passive smoke exposure.¹⁷

To characterize the influence of these common lifestyle exposures on ovarian reserve in the understudied African-American population, we assessed the duration, frequency, amount and pattern of use (e.g. binge drinking, cumulative alcohol exposure, cigarettes per day, and passive smoke exposure in utero, childhood and adulthood). We hypothesized that increased frequency and duration of alcohol consumption, cigarette smoking and secondhand smoke exposure would be associated with lower AMH levels.

Materials and Methods

Study Participants

A volunteer community sample of 1,696 African-American women in the Detroit, Michigan area were enrolled in an ongoing prospective cohort study, the Study of Environment, Lifestyle and Fibroids (SELF), whose primary objective is to study the incidence of fibroids in African-American women. Participants were 23 through 34 years of age at the time of recruitment and without a known history of uterine leiomyomata at the time of examination from November 2010 through December 2012. Recruitment and data collection procedures have been previously described.^{25, 26} Women with a history of hysterectomy, autoimmune disease or any cancer treated with radiation or chemotherapy were excluded.

Eligible participants who completed telephone interviews, all enrollment questionnaires and a clinic visit were enrolled. Participants provided written informed consent. The study was approved by the institutional review boards of the National Institute of Environmental Health Services and the Henry Ford Health System.

Exposure Ascertainment

Data on patient demographics, reproductive and medical histories were self-reported. Participants provided information on drinking, smoking and passive smoke exposure via self-administered computer-assisted web interviewing (CAWI) questionnaires created specifically for use in the SELF study.^{25, 26} Comprehensive questionnaires assessed the duration, frequency and amount of alcohol consumption, cigarette smoking and secondhand smoke exposure both currently, defined as within the last year, and at the time of maximum consumption.

Women answered questionnaires regarding alcohol intake, including history of regular drinking, age of initiation, number of drinks consumed in the last year and when drinking the most based on frequency of drinking and number of drinks consumed on days of consumption, frequency of binge drinking (4 or more drinks at single occasion) in last year and when drinking the most.” Women were categorized as ever drinkers if they reported a history of drinking at least 10 drinks in any one year and current drinkers if they reported drinking at least 10 drinks in the last year. Binge drinking was defined as consumption of four or more drinks on one occasion.²⁷

Consumption level was categorized as low (drinking less than once a week and never bingeing), moderate (drinking up to 2 days per week or binge drinking no more than monthly) and heavy (drinking more than 2 days per week or bingeing twice monthly or more). Cumulative alcohol exposure was denoted by level of consumption (low, moderate, high) and duration of drinking (years). In women with a history of heavy alcohol consumption, the impact of current drinking was assessed to evaluate the permanence of any association with heavy drinking and AMH levels.

Smoking questionnaires assessed history of ever smoking, age of initiation, age of cessation for past smokers, current number of cigarettes smoked per day as well as number of cigarettes smoked per day at the time of heaviest consumption. Regular smoking was defined as smoking at least 1 cigarette per day for more than 6 months. Participants answered questions regarding secondhand, or passive, smoke exposure, including caregiver smoked in home in childhood, number of years living with smoker in childhood, in utero smoke exposure, current passive smoke exposure in the home, proportion of time in adulthood living with smoker in home, and total number of hours per week when participant can smell tobacco smoke. Passive exposure to smoke in utero, childhood and adulthood were also assessed. To capture the impact of secondhand smoke as both an isolated and cumulative smoke exposure, passive exposure was separately assessed in non-smokers and again in all women.

Participants provided serum for AMH measurement during their clinic visit. Cycle day was not included in our analysis due to the low inter- and intra-cycle variability with AMH.²⁴ Stored serum aliquots were assayed at the Clinical Laboratory Research Core within the Pathology Department at Massachusetts General Hospital. Serum AMH was measured using the picoAMH ELISA (lower limit of detection 0.0016 ng/ml, 1 ng/ml=7.14 pmol/l) (Ansh Labs, Webster, TX). Samples were run at a 1/10 dilution, then neat for the samples that were low. AMH values that remained below the lower limit of detection (n=3) were assigned a value of 0.0011 ng/mL using an established formula.²⁸ The AMH ELISA has intra- and interassay coefficients of variation 6.9% and 6.5% respectively.

Statistical Analysis

The relationship among alcohol consumption variables and AMH levels in the cohort were assessed using multivariable-adjusted linear and logistic regression models. AMH levels were log-transformed to account for non-normal distribution and all models were adjusted for age, BMI, and current hormonal contraception (HC), variables that were previously shown to be significantly associated with AMH levels in this cohort.²⁹ Recognizing the non-linear association between age and ovarian reserve, main effects models included both an age and an age quadratic term. Considering the natural, age-related decline in AMH levels occurring at 25 years,^{30–31} sensitivity analyses were performed to examine interactions between age and exposure variables. This allowed for an age-related decline in AMH to differ between exposed compared to unexposed participants. Because non-drinkers may represent a highly selected group in the U.S., as suggested by a J-shaped distribution for the effects of alcohol on adverse health outcomes³², a separate analysis was restricted to current drinkers, as has been done in previous investigations³³.

Linear regression models with log AMH as the dependent variable generated adjusted estimates of β associated with each exposure of interest. Percent differences and 95% confidence intervals (CIs) in serum AMH between exposure groups were calculated from the β s as follows $[\exp(\beta) - 1] * 100$ and presented with corresponding 95% confidence intervals (CIs) or p-values. Significant associations in linear regression models were further explored in multivariable-adjusted logistic regression models to assess odds of diminished ovarian reserve (DOR), defined as AMH <1, and CIs.

All analyses were carried out using Statistical Analysis Software version 9.4 (SAS Institute, Cary, NC). Continuous variables are presented as means or medians with (standard deviation or interquartile ranges). Potential confounders were assessed using simple linear regression and were considered for addition to the final model if they changed the risk ratio by more than 10%³⁴. Statistical significance was assumed for $p < 0.05$.

Results

A total of 1,654 reproductive-aged African-American women submitted comprehensive questionnaires on alcohol consumption and provided serum for AMH measurement. The mean age of participants was 29 years, median serum AMH concentration was 3.2 ng/mL, and most women were obese with a median BMI of 32 kg/m². Additional demographic details are presented in Table 1 and median AMH levels by age are presented in Figure 1.

Alcohol consumption

The majority (74%) of participants reported current (71%) or former (3%) drinking. The average age of drinking initiation was 20(± 3.3) years and most drinkers (84%) reported their heaviest consumption occurred after their teen years. Of all participants, 25% reported weekly or more frequent drinking and 54% reported binge drinking in the last year. When analysis was restricted to women who currently drink ($n=1168$), most (74%) reported binge drinking in the last year and of these, 26% reported binge drinking multiple times per month.

When drinkers and non-drinkers (reference category) were compared, there were no significant associations between AMH levels and any of the numerous drinking behaviors assessed, including past and current behaviors (Table 2). This included no association of current alcohol intake with AMH levels among women with a history of prior heavy alcohol intake. However, those who binge drank twice a week or more had a 21% lower AMH level compared to those who never drink (CI: -41, 7) (Table 2).

When analyses were limited to current drinkers, the influence of high frequency bingeing on AMH levels was stronger. Among women who reported binge drinking twice weekly or more frequently had 26% lower AMH levels compared to current drinkers who never binged (CI: -44, -2; $P=0.036$, Figure 1). This did not translate to increased odds of diminished ovarian reserve (OR: 0.85, CI: 0.5–2.7, $P=0.39$). Figure 1 demonstrates associations between binge drinking patterns and AMH levels among current drinkers. There was no association with teenage drinking, frequency or duration of drinking, current heavy drinking or ever bingeing (results not presented).

Cigarette smoking

Most women (73%) never smoked regularly, 7% formerly smoked and 19% were current smokers. Among current smokers, only 4% smoked a pack or more a day. The average age of smoking initiation was 18($\pm$ 4) years, cessation was 25($\pm$ 4) years and average duration of smoking was 6($\pm$ 5) years, none of which were associated with AMH levels (all $P>0.05$, Table 3).

Secondhand smoke exposure

When assessing the influence of environmental smoke exposure in never smokers, main results demonstrate no association between AMH levels and in utero, childhood and current secondhand exposure (all $P>0.05$, Table 3). There was no significant association for high passive smoke exposure as measured by the number of hours per day smelling smoke (31% lower for women with 10+ hours compared to those with none, CI -60, 20). Relationships remained nonsignificant when the analysis sample was expanded to include smokers rather than being limited to non-smokers (results not presented).

Age sensitivity analyses

Sensitivity analyses showed no significant exposure effects on the age-related rate of AMH decline for drinking and smoking-related variables (data not shown).

Comment

This work assessed the influence of patterns of alcohol consumption, cigarette smoking and passive smoke exposure on ovarian reserve as measured by AMH levels³⁵ in reproductive-aged African-American women. Major findings include an inverse association with frequent binge drinking and AMH levels in current drinkers. To our knowledge this is the first study to evaluate the impact of alcohol consumption and cigarette smoking on AMH levels in this demographic and the first in any population to evaluate how *patterns* of exposure to alcohol (e.g. binge drinking) and cigarette smoke (e.g. passive childhood and in utero smoke exposure) influence AMH. The comprehensive questionnaire permitted detailed assessment of current and former consumption patterns. Findings imply that current, frequent binge drinking may adversely impact AMH levels but that less heavy drinking, cigarette smoking and passive smoke exposure do not influence AMH levels in a cohort of healthy, young African-American women.

Though the impact of binge drinking on AMH has not been previously assessed, our finding of lower AMH levels in frequent binge drinkers is consistent with a Japanese study demonstrating worse ovarian function in current heavy drinkers¹⁸. Loss of significance when comparing frequent binge drinkers to never drinkers may reflect an “unhealthy non-drinker” effect^{33, 36}. On the other hand, the number of women with heavy exposure was small, and there was no suggestion of a dose-response, so the association may be a chance finding. However, there is biological plausibility for the detrimental effects of binge drinking. Acute alcohol ingestion has been associated with increased estradiol levels³⁷ and gonadotropins are cleared by the liver³⁸ such that alcohol-induced alterations in hepatic catabolism of estradiol or gonadotropins may impact hypothalamic-pituitary axis signaling. Alternatively, repeated

large volume alcohol exposures may overwhelm the protective mechanisms of the granulosa complex.³⁹ In our study population, AMH levels began declining at 25 years of age, in keeping with previous studies, such that that binge drinking in the late twenties might accelerate the natural decline of AMH.^{29–31, 40} Considering that binge drinking is common in young women in the U.S.,⁷ this finding is important to examine further.

The null associations between a wide range of alcohol drinking behaviors and AMH levels are in keeping with prior studies that failed to identify associations of AMH levels with ever drinking, daily consumption and number of drinks per day in Caucasian women.^{15, 16} Null associations between alcohol consumption patterns and AMH levels may reflect the durability of the protective mechanisms of the granulosa cells in reproductive-age women.³⁹ It is plausible that current heavy, alcohol consumption negatively impacts fertility and IVF outcomes¹⁰ but that this impact is temporary in the absence of repeated large volume exposures sufficient to cause permanent liver damage. Our finding that prior heavy alcohol intake was not associated with AMH levels but that current frequent binge drinking is associated with lower AMH levels supports this assertion, though future investigation assessing AMH levels by current drinking status among women with a history of frequent binge drinking is merited.

With regard to smoking, our results provide a detailed assessment of the impact of active and passive smoking in young women but are limited by small numbers of heavy smokers. Findings of the present work are consistent with studies that failed to identify a relationship with current smoking and AMH levels in young, healthy women.^{6, 21, 23, 24} On the other hand, studies in late reproductive-age and perimenopausal women^{15, 21} demonstrate decreased AMH levels in current smokers. Consistent with prior research demonstrating that menopause occurred 0.3–1.2 years earlier in middle-aged smokers,⁴¹ a recent genomic study identified an increased rate of follicular decline in middle-aged smokers, and used this finding to argue that an increased rate of follicular decline due to smoking might only be evident at mid-life.²² Considering the well-established relationship of smoking on premature ovarian aging^{42–44} it's plausible that smoking is associated with ovarian aging but that this is either not evident in younger women based on AMH or was not detected due to a low frequency of heavy smoking in our cohort.

Strengths of this study included novel investigation of the impact of alcohol intake and cigarette smoking on AMH levels in healthy, reproductive-aged African-American women. Comprehensive questionnaires permitted detailed characterization of exposure. Prevalence of lifestyle behaviors in our population was comparable to national estimates including prevalence of current drinking (71 vs. 80%, respectively), binge drinking (current smoking (19% vs. 18%),¹⁴ suggesting external validity. A large sample size further allows for external validity within the reproductive-aged female African-American population.

Limitations included cross-sectional analysis and use of a single ovarian reserve marker. However, AMH was measured using a sensitive and reliable (<7% coefficient of variation) assay and studies show high correlation between antral follicle counts and AMH.⁴⁵ The SELF study was not initially powered to detect associations between alcohol intake and AMH. Consequently, we cannot be certain whether our null associations are attributable to

an actual lack of association or to inadequate statistical power. An entirely African-American study population preserves internal validity, fills a gap in the AMH literature that predominantly involves white women but may limit generalization to populations with other demographic compositions. Our self-reported data introduces the possibility of under-reporting (social desirability bias), though this was reduced by the use of a self-administered computer-assisted web interviewing questionnaire⁴⁶. In addition, self-reported smoking data has been validated previously with serum cotinine measures for both African-Americans and Caucasians^{47–48}. Alcohol intake was collected with both the computer-assisted web interview (CAWI) developed for SELF and the web-based Block 2005 Food Frequency Questionnaire⁴⁹ and these surveys were completed at different times for most women. For analysis, data from the CAWI was used because the alcohol questions were more extensive and response categories allowed for reporting of higher alcohol intake. Still, the correlation between the two surveys for number of drinks per month during the past year was 0.75, indicating good reliability.

This study found that AMH levels were 26% lower in women who engage in current, frequent binge drinking even after adjustment for age, BMI, and hormone use. Other patterns of current and past alcohol consumption, cigarette smoking and smoke exposure were not associated with AMH. Remaining gaps in knowledge include assessment of whether threshold levels of exposure exist above which ovarian protective mechanisms are overwhelmed and whether the impairment in ovarian reserve as a result of repeated binge drinking represents a temporary insult, as our results suggest, or rather a permanent reduction in ovarian reserve. Reproduction of results in prospective investigations would confirm the findings presented herein. The study of longitudinal changes in AMH as a result of lifestyle factors would inform the transience of permanence of such associations over time and better characterize the impact of these common lifestyle behaviors on ovarian reserve.

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Figure 1.
Median AMH (ng/mL) by age (years) (n=1654)

Figure 2.

Binge drinking pattern and AMH levels among 1168 current drinkers

Frequent binge: binge drinking at least twice weekly vs never bingers

Weekly binge: binge drinking at least once a week vs never bingers

Biweekly binge: binge drinking at least every 2 weeks vs never bingers

Monthly binge: binge drinking monthly or less vs never bingers

Table 1

Demographic characteristics 1,654 reproductive-aged African-American women

Demographic characteristic	N=1654 (100) ^a
AMH, ng/mL (median, IQR; range)	3.2, 1.7–5.3; <0.002–39
Age ^b , y (mean $\pm$ SD; range)	29 $\pm$ 4; 23–35
Body mass index, kg/m ² (median, IQR; range) ^c	32, 26–40; 16–79
Education (%)	
High school or less	367 (22)
Some college, but no degree	623 (38)
Bachelor's, associate or graduate degree	663 (40)
Mean number of pregnancies ^d (mean $\pm$ SD range)	3 $\pm$ 2; 1–15
Current contraception use (%)	454 (27)
History of polycystic ovarian syndrome (%)	52 (3)
Drinking	
Never	438 (26)
Ever	1216 (74)
Former	48 (3)
Current	1168 (71)
Smoking	
Never	1213 (73)
Former	123 (7)
Current	318 (19)
<10 cig/day	233 (14)
10–14 cig/day	57 (3)
15+ cig/day	28 (2)
In utero smoke exposure ^e	
Yes	160 (13)
No	1053 (87)
Childhood smoke exposure ^f	
Yes	633 (55)
No	513 (45)
Current secondhand smoke exposure ^g	
Yes	204 (17)
No	1008 (83)

Regression model adjusted for age, age², BMI and hormonal contraception use.

^aNo. (%) = 1654(100), unless otherwise indicated. Column totals may not sum to 100% due to rounding.

^bWomen ages 23–34 were recruited; some were 35 by the time all baseline activities and enrollment were completed.

^cNine women missing

^dAmong 1212 gravid women

^eAmong 1213 never smokers

^fAmong 1146 never smokers; 67 missing

^gAmong 1212 never smokers; 1 missing

Table 2

Associations of alcohol intake on anti-Müllerian hormone (AMH) levels among 1,654 reproductive-aged African American women

Alcohol variables	Descriptive statistics	% in AMH ^b (95% CI) ^c
Total Sample	N=1654 (100)	
Drinking status		
Ever drinkers	1216 (74)	3 (−8, 16)
Current drinkers	1168 (71)	3 (−9, 16)
Former drinkers	48 (3)	8 (−22, 49)
Never drinkers	438 (26)	Referent
Alcohol intake during years drank		
Heavy	330 (20)	0 (−14, 17)
Medium	755 (46)	4 (−9, 18)
Low	131 (8)	8 (−13, 33)
Never drinkers	438 (27)	Referent
Cumulative alcohol exposure ^a		
Heavy intake, 10 years	118 (7)	3 (−18, 28)
Heavy intake, 5–9 years	104 (6.5)	−7 (−26, 18)
Heavy intake, 1–4 years	108 (7)	4 (−17, 32)
Medium intake, 10 years	143 (9)	7 (−14, 31)
Medium intake, 5–9 years	247 (15)	−4 (−19, 14)
Medium intake, 1–4 years	365 (22)	8 (−7, 25)
Low intake, 10 years	8 (0.5)	−6 (−56, 101)
Low intake, 5–9 years	22 (1)	6 (−34, 69)
Low intake, 1–4 years	101 (6)	9 (−14, 38)
Never drinkers	438 (26)	Referent
Current vs. Never drinkers	N=1606 (97)	
Current intake		
Heavy	347 (22)	−1 (−15, 16)
Medium	562 (35)	6 (−8, 21)
Low	259 (16)	3 (−13, 22)
Never drinkers	438 (27)	Referent
Binging in last year		
2 or more times per week	58 (4)	−21 (−41, 7)
Once a week	63 (4)	20 (−10, 61)
2 to 3 times per month	189 (12)	−1 (−18, 20)
Once a month or less	556 (35)	7 (−6, 23)
None	302 (19)	0 (−15, 17)

Alcohol variables	Descriptive statistics	% in AMH ^b (95% CI) ^c
Never drinkers	438 (27)	Referent
Current intake in past heavy drinkers ^a	N=1108	
Heavy past, heavy current	330 (30)	0 (-15, 18)
Heavy past, medium current	242 (22)	1 (-16, 21)
Heavy past, low current	98 (9)	8 (-17, 39)
Never drinkers	438 (40)	Referent

Low: drink weekly, never binge; Medium: drink twice weekly, binge monthly; Heavy: drink > twice weekly, binge > monthly

^a Among 670 women with a history of heavy past drinking and 438 never drinkers

^b Calculated using following formula: $[\exp(\beta) - 1] * 100$.

^c Multivariable-adjusted model adjusted for age, quadratic age², BMI and hormonal contraception use

Table 3

Associations of cigarette smoking and secondhand cigarette smoke exposure on anti-Müllerian hormone (AMH) levels among 1,654 reproductive-aged African American women

Cigarette smoking variables	Descriptive statistics	% in AMH (95% CI) ^e
Total Sample	N=1654 (100)	
Smoking status (%)		
Current	318 (19)	1.9 (−11.0, 16.6)
Former	123 (7)	7.5 (−12.2, 31.7)
Never	1213 (73)	Referent
Age at initiation of smoking (%)		
15 or younger	82 (5)	9.2 (−14, 39)
15–18	175 (11)	9.7 (−8, 30)
19–20	71 (4)	−3.2 (−25, 26)
21–23	74 (5)	3.0 (−20, 33)
24 and over	39 (2)	−20.0 (−44, 14)
Never smokers	1213 (73)	Referent
Current smokers	N=1531 (93)	
Current consumption		
< 10	233 (15)	−1 (−16, 15)
10–14	57 (4)	10 (−18, 48)
15–19	16 (1)	32 (−24, 126)
20	12 (1)	−7 (−50, 74)
Never smokers	1213 (79)	Referent
Max consumption (cig/day)		
< 10	179 (12)	−2 (−17, 17)
10–14	58 (4)	5 (−22, 40)
15–19	44 (3)	18 (−16, 64)
20	37 (2)	−3 (−33, 39)
Never smokers	1213 (79)	Referent
Years of smoking (y)		
< 1	6 (0.4)	46 (−44, 283)
1–2	14 (1)	−40 (−66, 8)
3+	298 (19)	4 (−10, 19)
Never smokers	1213 (79)	Referent
Former smokers	N=1336 (81)	
Max consumption (cig/day)		
< 10	96 (7)	8 (−15, 37)
10	27 (2)	7 (−30, 64)

Cigarette smoking variables	Descriptive statistics	% in AMH (95% CI) ^e
Never smokers	1213 (91)	Referent
Years of smoking (y)		
< 1	7 (1)	-13 (-62, 99)
1-2	31 (2)	-1 (-33, 48)
3+	84 (6)	14 (-11, 46)
Never smokers	1213 (91)	Referent
Never smokers	N=1213 (73)	
In utero exposure		
Yes or probably yes	160 (13)	5 (-13, 28)
No or probably no	1053 (87)	Referent
Childhood secondhand smoke exposure ^a		
Yes	633 (55)	9 (-5, 25)
No	513 (45)	Referent
Childhood years living with smoker(s)		
1 year	91 (8)	12 (-13, 44)
2 years	65 (5)	-12 (-34, 19)
3 years	42 (4)	29 (-10, 86)
4-6 years	67 (6)	-2 (-26, 31)
7-9 years	54 (4)	-11 (-34, 25)
10+ years	373 (31)	11 (-5, 29)
None	521 (43)	Referent
Time as adult living with smoker in home		
Very little of the time	241 (20)	11 (-6, 32)
Less than half the time	123 (10)	10 (-12, 37)
More than half the time	190 (16)	7 (-12, 28)
None of the time	659 (54)	Referent
Currently lives with smoker in home ^b		
Yes	204 (17)	-1 (-17, 18)
No	1008 (83)	Referent
Time able to currently smell smoke (hours/day)		
< 1	533 (44)	4 (-10, 21)
1	154 (13)	1 (-19, 25)
2	23 (2)	-1 (-39, 59)
3-4	54 (4)	1 (-27, 40)
5-9	40 (3)	-5 (-34, 38)
10+	18 (1)	-31 (-60, 20)
Unexposed	391 (32)	Referent

^aSixty-seven women missing

^bOne woman missing

^cMultivariable-adjusted model adjusted for age, age², BMI and hormonal contraception use.

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