INVESTIGATION OF COMBINED ORAL CONTRACEPTION AND BACTERIAL VAGINOSIS IN US PREMENOPAUSAL INDIVIDUALS

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ABSTRACT

The most common cause of vaginal discharge is bacterial vaginosis (BV). BV, a dysbiosis of the vaginal microbiome, is inhibited by lactic acid, and lactic acid production is supported by estrogen. Use of estrogen-containing combined oral contraception (COC) has been associated with decreased BV prevalence across several studies. However, most studies relied on self-report to ascertain COC use. We conducted a cross-sectional study of COC use and BV using data from the National Health and Nutrition Examination Survey (NHANES) 2001-2004 cycles; data on COC use was collected from two sources. During the household interview, participants were asked about prescription medication use in the past month. During the NHANES exam, in a private interview, participants were asked about the current use of birth control pills. Vaginal fluid was collected, Gram stained, and scored using the Nugent criteria for BV (scores of 0-3, 4-6, and 7-10 corresponded to negative, intermediate, and positive BV). Among non-pregnant, premenopausal individuals ages 20-49 (unweighted n=1460), we conducted multinomial logistic regression to estimate the adjusted odds ratios (aOR) and 95% confidence intervals (CI), accounting for the complex survey sampling design. The weighted prevalence of prescription medication-derived current COC use was 7%. Current COC use was associated with 67% lower odds of intermediate Nugent-score BV (aOR 0.33; 95%CI 0.18-0.63) and 83% lower odds of positive Nugent-score BV (aOR 0.17; 95%CI 0.07-0.42) compared to non-use. In contrast, the weighted prevalence of self-reported current OC use was 18%. For self-reported current OC use, we observed lower odds of intermediate Nugent-score BV (aOR 0.50, 95%CI 0.34-0.75) and positive Nugent-score BV (aOR 0.48; 95%CI 0.30-0.79). COC use based on prescription information yielded a stronger association than that based on self-report. Further research investigating the pharmaceutical aspects of COC use on BV prevalence is warranted.

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TABLE OF CONTENTS

INTRODUCTION

A healthy vaginal microbiome has low diversity and consists mostly of *Lactobacillus* species (Doyle et al., 2018). Bacterial vaginosis (BV) is a dysbiosis or imbalance of the vaginal microbiome that results from the replacement of the normal *Lactobacillus* microbiome with increased levels of anaerobic bacteria (Walensky, 2021). Symptoms, such as increased vaginal pH, fishy odor, and abnormal vaginal discharge are typical with BV (Walensky, 2021). BV is the most common cause of vaginal discharge in premenopausal individuals, affecting between 5.8% and 29.2% of premenopausal individuals in the United States (Kenyon et al., 2013). In addition to burdensome symptoms, BV requires clinical care for diagnosis and treatment with prescription medication and can frequently recur. Furthermore, BV is associated with an increased risk of sexually transmitted infections, including HIV, gonorrhea, chlamydia, and HPV (Walensky, 2021), and adverse reproductive outcomes, such as preterm birth, pelvic inflammatory disease, endometritis, and infertility (Zhou et al., 2007). Given the prevalence of BV and associated sequelae, understanding modifiable risk factors for BV is critical.

One such modifiable factor that is protective against BV is estrogen. Estrogen supports glycogen being deposited in the vaginal epithelium. Lactobacilli metabolize glycogen to produce lactic acid which lowers the vaginal pH (Boskey et al., 1999; Mirmonsef et al., 2014) and has antimicrobial effects on gram negative bacteria (O'Hanlon et al., 2011). Thus, the production of lactic acid inhibits BV. A common source of exogenous estrogen is oral contraception (OC), specifically combined oral contraception (COC) that contains estrogen. Consistent with the protective effect of estrogen on BV, a number of studies have reported decreased BV prevalence with estrogen-containing oral contraception. However, these studies primarily ascertained data

on OC use by self-report and used one source of information. In addition, most prior studies were conducted in the clinical setting, which may limit the generalizability of the results to the general population. Thus, the purpose of the present study was to examine the association between current COC use and BV using available data on COC use from two sources – prescription medication information and self-reported questionnaire data - in a sample representative of US premenopausal individuals.

METHODS

Study design

We conducted a cross-sectional analysis using data from the National Health and Nutrition Examination Survey (NHANES) 2001-2004 cycles. NHANES is designed to assess the health and nutritional status of the civilian non-institutionalized United States population (National Center for Health Statistics, 2013). To produce data representative of the U.S. population, NHANES uses a complex, multistage probability sampling design, oversampling select subgroups and applying weights (National Center for Health Statistics, 2013). NHANES is conducted in 2-year cycles with data collection occurring through a household interview and the mobile examination center (MEC) visit (National Center for Health Statistics, 2013). During the household interview, trained interviewers administer a series of questionnaires to participants by computer-assisted personal interview (National Center for Health Statistics, 2013). The MEC visit comprises a physical examination and biospecimen collection in a controlled and consistent environment, allowing for standardized data collection (National Center for Health Statistics, 2013). As part of the MEC visit, participants also completed a series of computerized questionnaires in a private setting (National Center for Health Statistics, 2013).

Ethics Statement

The Michigan State University Human Research Protection Program determined that this study did not involve human subjects.

Outcome ascertainment

Data on the outcome of interest, BV, was collected in the NHANES 2001-2004 cycles (National Center for Health Statistics, 2013). During the mobile examination component, NHANES female participants ages 14-49 years of age were provided instructions for the self-

collection of vaginal fluid with a swab (National Center for Health Statistics, 2003; National Center for Health Statistics, 2001; National Center for Health Statistics, 2003). The NHANES field staff used the swabs to prepare slides that were shipped to the Magee-Women's Hospital in Pittsburgh, Pennsylvania, for laboratory analysis (National Center for Health Statistics, 2003; National Center for Health Statistics, 2001; National Center for Health Statistics, 2003; National Center for Health Statistics, 2004). At the laboratory, the slides were Gram stained and examined with microscopy to quantify the amount of lactobacilli species, *Gardnerella vaginalis* and anaerobic Gram-negative rods, and *Mobiluncus* species present in the vaginal fluid (National Center for Health Statistics, 2001; National Center for Health Statistics, 2003). The amount of different microorganisms present was then scored from 0 to 10 following the Nugent criteria (Nugent et al., 1991), with a lower score indicating normal flora and no BV. The Nugent score was categorized and interpreted as follows: 0-3 (negative BV); 4-6 (intermediate BV), and 7-10 (positive BV) (National Center for Health Statistics, 2001; National Center for Health Statistics, 2003).

Exposure ascertainment

The exposure of interest was current oral contraceptive (OC) use. In the NHANES 2001-2004 cycles, these data were available from two sources. One source was prescription medication information collected during the household interview using the Prescription Medication Questionnaire. NHANES survey participants were asked about any prescription medication use in the past month (National Center for Health Statistics, 2005; National Center for Health Statistics, 2007). Those who used prescription medications in the past month were asked about the specific medications used and how many days the participant had been using that medication (National Center for Health Statistics, 2005; National Center for Health Statistics,

2007). Participants were also asked to show the NHANES interviewer the medication container (National Center for Health Statistics, 2005; National Center for Health Statistics, 2007). Each prescription medication and its ingredients were coded using its Multum Lexicon therapeutic classification as identified by the generic drug code variable (National Center for Health Statistics, 2005; National Center for Health Statistics, 2007). Within the Multum Lexicon classification, a Multum Lexicon Level 2 category value of sex hormones and Level 3 category value of contraceptives was indicative of OC use (National Center for Health Statistics, 2007). We identified participants using COCs, which contain both an estrogen component (ethinyl estradiol or mestranol) and a progestin component. Using this information, we categorized participants as current users of COCs (yes, no).

The other source of data on OC use was collected during the MEC visit by computer-assisted personal interview with the MEC interviewer using the Reproductive Health Questionnaire (National Center for Health Statistics, 2004; National Center for Health Statistics, 2006). This questionnaire included the questions, "Have you ever taken birth control pills for any reason?" and "Are you taking birth control pills now?" (National Center for Health Statistics, 2004; National Center for Health Statistics, 2006). These questions did not inquire about the type of OC used (e.g., progestin-only pill use or COC use). Using these data, we created a composite variable on the current use of OCs (yes, no).

In the NHANES 2001-2002 cycle, the Reproductive Health Questionnaire included the additional question on OC use, "Please look at this chart and show me the brand of pills that you currently use" (National Center for Health Statistics, 2004). For each OC brand reported, we identified the formulation using the U.S. Food and Drug Administration FDA-Approved Drugs

Database (Drugs@FDA), including the type and dose of the estrogen and progestin components. We categorized COC use by ethinyl estradiol dose (20, 30, 35, and ≥40 mcg).

Covariate ascertainment

Covariate data relevant to the present analyses were collected in the following manner. Demographic data on self-reported age in years, race, highest level of education obtained, and poverty income ratio (defined as the ratio of the family's annual family income to the poverty line) were collected during the household interview (National Center for Health Statistics, 2004; NCHS National Center for Health Statistics, 2005). During the MEC visit, data on current smoking status, current alcohol consumption status, and sexual behavior, including the number of sexual partners in the past year, were collected by audio computer-assisted self-interviewing; the MEC interviewer was not present for privacy (NCHS National Center for Health Statistics, 2013). Height and weight were measured and used to estimate body mass index (BMI) in kilograms per square meter (National Center for Health Statistics, 2004; NCHS National Center for Health Statistics, 2005). Data on vaginal douching in the past month was collected using the reproductive health questionnaire. (National Center for Health Statistics, 2004; National Center for Health Statistics, 2006).

Study population

For the present analyses, we used data from the NHANES 2001-2004 cycles for which data on BV was available. We restricted the study population to premenopausal individuals not currently pregnant and/or breastfeeding. The study population was restricted in this manner as endogenous estrogen varies substantially based on menopausal, pregnancy, and lactation status (Shorey, 2023; Agarwal et al., 2015). Starting with individuals ages 20-49 years who were identified by the NHANES interviewer as female and for whom data on BV were available

(unweighted n = 2326), we excluded individuals who had a history of hysterectomy (unweighted n = 169, missing unweighted n = 189), history of bilateral oophorectomy (unweighted n = 1, missing unweighted n = 1), and those who were postmenopausal (unweighted n = 98, missing unweighted n = 14), currently pregnant (unweighted n = 337, missing unweighted n = 3), and currently breastfeeding (unweighted n = 50, missing unweighted n = 4). This resulted in an analytic sample of 1460 individuals (unweighted n). Prescription medication data on COC use in the past 30 days were available for the full analytic sample (n = 1460 unweighted n); data on self-reported OC use from the reproductive health questionnaire were available for 1431 participants (unweighted), comprising 98% of the full analytic sample.

Statistical analyses

We descriptively examined the distribution of demographic and reproductive factors by current COC status and Nugent score BV status. We conducted multinomial logistic regression to estimate the adjusted odds ratios (aOR) and 95% confidence intervals (CI) for the association between current COC use and intermediate and positive Nugent-score BV. We evaluated prescription medication-derived current COC use and self-reported current OC use in separate analyses. We selected variables *a priori* for adjustment using a directed acyclic graph (Supplemental Figure 1) and identified two models for adjustment. In Model 1, we adjusted for age (continuous) and education (≤ high school, > high school). In Model 2, we adjusted for Model 1 adjustment variables as well as for the number of sexual partners in the past year (≤ 1, > 1 partner), current smoking (yes, no), and current alcohol consumption status (yes, no). All analyses accounted for the complex survey sampling design and were conducted using SAS statistical software (version 9.4; SAS Institute Inc., Cary, NC, USA).

We conducted several sensitivity analyses to evaluate the robustness of our results. First, we repeated the analyses restricting the study population to those who reported not vaginal douching in the month before NHANES interview (unweighted n = 1167). We did not adjust for vaginal douching in our main analyses as we conceptualized that douching would not precede oral contraceptive use and thus would not operate as a confounder. We conducted this sensitivity analysis to understand the impact of this assumption on the results; we restricted the study population to those that did not vaginally douche in the past month given the low frequency of vaginal douching in the exposed group. Second, we repeated the analyses, restricting the study population to NHANES participants not currently using non-contraceptive estrogen-containing female hormones (e.g., menopause hormone therapy) (unweighted n = 1455). As the central hypothesis of this study focuses on exogenous estrogen in oral contraception on BV prevalence, we conducted this analysis to exclude exogenous estrogen exposure from non-contraceptive medications. Lastly, when considering self-reported OC use, we repeated the analyses, restricting the study population to ever users of OCs. This sensitivity analysis comparing current and past OC users was conducted to account for potential confounding from unmeasured factors associated with OC use and BV prevalence.

Using data on prescription medication-derived COC use, we explored the duration of current COC use as well as a refined definition of COC use, restricting the exposed group to those who showed the medication container to the NHANES interviewer in relation to BV. Using the self-reported current OC data for which OC brand information was available in the NHANES 2001-2002 cycle, we also explored the association between the ethinyl estradiol dose and BV.

RESULTS

In the study population, the weighted prevalence of prescription medication-derived current COC use was 7% (unweighted n=73); the weighted prevalence of self-reported current OC use was 18% (unweighted n=231). When examining the distribution of participant characteristics between prescription medication-derived current COC users and non-users, current COC users tended to be younger, racialized as non-Hispanic White, have a higher level of education (some college or more), and household income (poverty income ratio >3.5) (Table 1). Current COC users also more frequently reported never smoking, current alcohol consumption, being sexually active in the past year, no vaginal douching in the past month, and having a BMI ≥18.5 and <25 kg/m^2. We observed a similar distribution of participant characteristics between current self-reported OC users and non-users (Supplemental Table 1).

As for the outcome, the weighted prevalence of intermediate and positive Nugent-score BV were 28% (unweighted n = 399) and 29% (unweighted n = 483), respectively. Compared to participants with negative Nugent-score BV, participants with positive Nugent-score BV tended to be racialized as non-Hispanic Black and have lower educational attainment (≤High school) and lower household income (poverty income ratio ≤1.3) (Table 1). Participants with positive Nugent-score BV more frequently reported current smoking, ≥2 sexual partners in the past year, vaginal douching in the past month, and had a higher BMI (≥30 kg/m^2) than those with negative Nugent-score BV (Table 1). The distribution of participant characteristics was generally similar between those with intermediate and negative Nugent-score BV.

Using data on COC use derived from the prescription medication data, current COC use was associated with a 67% lower odds of intermediate Nugent-score BV (aOR: 0.33; 95% CI: 0.18, 0.63) and an 83% lower odds of positive Nugent-score BV (aOR: 0.17; 95% CI: 0.07, 0.42)

(Table 2) compared with non-use. When considering self-reported current OC use, we similarly observed lower odds of intermediate Nugent-score BV (aOR: 0.50, 95% CI: 0.34, 0.75) and positive Nugent-score BV (aOR: 0.48; 95% CI: 0.30, 0.79). However, the magnitude of the association was not as strong as that observed for prescription medication-derived COC use and was similar for intermediate and positive Nugent-score BV.

In our sensitivity analysis restricting the study population to those who had not vaginally douched in the past month, we observed similar results to those of the main analyses for prescription medication-derived current COC use (intermediate Nugent-score BV: OR 0.32, 95% CI: 0.17, 0.55; positive Nugent-score BV: OR 0.11, 95% CI: 0.04, 0.33) and self-reported current OC use (intermediate Nugent-score BV: OR 0.51, 95% CI: 0.33, 0.79; positive Nugent-score BV: OR 0.51, 95% CI: 0.30, 0.87) (Supplemental Table 2). After excluding current users of non-contraceptive female hormones, we also observed associations generally similar to that of the main analysis (Supplemental Table 3). In our sensitivity analyses restricting the study population to ever users of OCs, the odds of intermediate Nugent-score BV (aOR: 0.46; 95% CI: 0.29, 0.73) and positive BV (aOR: 0.46; 95% CI: 0.27, 0.79) with self-reported current OC use were similar to the estimated odds obtained in the main analyses (Supplemental Table 4).

When we attempted to conduct exploratory analyses on the duration of prescription medication-derived current COC use and ethinyl estradiol dose with self-reported current OC use in relation to Nugent-score BV, the small number of exposed individuals ($n<10$) with intermediate and positive Nugent-score BV limited the interpretation of results (data not reported). Among the current COC users defined using prescription medication data, the median duration of current COC use was 2.5 years with an interquartile range of 0.9-8.0 years, and 90% of current COC users showed the medication container to the interviewer. Among the current OC

users based on self-report and using the OC brand information provided in the NHANES 2001-2002 cycle, 9%, 19%, 65%, and 6% used COC formulations containing 20, 30, 35, and ≥40 mcg of ethinyl estradiol, respectively. The remaining 1.3% of self-reported OC users reported taking progestin-only pills.

Given the difference in weighted prevalence of prescription medication-derived COC use and self-reported OC use, in a *post hoc* analysis, we calculated the Kappa coefficient for agreement among individuals with data on both prescription medication-derived current COC use and self-reported current OC use (unweighted n = 1431) and observed a kappa of 0.40 (Supplemental Table 5). Participants who were categorized as "yes" for both reported prescription medication-derived current COC use and self-reported current OC use (unweighted n = 64) had a slightly older median age (median age 30 years, IQR: 23.4-34.8 years) than participants who self-reported current OC use but reported no prescription medication-derived current COC use (unweighted n = 167) (median age 29 years, IQR: 23.6-35.7 years).

DISCUSSION

We observed lower odds of intermediate and positive BV with prescription medication-derived current COC use and self-reported current OC use in a population of US premenopausal individuals. This association is biologically plausible. In premenopausal individuals, higher estrogen levels support glycogen being deposited in the vaginal epithelium (Boskey et al., 1999). Glycogen metabolites in the vaginal fluid function as a substrate for growth and are used by lactobacilli to produce lactic acid which lowers the vaginal pH (Mirmonsef et al., 2014). Lactic acid production by lactobacilli has broad-spectrum antimicrobial effects against Gram-negative bacteria but does not harm the lactobacilli itself (O'Hanlon et al., 2011). Thus, estrogen supports the maintenance of a eubiotic *Lactobacillus*-dominated vaginal microbiome, thereby inhibiting BV. COCs contain exogenous estrogen which increase the available glycogen in the vaginal epithelium and support the acidification of the vaginal fluid. A study which examined the structure of the vaginal microbiome with COC use reported that COC users tended to have a more stable and lactobacilli-dominated vaginal microbiome which may reduce the recurrence of BV (Tuddenham et al., 2023). Thus, our results of lower odds of intermediate and positive BV with current COC use are consistent with this evidence and the proposed biologic mechanism.

A number of studies have assessed the association between oral contraceptive use and BV. Similar to our study, most have reported an inverse association, regardless of whether participants used OCs or COCs (Vodstrcil et al., 2013; Calzolari et al., 2000; Rifkin et al., 2009; Brooks et al., 2017; Riggs et al., 2007; Barbone et al., 1990; Vodstrcil et al., 2019). However, the reduction in the odds of intermediate and positive BV with prescription medication-derived current COC use that we observed was larger in magnitude than the associations reported in prior studies. Many of the prior studies evaluating OC use in relation to BV did not have detailed

information on OC use, including whether specifically COCs were used. In addition, several studies only evaluated one formulation of OC. Furthermore, OC use was ascertained using one source of information, either an interview or clinical information. Results from prior studies using the interview method were generally similar to the results we obtained for self-reported current OC use, which included both COC and progestin-only pill users. However, prior studies relying on interviews to ascertain exposure had discrepant results for OC and COC use, with no clear pattern of a stronger association with COC use specifically emerging (Vodstrcil et al., 2013; Calzolari et al., 2000; Rifkin et al., 2009; Brooks et al., 2016; Riggs et al., 2007; Barbone et al., 1990; Vodstrcil et al., 2019). In contrast to prior studies using either self-report or clinical information to ascertain OC use, we observed associations stronger in magnitude using prescription information.

This study had several limitations. First, NHANES data is cross-sectional, so we cannot be certain that a participant's OC use preceded the development of BV. Although this is an inherent issue with the cross-sectional study design, the duration of current prescription medication-derived COC use (median 2.5 years) minimizes this concern. Second, confounding of the observed associations from unmeasured factors may exist. However, in our sensitivity analysis comparing current and past OC users, the odds of intermediate and positive BV were similar to those obtained in the main analysis. This suggests that our results are not explained by confounding from unmeasured factors.

Third, we observed only fair agreement (kappa 0.40) between prescription medication-derived COC use and self-reported current OC use. The greatest discordance in reporting was for those who reported no prescription medication-derived COC use in the past 30 days but self-reported currently using OCs. The discordant reporting may reflect differences in the two

methods used to capture OC use. For the collection of prescription medication data, participants were asked about any prescription medication use in the past month and to provide the specific name of the medication as well as to show the medication container to the NHANES interviewer during the household interview. It is possible that a participant may not have felt comfortable disclosing this information in the presence of others in the home, particularly as COCs are commonly prescribed for pregnancy prevention (National Center for Health Statistics, 2004; National Center for Health Statistics, 2006; National Center for Health Statistics, 2005; National Center for Health Statistics, 2007). In contrast, data on self-reported OC use were collected in a private setting during the MEC interview. Consistent with this speculation, the median age of participants with concordant reporting of OC use based on prescription information and self-reported interview data were slightly older than those only reporting OC use by self-report, although the difference in age was small. The possibility also exists that participants may have inadvertently overlooked reporting COC use when asked about prescription medication use; COCs can be prescribed for prevention rather than the treatment of an existing condition. In addition, the ascertainment of OC use by self-report used a question embedded within a series of reproductive health-related questions that included pregnancy history, which may have aided recall of current OC use.

Fourth, the present study was conducted using data collected in the years 2001-2004. Based on available data on ethinyl estradiol dose, over 70% of COC users used formulations with 35 mcg or greater of ethinyl estradiol. Over the past two decades, newer COC formulations with lower ethinyl estradiol doses (≤20 mcg) have been introduced, with formulations containing ≥35 mcg ethinyl estradiol being less frequently prescribed. In addition, prescribing practices have changed and now allow for continuous COC use and the avoidance of the placebo pill week

that would have not been the norm in 2001-2004. Lastly, due to the small number of individuals with intermediate and positive BV who currently used COCs, we were not able to evaluate specific aspects of COC use on BV prevalence, including duration of current COC use and dose of ethinyl estradiol.

That said, our study had several key strengths. First, BV was classified using the Nugent score. In the context of laboratory testing, the Nugent score is considered the gold standard method to diagnose BV (Walensky, 2021). The Nugent score is also a beneficial diagnostic measure as it allows for the diagnosis of intermediate and asymptomatic BV and can show more nuance than a diagnostic test yielding a binary (BV present/absent) result. Although a few prior studies used the Nugent criteria (Riggs et al., 2007; Vodstrcil et al., 2019), most studies used the clinical-based Amsel criteria to diagnose BV (Calzolari et al., 2000; Rifkin et al., 2009; Barbone et al., 1990), which has a lower sensitivity than the Nugent score (Muzny et al., 2023). Thus, the use of the Nugent score to define BV in the present study is an improvement over several prior studies.

Second, the present study benefitted from the availability of two sources of OC data – prescription medication information and self-reported questionnaire data. This allowed for the comparison of prescription medication-derived and self-reported OC use within the same population. In addition, we were able to ascertain COC use specifically with the prescription information and obtain information on ethinyl estradiol dose from the questionnaire data for a subset of participants. This is a refinement in COC ascertainment, compared with prior studies that used questionnaires but did not obtain detailed information about estrogen dose or used data from a randomized controlled trial in which only one formulation of COC was used (Vodstrcil et al., 2019). Importantly, given the discordance in reporting OC use based on prescription

information and reproductive health questions, the use of both OC ascertainment methods allowed us to more fully characterize OC use within the general population and its association with BV.

Lastly, the present study was conducted in a sample that is nationally representative of the US population. The results from the present study are more generalizable to US premenopausal individuals compared to prior studies primarily conducted in the clinical setting. In addition, by not restricting the study population to those obtaining care in the clinical setting, our study minimizes selection bias.

CONCLUSION

In US premenopausal individuals, current prescription medication-derived COC use and current self-reported OC use were associated with lower odds of intermediate and positive BV. Although the magnitude of the association was stronger with prescription medication-derived COC use, there was discordance in capturing COC use using prescription medication information and self-report. This suggests the importance of capturing both self-reported and prescription-based information to attain a more complete characterization of COC use. As COC formulations with lower ethinyl estradiol doses have been increasingly prescribed over the past two decades, along with continuous use, examination of COC ethinyl estradiol dose and frequency on BV prevalence in future studies would be informative.

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APPENDIX

Table 1. Participant characteristics by current combined oral contraceptive use and bacterial vaginosis status, National Health and Nutrition Examination Survey (NHANES), 2001-2004 (unweighted n = 1460).

	Current Combined Oral Contraceptive Use[a]		Bacterial Vaginosis Nugent Score		
Participant characteristic	Yes (unweighted n = 73) n[b] (%)[c]	No (unweighted n = 1,387) n[b] (%)[c]	Negative (unweighted n = 578) n[b] (%)[c]	Intermediate (unweighted n = 399) n[b] (%)[c]	Positive (unweighted n = 483) n[b] (%)[c]
Age at sample collection, years					
20-25	35 (41)	339 (24)	153 (26)	95 (23)	126 (25)
26-30	14 (18)	222 (16)	100 (17)	62 (16)	74 (14)
31-35	12 (20)	231 (17)	96 (17)	67 (17)	80 (17)
36-40	5 (8)	269 (19)	96 (16)	88 (20)	90 (20)
41-45	4 (8)	243 (17)	96 (16)	64 (18)	87 (17)
46-49	3 (5)	83 (7)	37 (8)	23 (6)	26 (7)
Race/Ethnicity					
Non-Hispanic White	57 (88)	631 (66)	319 (74)	210 (74)	159 (53)
Non-Hispanic Black	8 (5)	327 (14)	83 (8)	62 (8)	190 (25)
Mexican-American	4 (2)	318 (9)	133 (9)	95 (8)	94 (9)
Other Hispanic	1 (1)	59 (6)	23 (5)	16 (5)	21 (7)
Other Races	3 (4)	52 (5)	20 (4)	16 (5)	19 (6)
Education					
<HS graduate	7 (8)	320 (15)	116 (13)	77 (10)	134 (20)
HS graduate	8 (12)	321 (24)	123 (21)	77 (20)	129 (29)
Some college or associate's degree	30 (41)	465 (36)	190 (36)	144 (40)	161 (36)
College graduate	28 (39)	281 (25)	149 (30)	101 (30)	59 (15)
Poverty Income Ratio[d]					
≤1.3	10 (11)	416 (26)	144 (21)	99 (21)	183 (34)
>1.3 to ≤3.5	30 (42)	520 (38)	204 (36)	168 (42)	178 (39)
>3.5 and ≤5	32 (47)	381 (36)	205 (43)	118 (37)	90 (27)

Table 1. (cont'd)

Smoking status[d]					
Never Smoker	53 (73)	865 (59)	392 (66)	259 (62)	267 (49)
Former smoker	8 (11)	156 (14)	69 (13)	47 (14)	48 (14)
Current smoker	12 (16)	365 (27)	116 (21)	93 (24)	168 (37)
Alcohol consumption					
Never	5 (5)	219 (14)	85 (13)	64 (14)	75 (13)
Former	8 (12)	272 (16)	117 (17)	76 (15)	87 (16)
Current	60 (83)	896 (70)	376 (70)	259 (71)	321 (71)
Number sexual partners in past year[d]					
0	1 (1)	159 (12)	76 (13)	41 (10)	43 (8)
1	58 (79)	1001 (74)	422 (74)	306 (77)	331 (71)
≥2	14 (20)	211 (15)	74 (13)	48 (13)	103 (21)
Vaginal douching in past month					
No	65 (89)	1102 (83)	511 (90)	334 (86)	322 (71)
Yes	8 (11)	285 (17)	67 (10)	65 (14)	161 (29)
Body Mass Index (kg/m^2)[d]					
>7.5 and <18.5	2 (2)	43 (4)	18 (4)	14 (4)	13 (3)
≥18.5 and <25	42 (60)	487 (40)	233 (46)	155 (42)	141 (34)
≥25 and <30	12 (17)	355 (24)	136 (22)	107 (24)	124 (26)
≥30	17 (21)	485 (32)	186 (28)	120 (30)	196 (37)

Abbreviation: HS, high school.

[a]Defined using prescription medication data; use of combined oral contraception (containing both estrogen and progestin) in past 30 days, with the prescription medication name provided to the NHANES interviewer during the household interview.

[b]Unweighted n.

[c]Weighted column percent using NHANES complex survey sampling design.

[d]Data missing for poverty income ratio (unweighted n = 71), smoking status (unweighted n = 1) number of sexual partners in the past year (unweighted n=16), and body mass index (unweighted n=17).

Table 2. Adjusted odds ratios and 95% confidence intervals for the associations between current oral contraceptive use and Nugent score bacterial vaginosis, NHANES 2001-2004.

	Negative	Intermediate Nugent Score BV			Positive Nugent Score BV		
	n[a] (%)[b]	n[a] (%)[b]	Model 1 OR (95% CI)[c]	Model 2 OR (95% CI)[d]	n[a] (%)[b]	Model 1 OR (95% CI)[c]	Model 2 OR (95% CI)[d]
COC use in past 30 days based on prescription data[e]							
No	528 (41)	383 (29)	Reference	Reference	476 (30)	Reference	Reference
Yes	50 (74)	16 (18)	0.33 (0.18, 0.62)	0.33 (0.18, 0.63)	7 (8)	0.17 (0.07, 0.43)	0.17 (0.07, 0.42)
Self-reported current OC use[f]							
No	444 (40)	333 (29)	Reference	Reference	423 (31)	Reference	Reference
Yes	124 (58)	57 (23)	0.51 (0.34, 0.76)	0.50 (0.34, 0.75)	50 (19)	0.46 (0.28, 0.75)	0.48 (0.30, 0.79)

Abbreviations: BV, bacterial vaginosis; CI, confidence interval; NHANES, National Health and Nutrition Examination Survey; COC, combined oral contraceptive; OC, oral contraceptive; OR, odds ratio.

[a]Unweighted n.

[b]Weighted row percent.

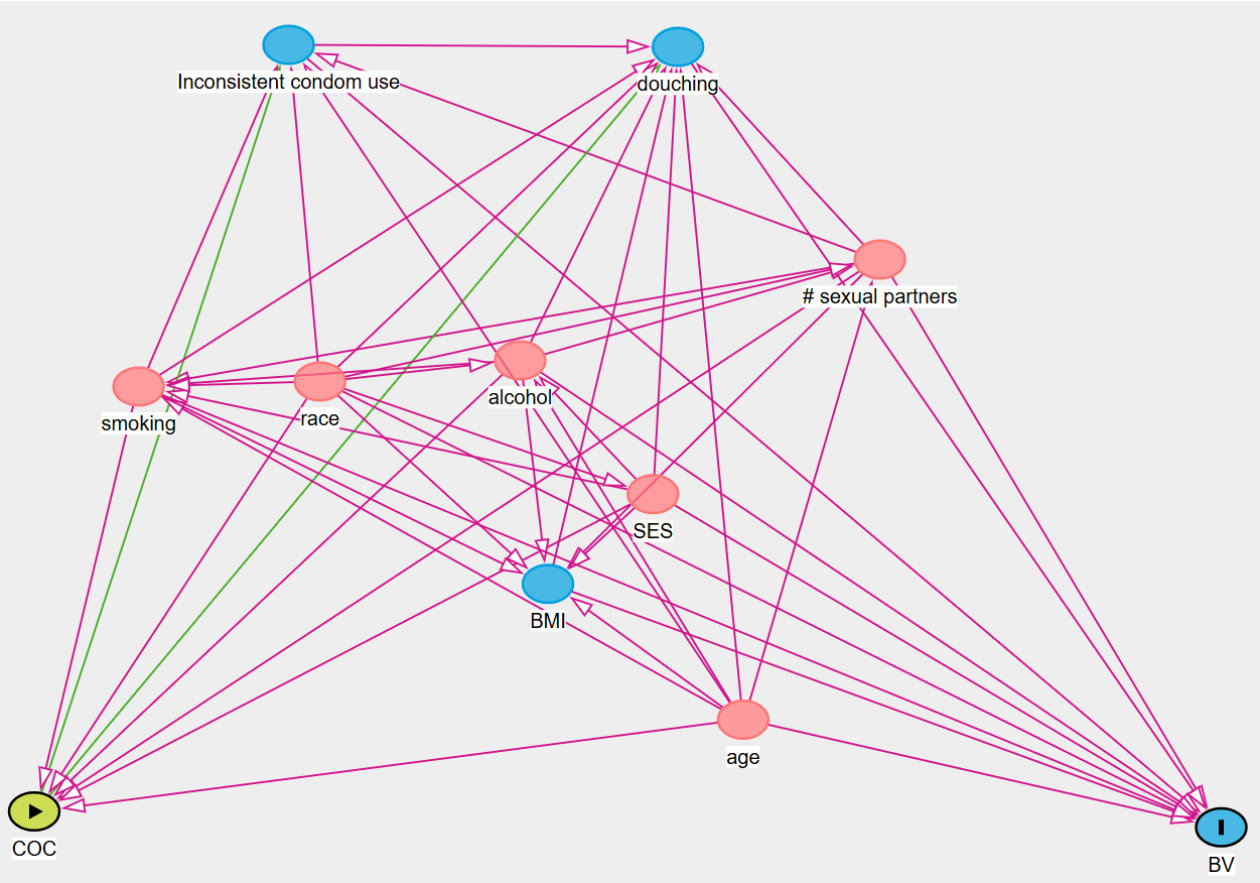
[c]Adjusted for age (continuous) and education (≤ high school, > high school).

[d]Adjusted for age (continuous), education (≤ high school, > high school), number of sexual partners in the past year (≤ 1, ≥2), current smoking (no, yes), and current alcohol consumption (no, yes).

[e]Current prescription medication-derived COC use, defined as use of combined oral contraception (containing both estrogen and progestin) in past 30 days, with the prescription medication name provided to the NHANES interviewer during the household interview, unweighted n = 1460.

[f]Self-reported current use of oral contraception (either progestin-only or combined oral contraception) ascertained via private, in-person interview using reproductive health questionnaire, unweighted n = 1431.

Supplemental Figure 1. A directed acyclic graph for the association between COCs and BV and their associated factors.



Supplemental Table 1. Participant characteristics by self-reported current oral contraceptive use and bacterial vaginosis status, National Health and Nutrition Examination Survey (NHANES), 2001-2004 (unweighted n = 1431).

	Self-reported Current Oral Contraceptive Use[a]		Bacterial Vaginosis Nugent Score		
Participant characteristic	Yes (unweighted n = 231) n[b] (%)[c]	No (unweighted n = 1,200) n[b] (%)[c]	Negative (unweighted n = 568) n[b] (%)[c]	Intermediate (unweighted n = 390) n[b] (%)[c]	Positive (unweighted n = 473) n[b] (%)[c]
Age at sample collection, years					
20-25	92 (39)	269 (22)	149 (26)	91 (23)	121 (24)
26-30	56 (22)	176 (15)	98 (17)	62 (17)	72 (15)
31-35	32 (16)	207 (17)	93 (17)	66 (17)	80 (18)
36-40	26 (10)	246 (20)	96 (16)	86 (20)	90 (21)
41-45	19 (9)	225 (19)	95 (16)	64 (18)	85 (16)
46-49	6 (4)	77 (7)	37 (8)	21 (5)	25 (6)
Race/Ethnicity					
Non-Hispanic White	147 (80)	525 (65)	314 (75)	204 (73)	154 (53)
Non-Hispanic Black	24 (5)	304 (15)	80 (8)	62 (8)	186 (25)
Mexican-American	46 (8)	272 (9)	131 (9)	93 (9)	94 (9)
Other Hispanic	7 (4)	51 (6)	23 (5)	15 (5)	20 (7)
Other Races	7 (3)	48 (5)	20 (3)	16 (5)	19 (6)
Education					
<HS graduate	29 (9)	289 (16)	112 (13)	76 (10)	130 (20)
HS graduate	32 (13)	291 (25)	121 (21)	76 (20)	126 (29)
Some college or associate's degree	90 (40)	396 (36)	186 (36)	141 (41)	159 (36)
College graduate	80 (38)	224 (23)	149 (30)	97 (29)	58 (15)
Poverty Income Ratio[d]					
≤1.3	40 (17)	374 (26)	139 (21)	96 (20)	179 (34)
>1.3 to ≤3.5	86 (36)	458 (39)	201 (36)	167 (43)	176 (39)
>3.5 and ≤5	93 (47)	310 (35)	203 (43)	113 (37)	87 (27)

Supplementary Table 1. (cont'd)

Smoking status[d]					
Never Smoker	172 (70)	730 (58)	386 (67)	254 (62)	262 (50)
Former smoker	25 (13)	133 (13)	67 (12)	45 (14)	46 (13)
Current smoker	34 (17)	336 (29)	114 (21)	91 (24)	165 (37)
Alcohol consumption					
Never	24 (8)	197 (14)	83 (13)	64 (14)	74 (13)
Former	30 (10)	245 (17)	116 (17)	74 (15)	85 (16)
Current	177 (82)	758 (68)	369 (70)	252 (71)	314 (71)
Number sexual partners in past year[d]					
0	8 (3)	148 (13)	73 (13)	41 (11)	42 (8)
1	191 (83)	846 (72)	416 (74)	297 (76)	324 (70)
≥2	30 (14)	192 (15)	73 (13)	48 (13)	101 (22)
Vaginal douching in past month					
No	208 (91)	936 (82)	503 (90)	326 (86)	315 (71)
Yes	23 (9)	264 (18)	65 (10)	64 (14)	158 (29)
Body Mass Index (kg/m^2)[d]					
>7.5 and <18.5	8 (3)	35 (4)	18 (4)	13 (3)	12 (3)
≥18.5 and <25	121 (55)	398 (39)	231 (46)	151 (42)	137 (34)
≥25 and <30	56 (23)	307 (24)	134 (22)	107 (25)	122 (26)
≥30	46 (19)	443 (33)	180 (28)	116 (30)	193 (37)

Abbreviations: HS, high school.

[a]Defined as self-reported current use of oral contraception (either progestin-only or combined oral contraception) ascertained via private, in-person interview using reproductive health questionnaire, unweighted n = 1431.

[b]Unweighted n.

[c]Weighted column percent using NHANES complex survey sampling design.

[d]Data missing for poverty income ratio (unweighted n = 70), smoking status (unweighted n = 1), number of sexual partners in the past year (unweighted n=16), and body mass index (unweighted n=17).

Supplemental Table 2. Sensitivity analysis of the adjusted odds ratios and 95% confidence intervals for the associations between current oral contraceptive use and Nugent score bacterial vaginosis excluding users of vaginal douches in the past month, NHANES 2001-2004.

	Negative		Intermediate Nugent Score BV		Positive Nugent Score BV		
	n[a] (%)[b]	n[a] (%)[b]	Model 1 OR (95% CI)[c]	Model 2 OR (95% CI)[d]	n[a] (%)[b]	Model 1 OR (95% CI)[c]	Model 2 OR (95% CI)[d]
COC use in past 30 days based on prescription data[e]							
No	463 (43)	321 (31)	Reference	Reference	318 (26)	Reference	Reference
Yes	48 (78)	13 (17)	0.31 (0.18, 0.53)	0.32 (0.17, 0.55)	4 (5)	0.11 (0.04, 0.31)	0.11 (0.04, 0.33)
Self-reported current OC use[f]							
No	385 (43)	276 (31)	Reference	Reference	275 (26)	Reference	Reference
Yes	118 (60)	50 (23)	0.52 (0.34, 0.79)	0.51 (0.33, 0.79)	40 (17)	0.49 (0.29, 0.83)	0.51 (0.30, 0.87)

Abbreviations: BV, bacterial vaginosis; CI, confidence interval; NHANES, National Health and Nutrition Examination Survey; COC, combined oral contraceptive; OC, oral contraceptive; OR, odds ratio.

[a]Unweighted n.

[b]Weighted row percent.

[c]Adjusted for age (continuous) and education (≤ high school, > high school).

[d]Adjusted for age (continuous), education (≤ high school, > high school), number of sexual partners in the past year (≤ 1, ≥2), current smoking (no, yes), and current alcohol consumption (no, yes).

[e]Use of combined oral contraception (containing both estrogen and progestin) in past 30 days, with the prescription medication name provided to the NHANES interviewer during the household interview, unweighted n = 1167.

[f]Self-reported current use of oral contraception (either progestin-only or combined oral contraception) ascertained via private, in-person interview using reproductive health questionnaire, unweighted n = 1144.

Supplemental Table 3. Sensitivity analysis of the adjusted odds ratios and 95% confidence intervals for the associations between current oral contraceptive use and Nugent score bacterial vaginosis excluding users of non-contraceptive estrogen hormones, NHANES 2001-2004.

	Negative		Intermediate Nugent Score BV		Positive Nugent Score BV		
	n[a] (%)[b]	n[a] (%)[b]	Model 1 OR (95% CI)[c]	Model 2 OR (95% CI)[d]	n[a] (%)[b]	Model 1 OR (95% CI)[c]	Model 2 OR (95% CI)[d]
COC use in past 30 days based on prescription data[e]							
No	526 (41)	383 (29)	Reference	Reference	473 (30)	Reference	Reference
Yes	50 (74)	16 (18)	0.33 (0.18, 0.62)	0.33 (0.18, 0.63)	7 (8)	0.17 (0.07, 0.43)	0.17 (0.07, 0.42)
Self-reported current OC use[f]							
No	436 (39)	326 (30)	Reference	Reference	415 (31)	Reference	Reference
Yes	122 (58)	57 (23)	0.51 (0.33, 0.77)	0.50 (0.33, 0.77)	49 (19)	0.45 (0.27, 0.75)	0.47 (0.29, 0.78)

Abbreviations: BV, bacterial vaginosis; CI, confidence interval; NHANES, National Health and Nutrition Examination Survey; COC, combined oral contraceptive; OC, oral contraceptive; OR, odds ratio.

[a]Unweighted n.

[b]Weighted row percent.

[c]Adjusted for age (continuous) and education (≤ high school, > high school).

[d]Adjusted for age (continuous), education (≤ high school, > high school), number of sexual partners in the past year (≤ 1, ≥2), current smoking (no, yes), and current alcohol consumption (no, yes).

[e]Use of combined oral contraception (containing both estrogen and progestin) in past 30 days, with the prescription medication name provided to the NHANES interviewer during the household interview, unweighted n = 1455.

[f]Self-reported current use of oral contraception (either progestin-only or combined oral contraception) in never users of non-contraceptive female hormones ascertained via private, in-person interview using reproductive health questionnaire, unweighted n = 1405.

Supplemental Table 4. Sensitivity analysis of the adjusted odds ratios and 95% confidence intervals for the associations between current OC and Nugent score Bacterial Vaginosis (BV) use among ever users of OCs (unweighted n = 1076), NHANES 2001-2004.

	Negative	Intermediate Nugent Score BV			High Nugent Score BV		
			Model 1	Model 2		Model 1	Model 2
	n[a] (%)[b]	n[a] (%)[b]	OR (95% CI)[c]	OR (95% CI)[d]	n[a] (%)[b]	OR (95% CI)[c]	OR (95% CI)[d]
Self-reported current OC use[e]							
No	321 (40)	230 (30)	Reference	Reference	294 (30)	Reference	Reference
Yes	124 (58)	57 (23)	0.46 (0.29, 0.73)	0.46 (0.29, 0.73)	50 (19)	0.42 (0.25, 0.71)	0.46 (0.27, 0.79)

Abbreviations: BV, bacterial vaginosis; CI, confidence interval; NHANES, National Health and Nutrition Examination Survey; OC, oral contraceptive; OR, odds ratio.

[a]Unweighted n.

[b]Weighted row percent.

[c]Adjusted for age (continuous) and education (≤ high school, > high school).

[d]Adjusted for age (continuous), education (≤ high school, > high school), number of sexual partners in the past year (≤ 1, ≥2), current smoking (no, yes), and current alcohol consumption (no, yes).

[e]Self-reported current use of oral contraception (either progestin-only or combined oral contraception) ascertained via private, in-person interview using reproductive health questionnaire.

Supplemental Table 5. Agreement between current combined oral contraceptive use ascertained using prescription medication data and current oral contraceptive use ascertained by self-report, NHANES 2001-2004.

		Self-reported current OC use[b, c]		
		No	Yes	Total
COC use in past 30 days based on prescription data[a, c]	No	1193	167	1360
	Yes	7	64	71
	Total	1200	231	1431
		Kappa Coefficient		0.40

Abbreviations: COC, combined oral contraceptive; OC, oral contraceptive.

[a]Defined using prescription medication data; use of combined oral contraception (containing both estrogen and progestin) in past 30 days, with the prescription medication name provided to the NHANES interviewer during the household interview, unweighted n = 1460.

[b]Self-reported current use of oral contraception (either progestin-only or combined oral contraception) ascertained via private, in-person interview using reproductive health questionnaire, unweighted n = 1431.

[c]Unweighted n.