IJADR International Journal of Alcohol and Drug Research

The Official Journal of the Kettil Bruun Society for Social and Epidemiological Research on Alcohol

doi: 10.7895/ijadr.381 IJADR, 2023, 11(1), 3 – 12 ISSN: 1925-7066

A systematic review on the impact of alcohol use on sexually transmitted infections

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Abstract

Alcohol use has been associated with multiple types of sexual risk behaviors, such as condomless sex or having multiple sexual partners, behaviors that are linked to the risk of sexually transmitted infections (STIs). The aim of this review was to present updated evidence to demonstrate an association between alcohol consumption and STIs and evaluate the causal nature of this link, as well as to present interventions that reduce alcohol consumption and its effect on STIs. We conducted a systematic review according to the PRISMA guidelines using PubMed and Embase databases. Cohort studies and case-control studies were included. Any level of alcohol use served as the exposure variable, with the outcome restricted to non-HIV STIs, as reviews on alcohol use and HIV already exist. In total, 11 publications satisfied the inclusion criteria. The evidence suggests that there is an association between alcohol use, especially heavy drinking occasions, and STIs, with eight articles finding a statistically significant association. In addition to these results, there is indirect causal evidence from policy studies, and from the field of decision-making and sexual behavior with experimental evidence, that alcohol use increases the likelihood of risk-taking sexual behavior. It is important to have a deeper understanding of the association to develop effective prevention programs at community and individual levels. Preventive interventions should be implemented targeting the general population, in addition to specific campaigns directed at vulnerable subpopulations in order to reduce the risks.

Introduction

Alcohol use has been associated with multiple types of sexual risk behaviors such as condomless sex or having multiple sexual partners (George, 2019; Khadr et al., 2016), behaviors that are linked to the risk of sexually transmitted infections (STIs). It has been difficult to establish causality between alcohol use and condomless sex in epidemiological studies due to personality factors that might be responsible for the inconsistent results between studies (Shuper et al., 2010, 2014). However, some studies based on experimental data found that alcohol use directly affects decision making (e.g. the intent to engage in unprotected sex) which is associated with risky sexual behaviours (e.g. condomless sex; Rehm et al., 2012; Scott-Sheldon et al., 2016).

The association between alcohol consumption and the incidence and course of human immunodeficiency virus (HIV) has been studied previously (Baliunas et al., 2010; Fisher et al., 2007; Kabapy et al., 2020; Rehm et al., 2017). To date, HIV has been included as an alcohol-attributable STI in the World Health Organization's (WHO) last comparative risk assessment or related exercises (Shield et al., 2020; World Health Organization, 2018) (for an overview of the reasoning, see Rehm et al., 2017). The *WHO Global Status Report on Alcohol and Health* (World Health Organization, 2018) also includes tuberculosis and lower

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Financial support: This work was supported by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) of the National Institutes of Health (NIH) under grants R01 AA028224 (JR) and R01 AA028009 (LLF, JR). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.
Declaration of interest: None

respiratory infections as communicable diseases causally impacted by alcohol use (Morojele et al., 2021). Given the existing literature, there may be evidence to incorporate STIs as an alcohol-attributable condition into the next comparative risk assessment. Our objective was to review the literature to gather the strongest evidence to support this decision.

Previous reviews have studied the association between alcohol use and STIs in specific populations, e.g. Chinese population (Li et al., 2010; Zhao et al., 2015), active duty service members and military veterans (Goyal et al., 2012), adolescents (Fortenberry, 1995), but those targeting the general population were published more than 15 years ago (Cook & Clark, 2005; Tüzün et al., 1999). A recent review (George, 2019) approached the association between alcohol and sexual behaviour suggesting that alcohol stimulates participants into a mind state that searches for sexual gratification despite the risks, promoting unsafe sexual relations. However, the reviews included cross-sectional studies where risk factors cannot imply causality, and some authors have suggested that the association found has mostly been based on poor quality studies (George, 2019; Tüzün et al., 1999).

Accordingly, our aim is to present updated evidence indicative of a causal association between alcohol consumption and STIs by selecting studies with the highest level of evidence, i.e., based on longitudinal design (cohort studies) and biological ascertainment of STIs (for both cohort and case-control studies). With these strict inclusion criteria, we have selected well-designed observational studies (Concato et al., 2000).

In addition to our systematic review, we present structural policy interventions to reduce alcohol consumption and its corresponding effect on STIs, based on Bradford-Hill list of causal criteria (Hill, 1965)

Methods

Systematic Search and Selection of Articles

A systematic search was conducted using electronic databases of PubMed/Medline and Embase from their inception to May 2021 (updated in June 2022) according to the PRISMA guidelines (PRISMA, 2015); search strategy and PRISMA checklist are presented in Appendices 1 and 2. The reference list of relevant articles was reviewed. All articles were screened independently by two of the authors using a two-step approach of first screening (a) the title/abstract and then (b) the full-text.

Articles that studied the association between alcohol consumption and STIs that were published in peer-reviewed journals in English or Spanish were selected. Cohort studies (with at least two quantitative measurement points) and case-control studies, all with biological ascertainment of STI, were included. These inclusion criteria excluded the vast majority of the literature, which involved articles demonstrating simple associations based on cross-sectional surveys using only verbal assessment for both the exposure and outcome, and often involved non-matching time periods (e.g., drinking over the past year, current STI). We restricted our search to observational studies and did not include experimental studies.

We included studies that reported alcohol consumption (defined by quantity, patterns or frequency) as the exposure variable, with the outcome restricted to non-HIV STIs. In global health estimates (World Health Organization, 2019), STIs are categorized as part of the 'Infectious and parasitic diseases group' (ICD-10 codes A50-A64, N70-N73), which includes syphilis, chlamydia, gonorrhoea, trichomoniasis, genital herpes and others, excluding HIV. The Global Burden of Disease Study (Global Health Data Exchange (GHDx), 2020) use the term 'sexually transmitted infections other than HIV' but has similar categories and definitions (ICD-10 codes A50-A60.9, A63-A64.0, B63, I98.0, K67.0-K67.2, M73.0-M73.8, N70-N71.9, N73-N74, N74.2-N74.8, Z11.3, Z20.2, Z22.4).

Data Extraction

Key information was extracted by two authors. Population characteristics (sample, mean age, gender), alcohol consumption measure, STI outcome measure, odds ratio (OR), relative risk (RR) and adjustments were extracted on a standardized spreadsheet. When available, we obtained results for specific subgroups of participants (e.g., pattern of alcohol use, type of STI).

Data Synthesis

Due to the heterogeneous results from the studies in terms of alcohol use pattern e.g. "alcohol abuse" vs "no abuse" (Crosby et al., 2008; Ghebremichael & Paintsil, 2011), quantity of alcohol use (Wiley et al., 2012; Wilson et al., 2014) and STI outcome (combined results of different STIs (Crosby et al., 2008; Hutton et al., 2008; Scott-Sheldon et al., 2013), we did not perform a meta-analysis. Instead, summaries of all the included studies were presented. To avoid stigmatization, we used the term "alcohol use", in quotes, throughout the manuscript, a term which has been used by authors of earlier publications.

Quality Assessment

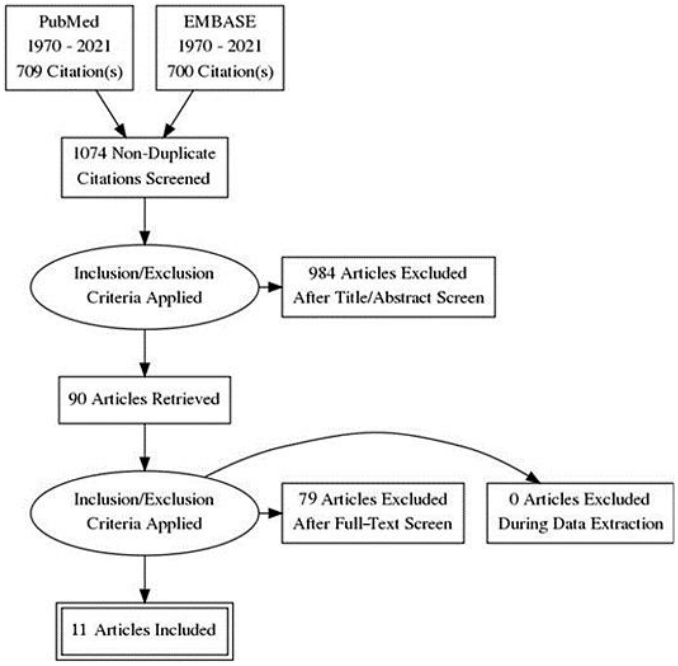
Certain minimal quality criteria were included in the search strategy. Thus, all studies had to include biologically diagnosed outcomes. Cohort studies with at least two quantitative measurement points were included. While this excluded most of the literature, the remaining articles were usually of moderate quality, well-designed, with relatively small sample sizes.

Results

Search results yielded 709 articles from PubMed/Medline and 700 articles from Embase (Figure 1). In total, 11 publications satisfied the inclusion criteria. As there are countless articles (mostly cross-sectional studies, not included in our review) on associations between alcohol use and STIs (for a random selection, see Connor et al., 2015; Herrera et al., 2016; Hojilla et al., 2020; Liu et al., 2016; Soe et al., 2018), we based our review solely on cohort and case control studies.

Figure 1

PRISMA Chart on the Literature Search on Associations between Alcohol Consumption and STIs.



Case-Control Studies

The six studies selected had mixed results. Four of them (Crosby et al., 2008; Ghebremichael & Paintsil, 2011; Hutton et al., 2008; Wiley et al., 2012) provided statistically significant associations between alcohol use and STIs (eight out of 33 estimations were statistically significant, see Table 1).

The study by Crosby and colleagues (2008) found that after controlling for age and women's self-efficacy for condom use negotiation, women's intoxication while having sex was significantly associated with having condomless sex (OR 1.92, 95% IC 1.36--2.71) and concluded that the risk of testing positive for at least one of the three STIs analyzed was 1.4 times greater for women who had had sex with an intoxicated male.

Ghebremichael et al. conducted two different studies with a sample of men (Ghebremichael & Paintsil, 2011) and women (Ghebremichael et al., 2009) in Tanzania. In men, "alcohol abuse", age at first sexual intercourse, multiple sexual partners, and casual sex were associated with a high prevalence of STIs. In women, "alcohol abuse" was directly associated with STI symptoms (OR 1.61; 95% CI: 1.08-2.40) and number of sexual partners in the last three years (OR 1.66; 95% CI: 1.01-2.73). They did not find a significant association between testing positive for an STI and "alcohol abuse" in women but their number of sexual partners was associated with STIs (OR 2.41; 95% CI: 1.46-4.00).

Another study found a significant association between alcohol consumption and a diagnosis of gonorrhea (Hutton et al., 2008). Binge drinkers had twice the risk compared to those who did not drink. Women binge drinkers had five times the rate of gonorrhea compared to women who did not drink. No association was found between alcohol consumption and chlamydia or syphilis.

Scott-Sheldon et al. (2013) found that quantity and frequency of alcohol use were both associated with having multiple sexual partners, and that the quantity of alcohol consumption moderated the association between sexual partners and trichomoniasis (interaction of number of sexual partners and drinks per drinking day [OR = 1.03, p = 0.04], drinks per drinking week [OR = 1.01, p = 0.04] and peak consumption [OR = 1.02, p = 0.02]).

Finally, Wiley and colleagues (2012) found no association between alcohol consumption and the detection of index HPV DNA. However, they reported that women who consumed one to four drinks weekly were actually less likely to test positive for anti HPV16/18 antibodies than non-drinkers, and suggested that alcohol use might in fact blunt the immune response to HPV and not that women with higher consumption were less exposed to index HPVs.

The limitations of these studies concerned a lack of representativeness of the sample, recall bias, that alcohol use might be underreported due to social desirability bias, and the difficulty of determining the temporal relationship.

Table 1

Characteristics of Case Control Studies on the Association between Alcohol Consumption and Risk of STIs

Study	Sample	Mean age years (SD)	STD measure (diagnostic test)	AC measure/categories	Odds ratio (95% confidence interval)		
					Men	Women	Both
Crosby et al., 2008	715 African American women, USA	17.8 (1.7)	Trichomonas (PCR), chlamydia and gonorrhea (Abbott LCx Probe System, then Amplified DNA assay)	Alcohol intoxication	1.44 (1.03–2.02)*	1.29 (0.90–1.83)	
Ghebremichael & Paintsil, 2011	544 men, Tanzania	37 (8.9)	HSV-2 (EIA), syphilis (RPR and/or TPHA), chlamydia, trichomonas, and mycoplasma (M-PCR assay)	"Alcohol non-abuse" (CAGE 0-1), "alcohol abuse" (CAGE 2-4)	1.53 (1.33–3.88)* [a]		
Ghebremichael et al., 2009	977 women, Tanzania	No data	HSV-2 (EIA), syphilis (RPR and/or TPHA) and chlamydia, gonorrhea, trichomonas, and mycoplasma (M-PCR assay)	"Alcohol non-abuse" (CAGE 0-1), "alcohol abuse" (CAGE 2-4)		0.86 (0.55–1.34)	
Hutton et al., 2008	671 (320 men, 351 women), USA	Calculated by alcohol group	Gonorrhea (culture)	AC no binge	2.44 (1.01–5.86)*	2.23 (0.53–9.38)	2.31 (1.10–4.84)*
				Binge drinking	2.10 (0.91–4.88)	5.33 (1.35–21.01)*	2.67 (1.31–5.45)*
			Chlamydia (PCR)	AC no binge	1.07 (0.32–3.55)	0.47 (0.12–1.79)	0.7 (0.29–1.70)
				Binge drinking	0.99 (0.33–3.01)	1.06 (0.32–3.48)	0.92 (0.41–2.07)
			Syphilis (serology)	AC no binge	2.75 (0.45–16.77)	0.24 (0.03–2.19)	0.94 (0.28–3.14)
				Binge drinking	2.27 (0.38–13.60)	1.21 (0.29–5.06)	1.41 (0.48–4.17)
Scott-Sheldon et al., 2013	580 women, USA	28 (9)	Trichomonas (rapid test) and chlamydia (PCR), gonorrhea (culture), bacterial vaginosis (Amsel's criteria) as covariates	Drinking days		1.04 (0.91 to 1.19) [a]	
				Drinks per drinking day		0.95 (0.85 to 1.05) [a]	
				Frequency of heavy drinking		0.99 (0.95 to 1.04) [a]	
Wiley et al., 2012	2255 women, USA	20.1 (1.7)	HPV 6/11 (Antibody in Serum)	1–4 drinks		0.8 (0.59–1.10)	
				5/more drinks		0.58 (0.34 – 1.00)	
			HPV 6/11 (DNA in Cervicovaginal Specimen)	1–4 drinks		1.08 (0.71–1.64)	
				5/more drinks		0.96 (0.51–1.83)	
			HPV 16/18 (Antibody in Serum)	1–4 drinks		0.72 (0.53–0.99)*	
				5/more drinks		0.49 (0.28–0.87)*	
			HPV 16/18 (DNA in Cervicovaginal Specimen)	1–4 drinks		0.95 (0.7–1.31)	
				5/more drinks		0.85 (0.53–1.37)	

*Statistically significant results

[a] Univariate analysis

Note: *PCR:* polimerase chain reaction; *AC:* alcohol consumption; *RPR:* rapid plasma regain; *TPHA:* Treponema pallidum hemagglutinantion assay; *EAI:* enzyme immune assay; *HPV:* human papillomavirus.

Table 2

Characteristics of Cohort Studies on the Association between Alcohol Consumption and Risk of STIs

Study	Sample	Mean age (SD)	STD measure (diagnostic test)	AC measure/categories		Relative risk (95% confidence interval) Women	Both
Boden et al., 2011	1265 (635 men, 630 women), New Zealand	No data	Any self-reported sexually transmitted infection contrasted by clinical reports	AC in the last year (quantity and frequency variables classified by percentile)	71st to 90th percentile		1.34 (1.09–1.67)* [a]
					91st to 100th percentile		1.81 (1.18–2.78)* [a]
Miller et al., 2001	1034 (485 men, 549 female), Australia	No data	Gonorrhea (PCR)	"Alcohol abuse" (binge drinking or regular heavy use)			1.46 (p = 0.007)* [b]
			Chlamydia (PCR)				1.18 (p = 0.282) [b]
			Syphilis (ELISA or FTA-Abs, RPR test for the positive results)				0.63 (p = 0.423) [b]
Seth, Sales, et al., 2011	393 African American women, USA	17.9 (1.7)	Trichomonas (PCR)	High alcohol quantity (3/more drinks in one sitting)		2.00 (1.11 – 3.60)*	
			Gonorrhea (Abbott LCx Probe System, then Amplified DNA assay)			1.83 (0.86 – 3.89)	
			Chlamydia (Abbott LCx Probe System, then Amplified DNA assay)			1.10 (0.62 – 1.93)	
Seth, Wingood, et al., 2011	848 African American women, USA	22 (3.61)	Chlamydia (Amplified DNA assay)	Alcohol consumption in the past 30 days at baseline (frequency)		2.23 (1.29 – 3.85)*	
			Chlamydia and/or gonorrhea (Amplified DNA assay) and/or trichomonas (PCR)			1.69 (1.09 – 2.62)*	
Wilson et al., 2014	474 women, Kenya	29 (IQR 25.4)	Gonorrhea and chlamydia (Gen-Probe APTIMA Combo 2 assay), trichomonas (microscopic)	Number of alcohol drinks consumed in a week	1–7 drinks	1.0 (0.5–1.9)	
					8/more drinks	1.0 (0.4–2.4)	

*Statistically significant results

[a] Adjusted by fixed effects and observed covariates

[b] Univariate analysis

Note: PCR polimerase chain reaction, AC alcohol consumption, RPR rapid plasma regain

Cohort Studies

Four out of the five cohort studies included showed significant associations between at least one measure of alcohol use and STIs (six out of twelve estimations were statistically significant, see Table 2).

A study by Boden and colleagues (2011) identified that individuals with the highest level of alcohol consumption or "alcohol abuse" symptoms had 2.5 times higher rates of STIs compared to those with the lowest level of alcohol consumption. When adjusting for non-observed fixed confounding factors, the magnitude of the associations was reduced but remained statistically significant.

Other studies targeted a range of specific populations. A study conducted in an Aboriginal community in Australia (Miller et al., 2001) found that "alcohol abuse" was a significant predictor of incident gonorrhea (RR 1.6 compared with people who did not "abuse alcohol"), but not of incident chlamydia or syphilis. A study exploring alcohol use as a longitudinal predictor of sexual behaviors and STIs among African American adolescent females (Seth, Sales, et al., 2011) found that a high quantity of alcohol use predicted a positive STI test for trichomonas vaginalis. However, there were no significant findings for alcohol use predicting gonorrhea or chlamydia infection over the 12-month follow-up period. In another publication using the same cohort (Seth, Wingood, et al., 2011), women who consumed alcohol in the past 30 days were more likely to test positive for chlamydia or for any of the STIs studied compared with those who abstained. This study highlights the relationship between alcohol consumption at non-heavy levels with STIs and risky sexual behaviors.

A study conducted among African women reporting transactional sex (Wilson et al., 2014) found no statistically significant association between alcohol use and incident STI in HIV-negative women. However, the association was significant with an increased risk of STIs in the HIV-positive

women who reported consumption of one to seven drinks per week (*OR* 2.3 [95% *CI*: 1.0, 5.5], $p = 0.05$).

The limitations of these studies included heterogeneous samples, the possibility that alcohol use may have been underreported due to social desirability bias, and only having one measurement of alcohol consumption (at baseline).

Indirect Causal Indicators: Alcohol Policy Interventions and Risk of STI

An ecological analysis described a significant correlation between changes in alcohol *per capita* consumption and in the reported gonorrhea and syphilis incidence rate (Chesson et al., 2003). They found that for each 1% increase in *per capita* alcohol consumption, an increase of 0.4% to 0.6% in gonorrhea incidence and 2.5% to 3.6% in syphilis incidence was demonstrated. Successful interventions to reduce alcohol consumption also reduce the rates of STIs. In the classic meta-analyses on the effect of increasing alcohol taxation on disease and mortality outcomes (Wagenaar et al., 2010), four articles which described the effects of alcohol taxes or prices on rates of STIs and risky sexual behavior were identified. From these four articles, 28 out of a total of 37 individual estimates, showed a statistically significant inverse association. More recently, studies in the US (Staras et al., 2014) and in Australia (Gilmore et al., 2020) found decreases in gonorrhea and chlamydia rates following an alcohol tax increase. Similarly, a study in the Netherlands (Den Daas et al., 2019) showed an association between increasing the minimum purchasing age and chlamydia rates in the affected age group.

Discussion

The evidence suggests that there is an association between alcohol consumption and the risk of contracting an STI, as seen in eight out of eleven case-control and cohort studies presented in this review. The association between alcohol consumption and STIs has been known for a long time (Marshall, 1908). However, such associations cannot establish causality, which needs to come from establishing convincing pathways, both behavioral and biological, for the impact of alcohol use on sexual behavior (Rothman et al., 2008). We also have to be cautious when interpreting the results due to the limitations encountered when synthesizing this complex topic. It has been observed in certain sub-populations, such as the Aboriginal community or African-American women, that the incidence of STIs is linked to alcohol consumption (Miller et al., 2001; Seth, Sales, et al., 2011; Seth, Wingood, et al., 2011; Wilson et al., 2014). In addition, alcohol use has also been shown to impact disease course (Cook & Clark, 2005; George, 2019; Tüzün et al., 1999; Wiley et al., 2012; Wilson et al., 2014). In contrast with the most recent systematic review (Cook & Clark, 2005), our study summarized results of the existing literature with strict inclusion criteria by selecting well-designed observational studies in this area of research. We found more recent studies, all of them published after the year 2000, which enable us to present the most up-to-date evidence on this topic. In addition, our search was not restricted to specific populations as it was in other reviews.

Alcohol use, especially heavy drinking, impacts on both sexual risk behaviour and the immune system. With respect to decision-making, there is good evidence that alcohol use increases (sexual) risk-taking behavior as has been seen in experimental studies and reviews (Eakins et al., 2022; Kalichman et al., 2007; Lan et al., 2017; Rehm et al., 2017; Sandfort et al., 2017; Scott-Sheldon et al., 2016; Shuper et al., 2009, 2017; Strathdee et al., 2021; Vagenas et al., 2013; Woolf-King & Maisto, 2011); the most studied example being that it increases the chance of not using condoms. While condoms do not protect against all STIs—providing no protection if the condom does not fully cover the infected areas or sores—condom use effectively reduces the overall risk of contracting an STI (Centers for Disease Control and Prevention (CDC), 2021).

Rehm and colleagues (2017) gave a detailed overview on the causal reasoning of the impact of alcohol use on STIs with a focus on HIV/AIDS. Given that many patients are unaware of their STI status, people with STIs exhibit similar behavior than do those without STIs. This review showed strong evidence on the impact of alcohol use (mainly heavy drinking occasions before or during sexual encounters) on riskier sexual practices. As indicated, this relationship applies to HIV/AIDS infections as well as to all STIs, although in some cases (e.g., HPV infection; Comerlato et al., 2020) we should consider gender differences based on the appearance of symptoms.

Alcohol control policies have shown a positive association with reduced STIs in the population (Cohen & Scribner, 2000), specifically observed for a decrease on the STI's rates when alcohol taxation increased (Gilmore et al., 2020; Staras et al., 2014). These studies suggested indirect casual evidence between alcohol use and STIs. At the individual level, reducing alcohol consumption may reduce the risk of STIs. The assessment for alcohol consumption together with the provision of brief interventions should be considered by clinicians who treat individuals at risk for STIs (Appel et al., 2006; Harris et al., 2018). Further investigation should address the direct effect on STI infection rates based on the implementation of alcohol policies, and specific studies on alcohol-related sexual risk reduction interventions that target at-risk drinkers should be conducted.

There are some limitations of this review that should be mentioned. The majority of the studies that the systematic review yielded were of poor quality, often cross-sectional surveys based on self-reports for both exposure and outcomes. Previous reviews on the subject have been less restricted in their inclusion criteria but they have been critical of the challenges involved in summarizing such a complex association – which is normally a result of impulsive sexual behaviour and risky sexual practices. Also, for practical and ethical reasons, randomized trials that directly assess the impact of alcohol consumption on STI outcomes are not performed, and to date we are not aware that such studies have been conducted. Despite this, the more highly controlled studies, which have longitudinal designs (cohort studies) and biological measurement for the outcomes, also support an association. The articles we included presented different types of alcohol measurements (e.g. quantity or frequency of alcohol consumed) and STI-

related outcomes (e.g., any confirmed biologically STI, one specific STI). This limited the standardization of studies and made it difficult to compare the risks of alcohol use. Nevertheless, the causal pathways for alcohol use are largely similar between all STIs, and overall we observed an increased risk of STI for drinkers compared to non-drinkers. Finally, this study faced limitations regarding study design in the existing literature. There is a limitation when addressing confounders or modifiers in the relationship between alcohol use and STIs. As for case-control studies, recall bias may have caused an overestimation of the association.

In conclusion, our systematic review presented evidence that showed an association between alcohol use and STIs. Alcohol increases the risk of STIs through risky sexual behaviour (Crosby et al., 2008; Scott-Sheldon et al., 2013) and might increase the biologic susceptibility to an STI as seen in the literature (Wiley et al., 2012). In addition to these results, there is indirect causal evidence from policy studies, and from the field of decision-making and sexual behavior with experimental evidence, that alcohol use increases the likelihood of risk-taking sexual behavior. It is possible that alcohol use might directly increase STIs, but given the complexity of the literature and the heterogeneity of results, it remains difficult to definitively establish causality. Future research that analyzes whether a reduction of alcohol consumption might lead to a reduced risk of future STIs could provide stronger evidence for understanding the casual link between alcohol use and STIs. Preventive interventions which target the general population as well as more specific campaigns directed at vulnerable subpopulations should be implemented in order to reduce these risks. Improving sexual health must take into account the important role of alcohol use in sexual behavior.

Abbreviations

STI: Sexually transmitted infection
HIV: Human immunodeficiency virus
DALY: Disability-adjusted life years
WHO: World Health Organization
AIDS: Acquired immunodeficiency syndrome
OR: Odds ratio
RR: Relative risk
MSM: Men who have sex with men
HPV: Human papilloma virus

Authors' Contributions

Conceptualization, J.R.; methodology, J.R.; investigation, L.LF., O.H. and J.R.; data extraction, L.LF. and J.R.; writing—original draft preparation, L.LF.; writing—review and editing, all authors.; supervision, J.R and P.S.; project administration, J.R.; funding acquisition, J.R. All authors have read and agreed to the published version of the manuscript. Each author certifies that their contribution to this work meets the standards of the International Committee of Medical Journal Editors.

Acknowledgements

We would like to acknowledge Astrid Otto for copy-editing the manuscript.

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