

SHORT COMMUNICATION

Sexual behavior and risk of diagnosis with multiple sclerosis: A retrospective case–control study

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Abstract

Adolescence is a critical window during which psychosocial factors have significant effects on the lifetime risk of multiple sclerosis (MS). Sexual behavior is relevant early in adulthood and has not been described in its relationship to MS. Using a retrospective secondary analysis of cross-sectional data in the TriNetX database, we investigated the connection between orientation of sexual behavior and MS risk. We identified 13,595 males and 9,589 females with same-sex behavior and 64,409 males and 137,450 females with opposite-sex behavior. Cohorts were balanced on age, race, and ethnicity. Males engaging in same-sex behavior had a 2.80-fold higher risk of MS diagnosis (95% confidence interval [CI]: 1.66 – 4.73), and females engaging in same-sex behavior had a 2.30-fold higher risk of MS diagnosis (95% CI: 1.65 – 3.20). Our findings thus advance the understanding of MS risk in the context of social determinants of health.

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1. Introduction

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system with heterogenous symptomatology due to variably affected neuronal tracts^[1]. While some factors such as Epstein–Barr virus (EBV) infection are well established as being associated with an increased risk of MS, certain factors such as adolescent obesity and sunlight exposure have been identified recently, reinforcing the importance of continued research into MS risk factors^[2]. Many studies have recently focused on adolescence, as it has been identified as a particular time window during which lifestyle and environmental factors seem to have the greatest effect on the lifetime risk of MS^[3].

Adolescence and young adulthood are also associated with the development of patterns of sexual behavior and identity formation^[4]. While personal identities such as gay, lesbian, bisexual, or queer may arise later in life, sexual behavior with individuals of the same sex often initially occurs in adolescence^[5]. Despite the known impact of same-sex behavior on other neurologic conditions, such as amyotrophic lateral sclerosis and dementia^[6,7], research into the intersection between MS and sexual behavior has been limited^[8].

Individuals who engage in same-sex sexual behavior are a unique subset of the general population, with known health disparities relating to stigma and discrimination^[9,10]. In addition, they also have unique healthcare needs that may impact MS care, such as use of pre-exposure prophylaxis medications in men who have sex with men^[11]. Other unique factors, such as monkeypox vaccination, are also greatly increased in this population^[12]. Research into the current gap of knowledge regarding the ways in which MS differs in this unique subpopulation could hold potential implications for future treatment. As a first step, we sought to investigate the association between orientation of sexual behavior and MS risk.

2. Methods

We collected aggregate, de-identified data from the TriNetX research database. TriNetX is a health information database with over 85 million unique patient records. We obtained data from the past 20 years ranging from April 3, 2002, to April 3, 2022, at 58 large health-care organizations. Subject inclusion and exclusion criteria were defined using International Classification of Diseases (ICD) codes. We created an investigative cohort defined by the presence of same-sex high-risk sexual behavior (ICD-10: Z72.52) and/or bisexual high-risk sexual behavior (ICD10: Z72.53) and the absence of opposite-sex high-risk sexual behavior (ICD-10: Z72.51)^[13]. A comparator cohort was created, defined by the presence of opposite-sex high-risk sexual behavior (ICD-10: Z72.51) and the absence of same-sex high-risk sexual behavior (ICD-10: Z72.52, Z72.53). Finally, a third control cohort was created from patients who participated in any virtual visit encounter in the TrinetX database and lacked any previous history of high-risk sexual behavior (ICD-10: Z72.5). All patients were 18 years or older. The data were extracted from TriNetX on April 3, 2022.

The two investigative cohorts were stratified by sex; males with exclusively same-sex behavior were compared to males with opposite-sex behavior. We balanced cohorts based on age, sex, race, ethnicity, infectious mononucleosis, and EBV seropositivity using the TriNetX software, which uses nearest-neighbor matching with a difference between propensity scores less than or equal to 0.1. After matching, we investigated the outcome of lifetime diagnosis of MS (ICD-10: G35). Rates of diagnosis were used to calculate risk ratio and odds ratio [OR]. Significance for this study was set at $P < 0.05$. This study only utilized aggregated, deidentified patient data and thus was exempted from review by the Colorado Multiple Institutional Review Board (COMIRB).

3. Results

We identified 234,022 adults with high-risk sexual behavior. Of these patients, we identified 13,595 males and

9,589 females with same-sex behavior and 64,409 males and 137,450 females with opposite-sex behavior. Our control cohort consisted of 711,077 adults without documented high-risk sexual behavior. Full characteristics for the cohorts, including age, race, ethnicity, other diagnoses such as infectious mononucleosis, and laboratory values for EBV antibody, are tabulated in [Table 1](#).

The risk of MS was significantly higher for individuals engaging in same-sex behavior compared to individuals engaging in opposite-sex behavior. Males engaging in same-sex behavior had a 2.80-fold higher risk of MS diagnosis (95% confidence interval [CI]: 1.66 – 4.73) and females engaging in same-sex behavior had a 2.30-fold higher risk (95% CI: 1.65 – 3.20) of MS diagnosis ([Figure 1](#)). There was no significant risk difference between adults engaging in any form of high-risk sexual behavior compared to adults not engaging in high-risk sexual behavior ($P = 0.41$). [Table 2](#) contains information on cohort size and number of patients with the outcome of interest.

4. Discussion

Our study found a significant association between same-sex sexual behavior and the lifetime risk of MS. The association was prominent in both male and female patients, indicating a need for targeted research in this understudied area. Importantly, the lifetime risk of MS in this population was found to be over twice that of individuals engaging only in opposite-sex sexual encounters. The risk for males was nearly 3 times higher (OR: 2.80, 95% CI: 1.66 – 4.73) whereas the risk for females was 2.3 times higher (OR: 2.30, 95% CI: 1.65 – 3.20). These ratios were calculated after adjusting for age, sex, race, and ethnicity, in addition to the recently identified risk factor of EBV seropositivity, which had a notably low prevalence in our study population. This allowed the impact of sexual behavior on MS to be isolated as much as possible. This finding invokes the need for further inquiry into MS in this unique population.

One theory for this increased risk could lie in an increased level of stress experienced by these individuals, notably during their adolescent years. Youths engaging in same-sex behavior but identifying as heterosexual experience higher rates of bullying and suicidality^[14], which are types of adverse childhood experiences^[15]. Adverse childhood experiences are known to be linked to increased neuroinflammation, increased autoimmune diseases, and earlier age of MS diagnosis, which could be a contributing factor to the large association we found^[16]. Youths who engage in same-sex behavior and identify as LGBTQ+ also experience higher rates of adverse childhood experiences^[17]. Future research could investigate the

Table 1. Comparison of characteristics between (a) adults engaging in all forms of high-risk sexual behavior versus adults not engaging in high-risk sexual behavior; (b) males engaging in high-risk homosexual and/or bisexual behavior versus males engaging in high-risk heterosexual behavior; (c) females engaging in high-risk homosexual and/or bisexual behavior versus females engaging in high-risk heterosexual behavior

Cohort demographics before matching for age, sex, race, ethnicity, infectious mononucleosis, and EBV seropositivity						
Variable	Adults engaging in high-risk behavior	Adults not engaging in high-risk sexual behavior	Males engaging in same-sex high-risk behavior	Males engaging in opposite-sex high-risk behavior	Females engaging in same-sex high-risk behavior	Females engaging in opposite-sex high-risk behavior
N	234,022	711,077	13,595	64,409	9,589	137,450
Current age, mean (\pm SD)	35.4 (14.2)	49.2 (20)	46.5 (19.4)	36.1 (13.6)	56.8 (20.7)	32.3 (11.3)
Sex (male, female)	37%, 63%	41%, 59%	100%, 0	100%, 0	0, 100%	0, 100%
Race						
White (n)	50% (117,194)	75% (529,825)	71% (9,645)	49% (32,157)	80% (7,632)	46% (63,497)
Black or African American (n)	31% (66,890)	9% (67,016)	12% (1,663)	30% (20,040)	12% (1,148)	35% (47,151)
Ethnicity						
Hispanic or Latino (n)	14% (31,494)	53% (374,785)	13% (1,781)	13% (8,876)	6% (600)	14% (19,170)
Other diagnoses						
Mood disorders	25% (57,895)	14% (101,370)	30% (4,038)	16% (10,818)	48% (4,618)	27% (36,654)
Anxiety disorders	21% (49,874)	19% (133,785)	28% (3,804)	14% (9,285)	46% (4,441)	23% (30,728)
Infectious mononucleosis	0.7% (1,711)	0.4% (3,074)	0.3% (43)	0.7% (456)	0.4% (35)	0.8% (1,141)
Laboratory value						
Presence of EBV nuclear IgG antibody	0.02% (50)	0% (0)	0.08% (10)	0.02% (13)	0.1% (10)	0.02% (32)
Cohort demographics after matching for age, sex, race, ethnicity, infectious mononucleosis, and EBV seropositivity						
N	220,969	220,969	12,383	12,383	7,128	7,128
Current age, mean (\pm SD)	35.8 (14.5)	35.3 (14.8)	43.0 (16.7)	43.0 (16.6)	48.8 (17.5)	48.9 (17.7)
Sex (male, female)	37%, 63%	39%, 61%	100%, 0	100%, 0	0, 100%	0, 100%
Race						
White (n)	53% (116,277)	56% (123,983)	68% (8,434)	68% (8,436)	74% (5,237)	73% (5,203)
Black or African American (n)	29% (64,086)	17% (36,572)	13% (1,633)	18% (2,173)	16% (1,117)	17% (1,183)
Ethnicity						
Hispanic or Latino (n)	14% (31,494)	14% (31,485)	14% (1,770)	15% (1,906)	8% (584)	9% (617)
Other diagnoses						
Mood disorders	25% (55,850)	16% (36,172)	29% (3,584)	20% (2,466)	49% (3,459)	36% (2,553)
Anxiety disorders	22% (48,261)	19% (43,042)	27% (3,334)	17% (2,094)	46% (3,305)	31% (2,207)
Infectious mononucleosis	0.8% (1,649)	0.8% (1,662)	0.3% (43)	0.3% (32)	0.5% (32)	0.4% (28)
Laboratories						
Presence of EBV nuclear IgG antibody	0.02% (47)	0% (0)	0.08% (10)	0.08% (10)	0.08% (10)	0.08% (10)

Abbreviations: EBV: Epstein–Barr virus, SD: Standard deviation, CI: Confidence interval.

impact of self-identity on MS; however, as sexual behavior can be more easily divided into clear categories, it is more appropriate than sexual identity for this initial step into sexuality-focused MS research.

Given our findings, the lack of clinical studies characterizing MS disease course and pharmacologic treatment response in individuals engaging in same-sex

behavior is a glaring oversight, as other subgroups have been shown to have important clinical differences. African American patients are known to experience a more aggressive MS disease course, with more frequent relapses, worse post-relapse recovery, and faster transition to secondary progressive MS^[12]. Increased severity of MS progression has similarly been demonstrated in Hispanic

Table 2. Outcome of diagnosis with multiple sclerosis (G35) between (a) adults engaging in all forms of high-risk sexual behavior versus adults not engaging in high-risk sexual behavior; (b) males engaging in high-risk homosexual and/or bisexual behavior versus males engaging in high-risk heterosexual behavior; (c) females engaging in high-risk homosexual and/or bisexual behavior versus females engaging in high-risk heterosexual behavior; cohorts are matched for age, race, and ethnicity

Cohort	N	Patients with outcome of multiple sclerosis	Risk	Risk ratio	Odds ratio (95% CI)	P-value
High-risk sexual behavior versus absence of high-risk sexual behavior						
Adults engaging in high-risk sexual behavior	220,969	742	0.336%	0.959	0.959 (0.867, 1.060)	0.4103
Adults not engaging in high-risk sexual behavior	220,969	774	0.350%			
Male same-sex high-risk behavior versus male opposite-sex high-risk behavior						
Males engaging in same-sex high-risk behavior	12,593	53	0.428%	2.789	2.797 (1.653, 4.708)	<0.0001
Males engaging in opposite-sex high-risk behavior	12,593	19	0.153%			
Female same-sex high-risk behavior versus female opposite-sex high-risk behavior						
Females engaging in same-sex high-risk behavior	7,128	116	1.627%	2.275	2.296 (1.639, 3.156)	<0.0001
Females engaging in opposite-sex high-risk behavior	7,128	51	0.715%			

Abbreviation: EBV: Epstein–Barr virus.

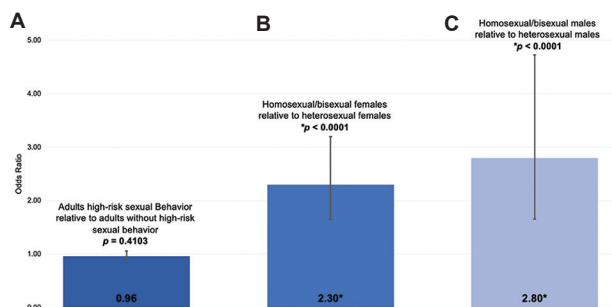


Figure 1. Odds ratio (OR) of multiple sclerosis diagnosis between (A) adults engaging in all forms of high-risk sexual behavior versus adults not engaging in high-risk sexual behavior (OR: 0.96; $P = 0.4103$); (B) females engaging in high-risk homosexual and/or bisexual behavior versus females engaging in high-risk heterosexual behavior (OR: 2.30*; $*P < 0.0001$); (C) males engaging in high-risk homosexual and/or bisexual behavior versus males engaging in high-risk heterosexual behavior (OR: 2.80*; $*P < 0.0001$) – all cohorts are matched for age, race, ethnicity, infectious mononucleosis, and Epstein–Barr virus seropositivity.

Americans^[13]. Our results generate further questioning around whether negative MS outcomes may analogously apply to this sexual minority population. Regarding pharmacologic treatment, recent research has shown that men who have sex with men are far more likely than the general population to use pre-exposure prophylaxis medications or to have been immunized with the recent monkeypox vaccine, which may interact in unforeseen ways with common therapies for MS^[11,12]. The gap in research for individuals engaging in same-sex behavior

may be hindering the development of adequate treatment and identification strategies for this patient population already known to be at risk for negative health outcomes due to societal and health-care inequalities^[8-10].

Our findings may be useful for a range of providers interested in comprehensive patient care, not only those who focus on the LGBTQ+ population. Patients present for care with a wide variety of concerns, and sexual health is an important aspect of overall wellness^[4]. The strong association noted in our study could help identify individuals in the prodromal stage of MS development. The prodrome may be useful for successful intervention in slowing or stopping MS progression, but a prerequisite is successful identification^[18]. As all patients in our study disclosed their patterns of sexual behavior to a health-care provider, our data are reflective of individuals who may have shown prodromal symptoms and have a known personal factor that may increase a provider’s index of suspicion for MS.

As with all retrospective database studies, our study was limited by the de-identified, aggregate nature of the data which prevented us from longitudinally investigating specific characteristics or obtaining detailed socioeconomic status information, which could be a confounding factor. It is also worthwhile to note that patients engaging in exclusively same-sex or opposite-sex behavior may not identify with any specific sexual identity. Up to 11% of individuals identifying as heterosexual may have same-

sex behaviors, and up to 30% of individuals engaging in same-sex behaviors may identify as heterosexual^[19]. The ICD-10 codes utilized may also underestimate the true risk, as codes are entered manually by providers and may be neglected in some cases.

Our findings advance the understanding of MS risk in a unique patient population known to be at risk for negative health outcomes^[15,19]. Early identification is a crucial factor in the evolution of MS and can enable patients to experience a longer time without debilitating symptoms^[20]. It is our hope that these findings could enable health-care providers to suspect and diagnose MS earlier in patients who might otherwise go unnoticed. Future study should seek to rectify the absence of sexuality-focused research in the field of MS, with an eye toward ensuring better patient outcomes and promoting health-care equity.

5. Conclusion

In conclusion, our study uncovered a novel correlation between same-sex sexual behavior and an elevated risk of MS, underscoring the importance of exploring this association further. Both male and female individuals engaging in same-sex behavior demonstrated a notably higher likelihood of MS diagnosis compared to those with opposite-sex behavior, emphasizing the need for targeted research in this understudied area.

However, it is crucial to acknowledge the limitations of our study. The use of de-identified, aggregate data restricted the detailed exploration of individual characteristics and socioeconomic factors, potentially influencing the observed results. Additionally, the complexity of sexual behavior and identity suggests that the ICD-10 codes used may not fully capture the nuanced experiences of individuals.

Moving forward, future investigations should delve deeper into the impact of adverse childhood experiences related to same-sex behavior, shedding light on potential stress-related mechanisms underlying the increased MS risk. Moreover, there is a pressing need for research focusing on disease progression and treatment responses in individuals engaging in same-sex behavior, ensuring that health-care providers can tailor interventions effectively. Addressing these gaps will not only enhance our understanding of MS in this specific population but also pave the way for more inclusive and equitable health-care practices.

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Conflict of interest

The authors have no conflicts of interest to disclose.

Author contributions

Conceptualization: Matthew Kennis, Elijah W. Hale

Data curation: All authors

Formal analysis: All authors

Investigation: All authors

Writing – original draft: All authors

Writing – review & editing: All authors

Ethics approval and consent to participate

This study only utilized aggregated, deidentified patient data and thus was exempted from review by the COMIRB.

Consent for publication

Not applicable.

Availability of data

The original contributions presented in the study are included in the article; further inquiries can be directed to the corresponding author.

Further disclosure

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