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Authors

Navadeh, Soodabeh
Mirzazadeh, Ali
McFarland, Willi
[et al.](#)

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Using expert opinion to quantify unmeasured confounding bias parameters

Soodabeh Navadeh, MD, MPH,^{1,2} Ali Mirzazadeh, MD, MPH, PhD,^{1,3} Willi McFarland, MD, PhD,^{3,4} Sarah Woolf-King, PhD, MPH,⁵ Mohammad Ali Mansournia, MD, MPH, PhD²

ABSTRACT

OBJECTIVE: To develop and apply a method to quantify bias parameters in the case example of the association between alcohol use and HIV-serodiscordant condomless anal sex with potential confounding by sensation seeking among men who have sex with men (MSM), using expert opinion as an external data source.

METHODS: Through an online survey, we sought the input of 41 epidemiologist and behavioural scientists to quantify six parameters in the population of MSM: the proportion of high sensation seeking among heavy-drinking MSM, the proportion of sensation seeking among low-level drinking MSM, and the risk ratio (RR) of the association between sensation seeking and condomless anal sex, for HIV-positive and HIV-negative MSM.

RESULTS: Eleven experts responded. For HIV-positive heavy drinkers, the proportion of high sensation seeking was 53.6% (beta distribution [$\alpha = 5.50$, $\beta = 4.78$]), and 41.1% (beta distribution [$\alpha = 3.10$, $\beta = 4.46$]) in HIV-negative heavy drinkers. In HIV-positive low-level alcohol drinkers, high sensation seeking was 26.9% (beta distribution [$\alpha = 1.81$, $\beta = 4.92$]), similar to high sensation seeking among HIV-negative low-level alcohol drinkers (25.3%) (beta distribution [$\alpha = 2.00$, $\beta = 5.89$]). The lnRR for the association between sensation seeking and condomless anal sex was ln(2.4) (normal distribution [$\mu = 0.889$, $\sigma = 0.438$]) in HIV-positive and ln(1.5) (normal distribution [$\mu = 0.625$, $\sigma = 0.391$]) in HIV-negative MSM.

CONCLUSION: Expert opinion can be a simple and efficient method for deriving bias parameters to quantify and adjust for hypothesized confounding. In this test case, expert opinion confirmed sensation seeking as a confounder for the effect of alcohol on condomless anal sex and provided the parameters necessary for probabilistic bias analysis.

KEY WORDS: Unmeasured confounder; sensation seeking; men who have sex with men; alcohol use; condomless anal sex; bias analysis

La traduction du résumé se trouve à la fin de l'article.

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Potentially HIV-discordant unprotected anal intercourse is defined as having condomless anal intercourse between an HIV-negative and an HIV-positive partner, and has been used as a measure for sex of highest HIV transmission and acquisition risk among men who have sex with men (MSM).^{1,2} Previous research showed that this risk was higher in heavy alcohol drinkers than in low-level alcohol drinkers or non-drinkers in both HIV-positive and HIV-negative MSM.¹

Sensation-seeking personality trait is identified as the intention to be involved in various high-risk activities. Among MSM, sensation seeking can act as a risk factor for HIV through high-risk behaviours such as having condomless intercourse.³ On the other hand, Kalichman et al. showed that sensation seeking is also a risk factor for heavy alcohol use.⁴ Therefore, sensation seeking can predict alcohol consumption during sexual activities among MSM. Based on this scenario, sensation seeking could be a confounder for the effect of alcohol use on risky sex among MSM.

Since sensation seeking is not often included in behavioural surveys of populations at risk for HIV,⁵ it would be an unmeasured confounder in many studies and could not be adjusted for using conventional statistical methods. An alternative approach to adjust for unmeasured confounders is Bayesian bias analysis. The Bayesian method uses prior distributions for the bias parameters

as inputs to estimate the adjusted effects.⁶ Using expert opinion is one method to derive prior distributions, especially when internal data sources (such as directly measured confounders or qualitative internal substudies) are not available.⁷

In the above example, the bias parameters needed are the prevalence of the confounder (sensation seeking) among exposed (heavy drinkers) and unexposed (low-level drinkers) and the association between the confounder and outcome (condomless anal sex).⁶

Using expert opinion, this study aims to derive the prior distributions of bias parameters to adjust an unmeasured confounder when internal data sources are not available.

Author Affiliations

1. Global Health Sciences, University of California, San Francisco, CA
2. Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran
3. Department of Epidemiology and Biostatistics, University of California, San Francisco, CA
4. San Francisco Department of Public Health, San Francisco, CA
5. Department of Medicine, Center for AIDS Prevention Studies, University of California, San Francisco, CA

Correspondence: Dr. Mohammad Ali Mansournia, Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, PO Box: 14155-6446, Tehran, Iran, Tel: +98-21-88989123, E-mail: mansournia_ma@yahoo.com

Conflict of Interest: None to declare.

METHODS

Study participants

We conducted an expert panel survey by approaching 41 researchers and clinicians knowledgeable about high-risk behaviour among MSM. We used three different methods to find experts. In a publicly announced lecture on our research area, we identified 7 experts among our university's faculty. An additional 24 experts were identified as the corresponding authors of peer-reviewed published papers on alcohol use, sensation seeking, and risky sexual behaviour in medical databases such as PubMed. In both methods we asked the experts to introduce us to other experts in the related area of research. Ten experts were located using this referral method.

Measures

Each expert received an online survey and a follow-up reminder on each of weeks 2 and 4. After explaining the study objectives and acquiring their consent, we sent them a short electronic survey asking them to provide their best guess for the bias parameters in the causal diagram shown in Figure 1.

Experts were asked to guess the prior mode and 95% limits for the following bias parameters in the population of HIV-positive and HIV-negative MSM separately:

- Proportion of high sensation-seekers among heavy alcohol-drinking MSM.
- Proportion of high sensation-seekers among low-level alcohol-drinking MSM.
- Risk ratio (RR) of the association between sensation seeking and potentially HIV-discordant condomless anal sex.

The RR of the association between sensation seeking and alcohol use, as one of the bias parameters, can be calculated from the first two questions (proportion of high sensation seekers).

To simplify the exercise, we asked experts to consider alcohol use and sensation seeking as dichotomous variables of high and low. Using the definition of the National Institute on Alcohol Abuse and Alcoholism (NIAAA) for alcohol use, we indicated that a low-level drinker is one who “has no more than 4 drinks on any single day and no more than 14 drinks per week”. Heavy drinkers were defined as “drinking 5 or more drinks on the same occasion on each of 5 or more days in the past 30 days”. In the US, one “standard” drink contains roughly 14 g of pure alcohol.⁸

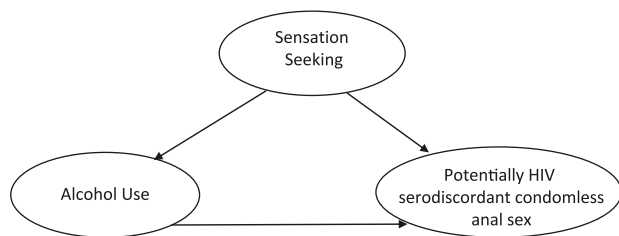


Figure 1. Directed acyclic graph of the association between alcohol use and potentially HIV-serodiscordant condomless anal sex with potential confounding by sensation seeking.

For sensation seeking, we clarified to participants to consider the definition of Newcomb et al.⁹ In this definition, people are categorized into low and high sensation-seekers based on their scores earned from Hoyle et al.'s 8-item brief sensation-seeking scale. We posited that experts consider high sensation-seekers as those scoring high in the scores ranging from 1 to 5.⁹

Statistical analysis

We used descriptive statistics and a non-parametric bootstrap method with 10,000 repetitions, due to small sample size, to summarize the observed data and calculate the mean, 95% confidence interval (CI) and 95% simulated interval (SI) for each prior mode and 95% prior limits reported by experts. For the non-parametric bootstrap, we used the frequency distribution of the experts as our best guess of the probability distribution of each bias parameter. We then ran 10,000 iterations, each one generating a new bootstrap replicate. From these replicates samples, we generated the sampling distribution and calculated the mean and 95% SI for each bias parameter.

Since the third bias parameter was the RR, we used the logarithmic scale and calculated the geometric mean.

Histograms were used to show the distributions of the sensation-seeking bias parameters based on the observed data. We chose the beta distribution as the prior for proportions and normal distribution as the prior for lnRR (natural logarithm of RR); we used the moment method on the reported prior modes to determine the bias distribution parameters. We used Stata Version 14 for the descriptive and bootstrap analysis and R software Version 3.2 for other analyses.

RESULTS

Eleven of the 41 experts approached agreed to participate. Five were faculty of our university, three were the corresponding authors of peer-reviewed published papers on the topic of alcohol use and risk behaviour, and three were referred experts from other participants.

Table 1 shows the prior mode and 95% prior limits of the bias parameters along with the 95% CIs and 95% SIs. Based on the experts' opinions, the means of the prior mode for the proportion of high sensation seekers among heavy alcohol-drinking HIV-positive and HIV-negative MSM were 53.6% (95% SI 45.2%–61.9%) and 41.0% (95% SI 31.6%–50.4%) respectively. According to the experts' responses, the proportion of high sensation seeking varied from 37.2% (95% SI 26.2%–48.2%) to 68.2% (95% SI 60.6%–75.8) among HIV-positive heavy drinkers. Likewise, the parameter varied from 29.5% (95% SI 19.8%–39.2%) to 54.6% (95% SI 44.4%–64.8%) among HIV-negative heavy-drinking MSM.

The prior modes and 95% prior limits of the second bias parameter (i.e., the proportion of high sensation-seekers among low-level alcohol-drinking MSM) were similar for HIV-positive and HIV-negative MSM. The means were 26.9% for HIV-positive MSM and 25.3% for HIV-negative MSM. The expert estimated RR of the association between sensation seeking and potentially discordant condomless anal sex (the third bias parameter) was 2.4 among HIV-positive MSM and 1.9 among HIV-negative MSM.

Figure 2 shows the empirical distribution of the reported prior modes for three bias parameters in HIV positives and HIV negatives, separately. The estimated bias parameters based on the

Table 1. Descriptive statistics of sensation-seeking bias parameters in the association between alcohol use and potentially HIV-serodiscordant condomless anal sex among men who have sex with men (MSM)

	Lower bound of 95% prior limit		Prior mode		Upper bound of 95% prior limit	
	Mean (95% CI)	Bootstrap 95% SI	Mean (95% CI)	Bootstrap 95% SI	Mean (95% CI)	Bootstrap 95% SI
Proportion of high sensation seeking (%)						
Among HIV-positive heavy alcohol-drinking MSM	37.2 (24.1–50.3)	26.2–48.2	53.6 (43.6–63.5)	45.2–61.9	68.2 (59.1–77.3)	60.6–75.8
Among HIV-negative low-level alcohol-drinking MSM	29.5 (18–41)	19.8–39.2	41.1 (29.9–52.2)	31.6–50.4	54.6 (42.4–66.8)	44.4–64.8
Proportion of high sensation seeking (%)						
Among HIV-positive low-level alcohol-drinking MSM	15.5 (7.9–23.2)	9–22	26.9 (16.2–37.6)	17.8–35.9	39.4 (25.8–53.1)	28.1–50.8
Among HIV-negative low-level alcohol-drinking MSM	15.2 (8.2–22.3)	9.3–21.2	25.3 (15.7–35)	17.2–33.5	37.5 (24.4–50.6)	26.6–48.5
Risk ratio of the association between sensation seeking and potentially HIV-serodiscordant condomless anal sex (%)						
Among HIV-positive MSM	1.4 (1.3–1.6)	1.3–1.6	2.4 (1.8–3.3)	1.9–3.1	3.3 (2.3–4.9)	2.4–4.6
Among HIV-negative MSM	1.1 (0.9–1.5)	0.9–1.4	1.9 (1.4–2.4)	1.5–2.3	2.7 (1.9–3.7)	2.1–3.5

Note: CI = confidence interval; SI = simulated interval.

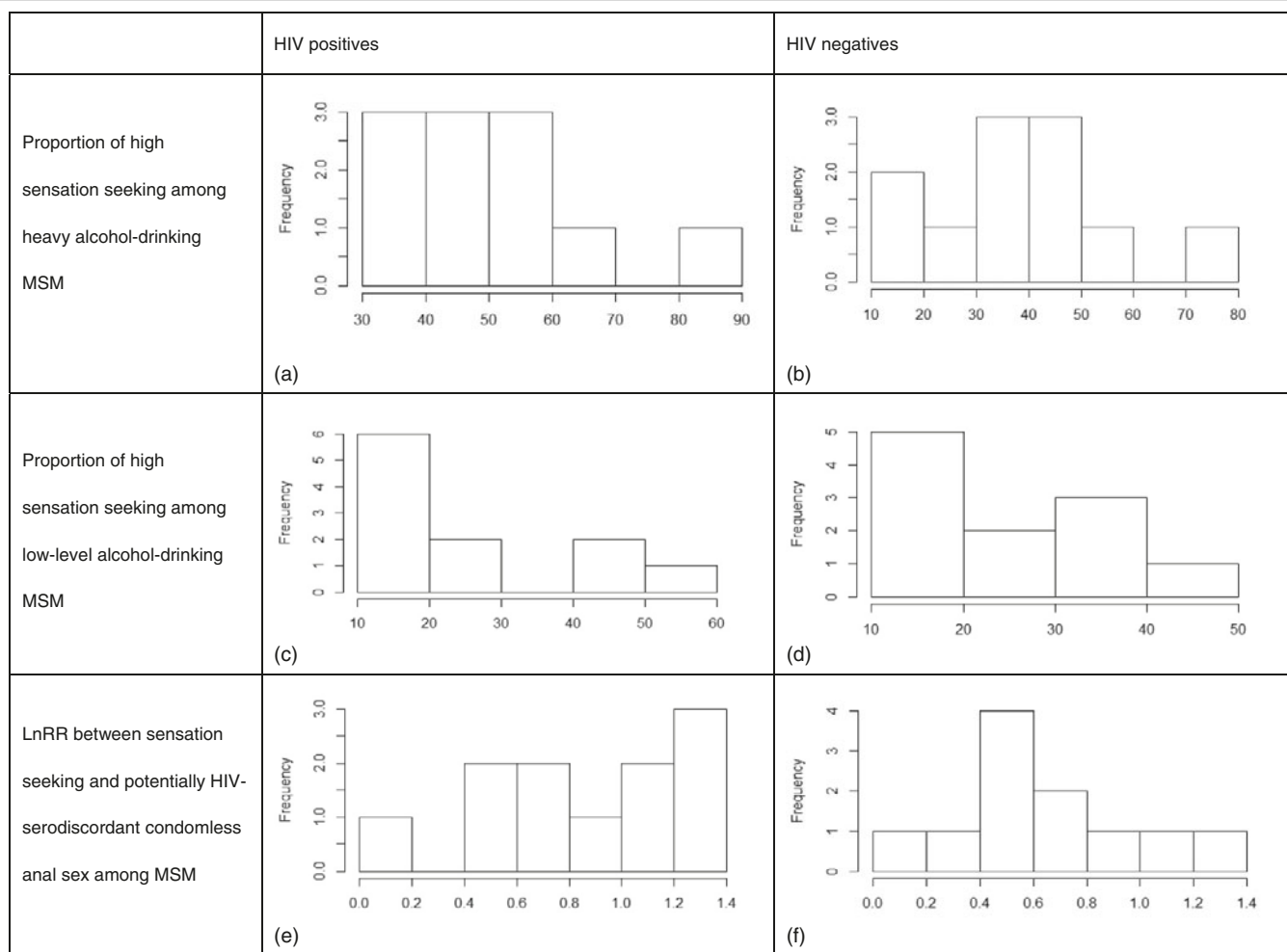


Figure 2. Distributions of sensation-seeking bias parameters in the association between alcohol use and potentially HIV-serodiscordant condomless anal sex with potential confounding by sensation seeking based on the observed data.

moment technique for the specified distributions of the priors are shown in Figure 3. The beta parameters (α, β) for the proportion of high sensation-seekers among HIV-positive heavy drinkers were (5.50, 4.78) respectively (Figure 3a). Since the first beta parameter is

considerably less than the second parameter (i.e., $\alpha < \beta$) for the proportion of high sensation seeking among low-level alcohol drinkers (Figures 3c and 3d), the beta distributions are skewed to the right. The prior for lnRR followed a normal distribution

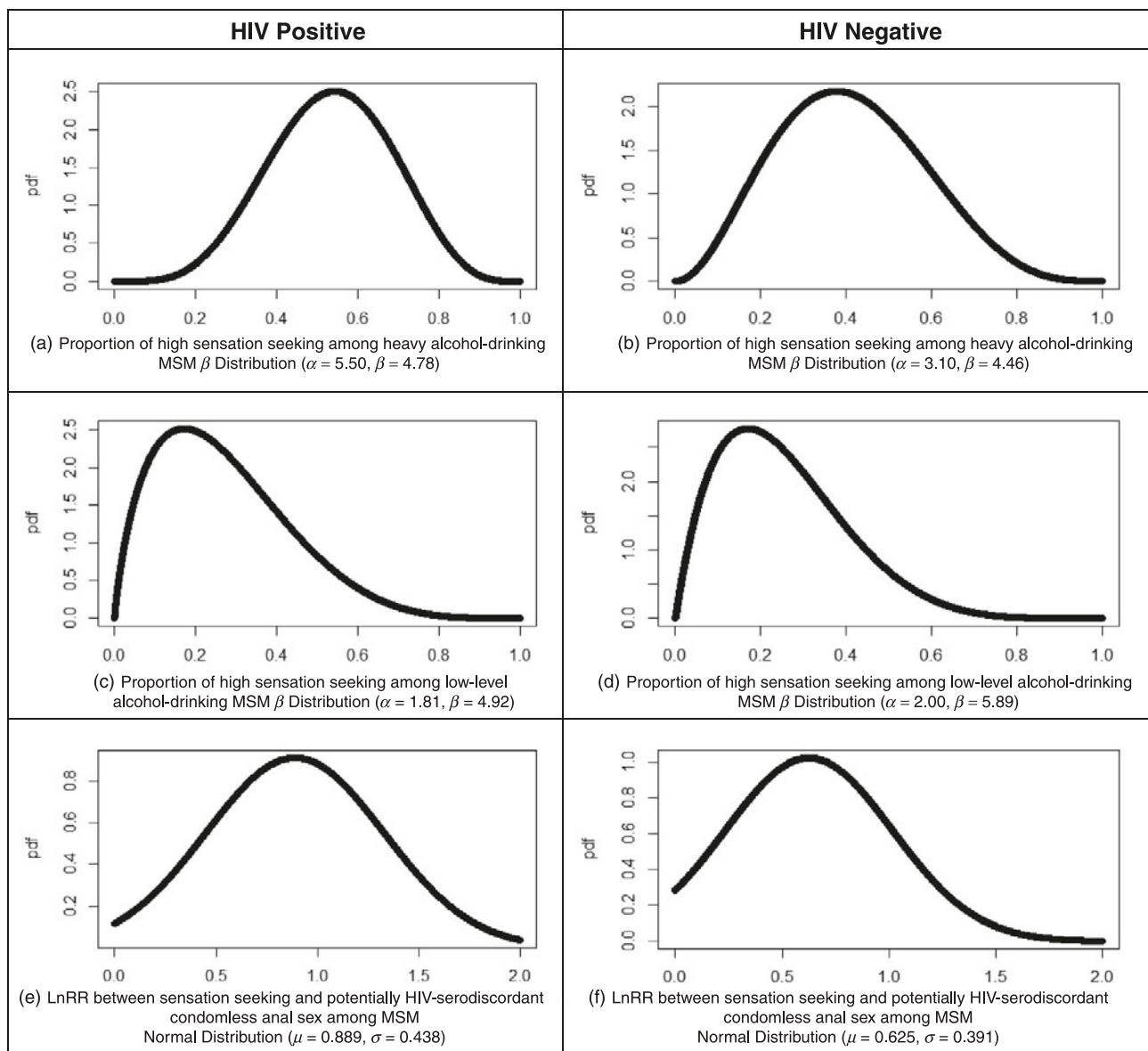


Figure 3. Prior distributions and the related parameters in the association between alcohol use and potentially HIV-serodiscordant condomless anal sex with potential confounding by sensation seeking.

with $\mu=0.9$ and $\sigma=0.4$ in HIV positives and $\mu=0.6$ and $\sigma=0.4$ in HIV negatives.

DISCUSSION

We found that expert opinion was feasible and informative in providing estimates of bias parameters necessary for probabilistic bias analysis. In our case study, experts estimated that around 50% of heavy-drinking MSM and 25% of low-level drinking MSM had high sensation seeking. Risk of having condomless anal sex among high sensation-seekers was approximately two-fold more than among low sensation-seekers. All these parameters were slightly higher in HIV-positive than in HIV-negative MSM. The exercise provided a confirmation that sensation seeking is a confounder for the effect of alcohol on sexual risk suggested by other studies.⁴ Our approach further quantified the level of the confounding.

There are different approaches to adjusting for measured confounders of the effect of interest, such as propensity scores, regression, stratification and matching. Instrumental variable analysis and Bayesian analysis are approaches to deal with unmeasured confounders.^{10,11} A valid instrument should be associated with the exposure (either because the instrument affects the exposure or because the exposure and instrument share a common cause), should affect the outcome only through the exposure, and should not share common causes with the outcome.¹¹ Thus, it is challenging to identify a valid instrument in most observational studies, including our study. Therefore we explored the use of Bayesian analysis in this study, with implications for other studies in similar circumstances.

The most crucial and difficult part of probabilistic or Bayesian bias analysis is prior specification.⁶ Although priors can be estimated by different methods, a good prior needs to be valid

and reliable.¹² One approach is to estimate the priors of unmeasured confounding by the magnitude of the measured confounding under the strong assumption of exchangeability of confounding effects of measured and unmeasured confounders.¹³ Another approach to estimate priors is using the internal data sources, such as validation substudies.⁶ The third approach is to consult experts on their beliefs. Expert opinion is useful when the effects of measured and unmeasured confounders are not similar, or are undetermined, and internal data sources are not available.^{6,12,14-16} In brief, we used this method to quantify an abstract concept into quantified bias parameters.

Behavioural surveys among MSM usually estimate the association between alcohol use and risky sex without considering the effect of sensation seeking,¹ which is a potential confounder in this causal pathway.⁴ Using the findings of this study, investigators can consider the confounding effect of sensation seeking and estimate the adjusted effect of alcohol use on risky sex among MSM.

Limitations

Our findings have limitations. The most important is the limited number of experts who responded to the survey. The understandable reason is that quantifying the bias parameters is not easy for the expert in the absence of their own data.¹² The marked difference between the observed data distributions (Figure 2) and the specified prior distributions (Figure 3) can be due to the small sample size. Despite the limitation of our study, the distribution of parameters looks to be precise enough to conduct the bias analysis. Furthermore, in Bayesian analysis of epidemiologic data, prior specification could be based on just one expert opinion which may be biased or overconfident. We used 11 experts' opinion to have more rigorous priors.^{17,18}

CONCLUSION

We found that experts' opinion is feasible and can be used to quantify the level of confounding. The resulting parameters can be used to adjust for confounding (bias analysis) and to make causal inferences. In particular, our approach is applicable to situations where the study did not measure a confounder, and therefore conventional methods to adjust for confounding, such as stratification, matching and multiple regressions, cannot be implemented. This situation is all too common in observational studies in multiple fields.

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RÉSUMÉ

OBJECTIF : En utilisant l'opinion d'experts comme source de données externe, élaborer et appliquer une méthode pour chiffrer les paramètres de biais dans le cas de l'association entre la consommation d'alcool et le sexe anal sans condom entre partenaires sérodifférents pour le VIH, avec un facteur de confusion possible, la recherche de sensations, chez les hommes ayant des relations sexuelles avec des hommes (HARSAH).

MÉTHODE : Au moyen d'un sondage en ligne, nous avons sollicité l'opinion de 41 épidémiologistes et spécialistes du comportement pour chiffrer six paramètres dans la population des HARSAH : la proportion de chercheurs de sensations fortes chez les HARSAH grands buveurs d'alcool, la proportion de chercheurs de sensations chez les HARSAH petits buveurs d'alcool, et le risque relatif (RR) de l'association entre la recherche de sensations et le sexe anal sans condom chez les HARSAH séropositifs et séronégatifs.

RÉSULTATS : Onze spécialistes ont répondu. Chez les grands buveurs séropositifs, la proportion de chercheurs de sensations fortes était de 53,6 % (distribution bêta [$\alpha = 5,50, \beta = 4,78$]); elle était de 41,1 % (distribution bêta [$\alpha = 3,10, \beta = 4,46$]) chez les grands buveurs séronégatifs. Chez les petits buveurs séropositifs, les chercheurs de sensations fortes représentaient 26,9 % (distribution bêta [$\alpha = 1,81, \beta = 4,92$]), ce qui est comparable aux chercheurs de sensations fortes chez les petits buveurs séronégatifs (25,3 %) (distribution bêta [$\alpha = 2,00, \beta = 5,89$]). Le logarithme du risque relatif (lnRR) de l'association entre la

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recherche de sensations et le sexe anal sans condom était $\ln(2,4)$ (distribution normale [$\mu=0,889$, $\sigma=0,438$]) chez les HARSAH séropositifs et $\ln(1,5)$ (distribution normale [$\mu=0,625$, $\sigma=0,391$]) chez les HARSAH séronégatifs.

CONCLUSION : L'opinion d'experts peut être une méthode simple et efficace pour dériver des paramètres de biais afin de chiffrer les facteurs de confusion hypothétiques et d'apporter les ajustements nécessaires. Dans ce

cas type, l'opinion d'experts a confirmé que la recherche de sensations est un facteur de confusion de l'effet de l'alcool sur le sexe anal sans condom, et cette opinion a fourni les paramètres nécessaires à une analyse du biais probabiliste.

MOTS CLÉS : facteur de confusion non mesuré; recherche de sensations; hommes ayant des relations sexuelles avec des hommes; consommation d'alcool; sexe anal sans condom; analyse de biais