

# Hemoglobin A1c and Vaginitis: National Health and Nutrition Examination Survey 2001-2004 Experience

**Christina A. Stennett**

University of Maryland School of Medicine <https://orcid.org/0000-0001-5282-6785>

**Rodman Turpin**

University of Maryland at College Park

**Sarah J. Robbins**

University of Maryland School of Medicine

**Rebecca M. Brotman**

University of Maryland School of Medicine

**Ryan S. Miller** (✉ [rmiller@som.umaryland.edu](mailto:rmiller@som.umaryland.edu))

Division of Pediatric Endocrinology, University of Maryland School of Medicine <https://orcid.org/0000-0002-2656-7211>

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## Research note

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## Abstract

**Objectives:** It is well-documented that diabetes mellitus is associated with increased risk for vulvovaginal candidiasis. We sought to assess whether diabetes (assessed by HbA1c) might be similarly associated with other vaginitis outcomes (bacterial vaginosis (BV) and *Trichomonas vaginalis* (TV)) infection). We hypothesized that glucose may favor the growth of BV-associated bacteria, and high blood glucose may also affect host immune responses, potentially increasing risk for BV and TV infection. Our secondary data analysis utilized a large population-based study, the 2001-2004 U.S. National Health and Nutrition Examination Survey (NHANES).

**Results:** Among 2,442 reproductive-age women with available data, 54 (unweighted) had elevated HbA1c ( $>6.4$ ) indicating diabetes, 112 had borderline HbA1c (5.7–6.4), 791 had BV by Nugent's Gram stain score (Nugent-BV), and 104 had TV. Borderline HbA1c, but not higher HbA1c, was significantly associated with Nugent-BV (OR=1.58, 95% CI: 1.11-2.25) and TV detection (OR=2.45, 95% CI: 1.10-5.44) in unadjusted logistic regression models. After adjustment for confounders, including race/ethnicity, recent douching, and body mass index, associations between borderline HbA1c and both vaginitis outcomes were null. Sample size was limited by few cases with diabetes, and multivariable modeling may require larger sample size. Future longitudinal studies with more diabetes cases may confirm these findings.

## Introduction

It is well-established that diabetes mellitus is associated with increased risk of infections, including pneumonia and sepsis.(1–3) Epidemiologic studies suggest that women with diabetes, especially those with poorly controlled blood glucose (hyperglycemia), have greater risk of genital infections, including vulvovaginal candidiasis(4, 5) and vaginal colonization by group B streptococcus in pregnancy.(6, 7) Several studies show an association between diabetes and urinary tract infections (UTI) in women; however, hyperglycemia has not been consistently correlated with UTI occurrence.(8)

Bacterial vaginosis (BV) and trichomoniasis are common forms of vaginitis in reproductive-age women, and both have been linked to adverse outcomes, such as preterm labor and increased risk for HIV.(9–12) BV is characterized by a vaginal microbiota that has low relative abundance of *Lactobacillus* spp. and is composed predominantly of strict and facultative anaerobic bacteria.(13) Few studies have evaluated diabetes and hyperglycemia as risk factors for BV or *Trichomonas vaginalis* (TV) infection. Hoosen et al. found no significant differences in random blood glucose levels between African and Indian women with and without BV symptoms (vulvovaginal itching and/or discharge).(14) However, other studies focusing on pregnant women (15) and older women (40–70 years) (16) found greater prevalence of BV-associated vaginal bacteria among those with diabetes compared to controls. A study of pregnant and non-pregnant women with diabetes presenting with vaginal discharge found that 24.5% were positive for TV.(17)

Hemoglobin A1c (HbA1c) positively correlates with average blood glucose over a 3-month period.(18) Acute hyperglycemia results in detectable glucose in tears,(19) as well as nasal (20) and tracheal (21)

secretions. Glucose favors the growth of BV-associated bacteria and other pathogens over the growth of vaginal lactobacilli *in vitro*,(22) suggesting a mechanism by which hyperglycemia could cause BV. Furthermore, high blood glucose levels interfere with host immune responses, potentially increasing risk for BV and TV infection.(23, 24)

In this cross-sectional analysis of a large nationally representative dataset, we examined the association between higher HbA1c and vaginitis, specifically, BV and TV prevalence.

## Materials And Methods

We analyzed data from National Health Examination and Nutrition Survey (NHANES), an ongoing biennial cross-sectional survey conducted by the National Center for Health Statistics. Designed to obtain health information that is representative of the U.S. civilian noninstitutionalized population, NHANES' multistage sampling design and data collection procedures have been well-described previously.(25–27) We combined data from two waves of NHANES collected from 2001 to 2002 and 2003 to 2004, the only waves that collected participants' vaginal samples. Reproductive-age women (ages 18–45 years) were included in this analysis if HbA1c and Nugent score data were available, resulting in a sample of 2,442 participants that is weighted to represent over 98 million U.S. reproductive-age women.

HbA1c was measured in whole blood samples using high-performance liquid chromatography.(28) HbA1c was categorized based on American Diabetes Association standards, with levels of 5.7–6.4% designated borderline (consistent with diagnosis of "prediabetes") and levels of 6.5% and greater indicating diabetes.(29) Participants self-collected vaginal fluids using a cotton-tipped swab, which was rolled onto a glass slide. Slides were Gram stained, and BV was assessed using Nugent scoring.(30) A Nugent score of 7–10 was defined as Nugent-BV positive,(31) a score of 4–6 was intermediate, and a score of 0–3 was negative. TV was detected from vaginal fluids extracted from self-collected vaginal swabs through polymerase chain reaction (PCR) with primers from a region of the 18S rRNA gene that produce a 312 base pair product.(32) A small percentage (2.7%) of participants were excluded in this analysis due to missing or uninterpretable TV data. All PCR results positive for TV were confirmed by Southern blot hybridization. Data collection and processing methods for the variables used in this analysis were consistent between the two NHANES waves.

We tested several variables as potential confounders, including race/ethnicity, age, education, income, marital status, fasting at sample collection, pregnancy, body mass index (BMI), and douching in the past month (all categorical). Variables were included in adjusted models as confounders if they were significantly associated (at 0.05 level) with HbA1c and either Nugent-BV or TV status by Rao-Scott chi-square tests. We used logistic regression to generate prevalence odds ratios (PORs). All analyses accounted for sample weights, strata, and clusters used in the complex sampling. However, we report unweighted prevalence estimates (n) in the results. We excluded pregnant women in a sensitivity analysis.

## Results

In the sample of 2,442 women, approximately 1.8% ( $n = 54$ ) had a HbA1c greater than 6.4, indicating diabetes, and 4.0% ( $n = 112$ ) had a borderline HbA1c level (5.7–6.4). Over 29.4% ( $n = 791$ ) were Nugent-BV positive (Nugent score  $\geq 7$ ), and TV was detected in 2.9% ( $n = 104$ ).

In unadjusted analyses, borderline HbA1c was associated with significantly higher odds of TV detection compared to normal HbA1c (POR = 2.45, 95% CI: 1.10–5.44); however, higher levels of HbA1c were not significantly associated with TV (Fig. 1). Similarly, borderline HbA1c was associated with significantly higher odds of Nugent-BV (POR = 1.58, 95% CI: 1.11–2.25) in the unadjusted model; however, there was no significant association with higher HbA1c.

Race/ethnicity, education, annual household income, douching in past month, and BMI were associated with HbA1c, Nugent-BV, and TV detection. After adjustment for these confounders, the associations between borderline HbA1c and both Nugent-BV and TV detection became null. The confounders that had the greatest attenuating effect on the POR estimates were race/ethnicity, recent douching, and BMI. A sensitivity analysis excluding the small percentage of pregnant women in the sample did not alter the findings.

## Discussion

In this analysis of nationally representative data, we did not identify an association between HbA1c and either Nugent-BV or TV detection in multivariable modeling. However, a borderline HbA1c, but not an HbA1c in the diabetes range, was significantly associated with TV detection and Nugent-BV in the unadjusted models, and the point estimates suggest positive associations. Findings relating borderline HbA1c to vaginitis suggests several possibilities: (1) Individuals in the NHANES sample who have an elevated HbA1c may be more likely than the general population to be on medication to control diabetes; while there is a presumed higher glucose exposure in this group due to higher HbA1c, anti-hyperglycemic medications may have beneficial effects on the vaginal microbiota. (2) Moderate levels of hyperglycemia may be advantageous to bacteria associated with BV, but higher glycemic levels seen in diabetes may not favor BV-associated bacteria.

The use of the large, nationally representative NHANES dataset is a strength. We found that the prevalence of BV and TV was 29.4% and 3.0%, respectively. These findings are similar to the nationwide prevalence estimates reported in previous NHANES studies.(26, 27) We were able to identify women with two of the three most prevalent forms of vaginitis nationwide. Vaginal candidiasis, another common form of vaginitis, was not assessed in these NHANES waves. However, the relationship between candidiasis and hyperglycemia has been established in other research.(33, 34)

## Conclusion

In summary, this study did not detect a statistically significant association between elevated HbA1c and either BV or TV in adjusted models. However, we found indications that borderline HbA1c may be associated with both outcomes in unadjusted models. Future studies with larger numbers of diabetes and TV cases would help to confirm these findings. An association between diabetes and BV and/or TV detection could have implications for wider screening and recognition of vaginitis in women with diabetes.

## Limitations

- HbA1c does not account for blood glucose variability, which may be as important as mean blood glucose levels in terms of disturbance of the vaginal microenvironment.
- The dataset does not provide information on whether participants have been diagnosed with diabetes, the type of diabetes, or if they are being treated with diabetes medications (including insulin and insulin sensitizers), all of which may affect the vaginal microbiota.
- The sample size is somewhat limited for modeling, as there were only 54 women with HbA1c in diabetes range and 104 TV cases detected. A larger sample size would allow us to fully evaluate relationships in multivariable modeling.
- Key factors affecting the vaginal microenvironment, such as recent antibiotic use and menstrual cycle phase, were not able to be assessed; longitudinal studies could better evaluate these time-varying factors.

## Abbreviations

**BMI:** Body mass index

**BV:** Bacterial vaginosis

**CI:** Confidence interval

**HbA1c:** Hemoglobin A1c

**NHANES:** National Health Examination and Nutrition Survey

**Nugent-BV:** Bacterial vaginosis assessed by Nugent's Gram stain score

**PCR:** Polymerase chain reaction

**POR:** Prevalence odds ratio

**TV:** *Trichomonas vaginalis* detected in cervical samples

**UTI:** urinary tract infections

# **Declarations**

## **Ethics approval and consent to participate:**

Not applicable

## **Consent for publication:**

Not applicable

## **Availability of data and materials:**

The datasets analyzed during the current study are available in the Centers for Disease Control and Prevention (CDC) National Center for Health Statistics (NCHS) National Health and Nutrition Examination Survey (NHANES) repository, <https://www.cdc.gov/nchs/nhanes/default.aspx>.

## **Competing interests:**

The authors declare that they have no competing interests.

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## **Authors' contributions:**

RB conceived the study. CS and RT conducted the statistical analysis. CS drafted the manuscript, and RB, RT, SR, and RM contributed significantly to reviewing and finalizing the paper.

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Not applicable

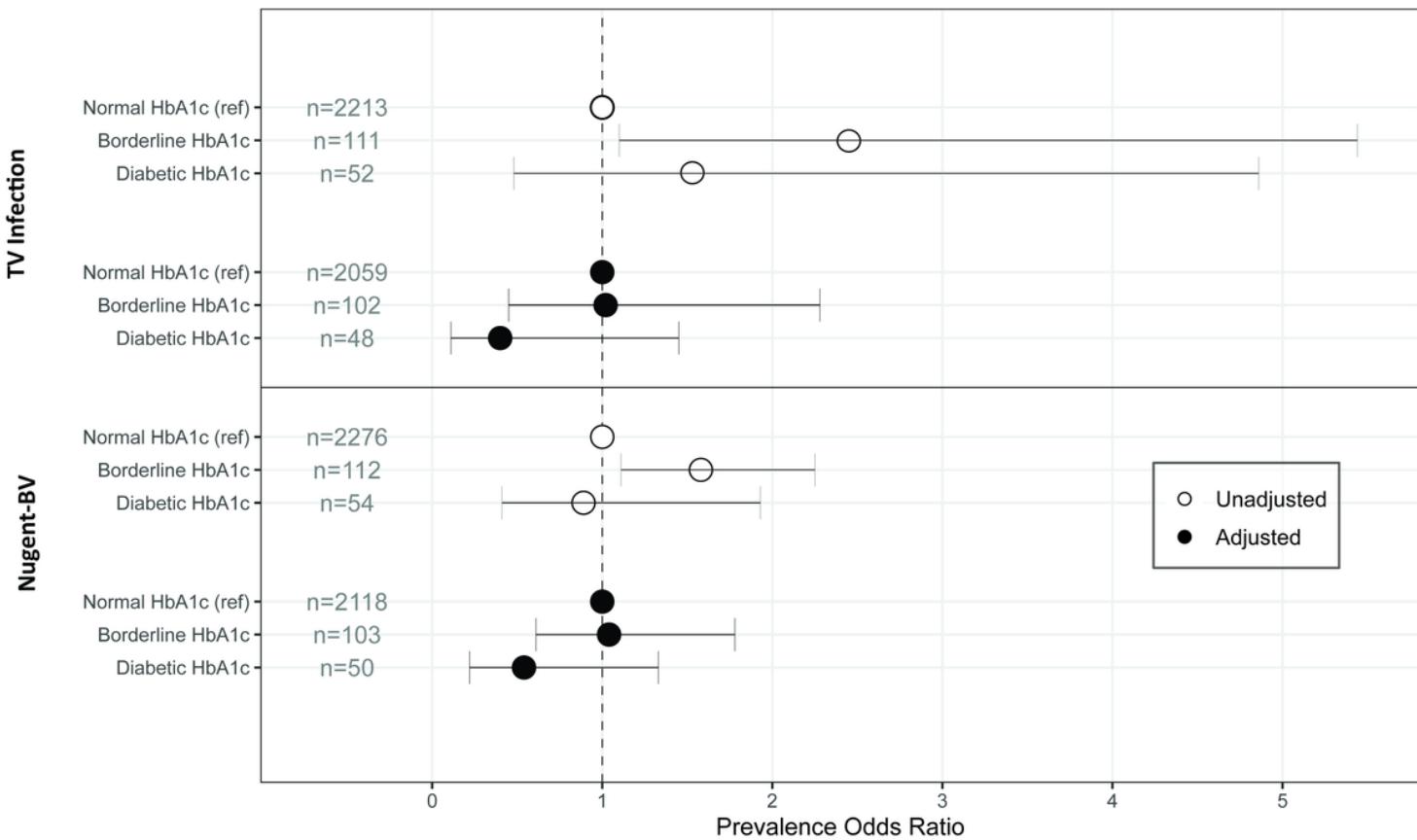
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## Figures



**Figure 1**

Prevalence odds ratios and 95% confidence intervals for the associations between HbA1c status and Nugent-BV or TV infection (N=2442). HbA1c levels were categorized as diabetic HbA1C ( $\geq 6.5$ ), borderline HbA1c (5.7-6.4), and normal HbA1c ( $\leq 5.6$ ), which was the reference in all models. Nugent-BV (score of 7-10) was compared to the normal/intermediate Nugent score (0-6) reference. Adjusted models include race/ethnicity, education, annual household income, douching in past month, and body mass index. Nugent-BV= bacterial vaginosis by Nugent score; TV= Trichomonas vaginalis.