RELATIVE RISK OF INJURY FROM ACUTE ALCOHOL CONSUMPTION: MODELING THE DOSE-RESPONSE RELATIONSHIP IN EMERGENCY DEPARTMENT DATA FROM 18 COUNTRIES

Cheryl J. Cherpitel
Yu Ye
Jason Bond
Alcohol Research Group
6475 Christie Avenue Suite 400
Emeryville, CA 94608 USA

Guilherme Borges
Universidad Autonoma Metropolitana
Instituto Nacional de Psiquiatria
Tlalpan, Mexico DF, MEXICO

Maristela Monteiro
Pan American Health Organization
Washington DC

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ABSTRACT

Aims To update and extend analysis of the dose-response relationship of injury and drinking by demographic and injury subgroups and country-level drinking pattern, and examine the validity and efficiency of the fractional polynomial approach to modeling this relationship.

Design Pair-matched case-crossover analysis of drinking prior to injury, using categorical step-function and fractional polynomial analysis.

Setting 37 emergency departments (EDs) across 18 countries.

Participants 13,119 injured drinkers arriving at the ED within six hours of the event.

Measurements The dose-response relationship was analyzed by gender, age, cause of injury (traffic, violence, fall, other), and country detrimental drinking pattern (DDP).

Findings Estimated risks were similar between the two analytic methods, with injury risk doubling at one drink (OR = 2.3 - 2.7) and peaking at about 30 drinks. Although risk was similar for males and females up to three drinks (OR = 4.6), it appeared to increase more rapidly for females and was significantly higher starting from 20 drinks (female OR = 28.6; CI (16.8, 48.9); male OR = 12.8; CI (10.1, 16.3)). No significant differences were found across age groups. Risk was significantly higher for violence-related injury than for other causes across the volume range. Risk was also higher at all volumes for DDP-3 compared with DDP-2 countries.

Conclusions There is an increasing risk relationship between alcohol and injury, but risk is not uniform across gender, cause of injury, or country drinking pattern. The fractional polynomial approach is a valid and efficient approach for modeling the alcohol-injury risk relationship.

INTRODUCTION

Alcohol is the 5th leading risk factor in the Global Burden of Disease (GBD) estimates, accounting for 3.9% of the GBD, and is the 3rd leading risk factor among men and 1st among those 15-35 years old (1). Injuries constitute a major part of this GBD: 24.4% of alcohol-attributable mortality and 33.2% of alcohol-attributable Disability-Adjusted Life Years (DALYs) (2). The relative risk (RR) of injury from alcohol consumption is one important component in estimation of alcohol-attributable non-fatal injury. Risk estimates have typically been derived from mortality rather than morbidity data, however, been based on chronic rather than on acute consumption (3), have not examined the dose-response relationship and have assumed a uniform risk across gender, age, cause of injury and country.

A systematic review of emergency department (ED) studies and meta-analysis of risk of injury from drinking prior to the event (4) found an overall odds ratio (OR) of 2.79, which varied according to study design (case-control OR = 3.81; case-crossover OR = 1.98) and recall period for case-crossover studies (usual frequency OR = 4.23; time-matched OR = 2.32). Studies reviewed did not examine injury risk by level of consumption, however. An earlier systematic review and meta-analysis of the dose-response relationship between acute alcohol use and injury (5) found injury risk increased nonlinearly with alcohol consumption, with study design having no effect. This review was not restricted to injury morbidity or to ED studies, however, or to alcohol involvement based on self-reports. A study of ED patients across 10 countries (6) has been drawn upon frequently in reporting risk estimates for injury morbidity from alcohol. This study found a dose-response relationship with ORs of 3.3, 3.9, 6.5 and 10.1 for 1, 2-3, 4-5 and 6+ drinks, respectively, consumed in the six hours prior to the injury event, but did not examine the dose-response relationship by gender, age, cause of injury, or country drinking pattern. The present study updates this report, adding data from eight additional countries (and 27 EDs) and extending

analyses to include dose-response estimates by gender, age, cause of injury and country-level drinking pattern.

A second objective linked to updating and extending analyses of RR of injury from alcohol is to explore the statistical approach used to model the dose-response relationship. Although categorized alcohol exposure levels (e.g., (6)) are commonly used to study the dose-response relationship because they produce risk estimates that are easy to interpret, they have disadvantages (7). They assume that the RR of injury changes abruptly at defined cut-points, making fluctuation in estimates across exposure categories difficult to interpret, and complicating studies of cross-group comparisons, with increased likelihood of overlapping risk estimates. Categorical step-function also typically generates standard errors and confidence intervals (CIs) for risk estimates that are much larger than those from models treating risk factors as continuous variables (8, 9), as does the fractional polynomial approach.

The fractional polynomial approach, as used in the meta-analysis of Taylor et al. (5), treats alcohol volume as a continuous measure, providing a more flexible approach to estimation of the risk function, in which a specific model is chosen by comparing model fit indices across a set of models which are able to represent a large range of possible risk function shapes. While fractional polynomial provides a smoother and more efficient RR estimate compared to the categorical step-function approach, it runs the risk of fitting the data poorly, and a validity check is needed to compare it with the more robust, non-parametric, step-function model before it can be reliably used to model the alcohol and injury relationship.

Aims of the present study are to update Borges et al.'s (6) prior work modeling the dose-response relationship of alcohol and injury using a larger global data set of ED studies, to extend these analysis to include important individual and country-level characteristics, and to examine the

fractional polynomial approach to modeling this relationship. These analyses are important for refining alcohol-attributable fraction (AAF) of injury morbidity, a key priority identified by the World Health Assembly (10) and informing the GBD, highly important since much of this burden is avoidable (11, 12). Additionally, examining the validity and efficiency of the fractional polynomial approach will provide important underpinnings supporting use of this approach in future analysis of dose-response relationships (13).

METHODS

Samples

Data analyzed include the 10 EDs in the 2001-02 WHO collaborative study on alcohol and injuries as reported by Borges et al. (6). Additional ED data, collected using the WHO study protocol (14), were collected from Switzerland (2006-07) (15), Ireland (2003-04), China and Korea (2009), as well as six countries from the Americas: Dominican Republic, Guatemala, Guyana, Nicaragua, Panama (2010-11) and Canada (2009) (16, 17). Total data cover 18 countries from 37 EDs (n=13,119, Table 1). Detailed information of these studies can be found elsewhere (18). Multiple ED sites in a country or region were selected based on the diversity and size of the population served in their respective locales.

In all studies, probability samples of patients aged 18 years and older who arrived at the ED within six hours of the injury event were obtained by approaching consecutive arrivals to each ED, with equal representation of each shift for each day of the week. Informed consent to participate was obtained, following which a 25-minute structured questionnaire (14) was administrated. Completion rates averaged 87% across all studies (range 59% to 100%). Reasons for non-interviews included refusing, incapacitation, leaving prior to completing the interview, in police

custody, and language barriers. Patients who were too severely injured to be approached in the ED were followed into the hospital and interviewed once their condition had stabilized.

Individual measures

Patients were asked about the cause of injury bringing them to the ED (categorized as falls, traffic, violence, other), drinking within six hours prior to the injury event, and drinking during the same six-hour period the previous week. Both time periods included the beverage-specific number, size and alcohol concentrations of drinks. Efforts were made to also include data on all alcohol beverage types consumed locally. Total volume for each time period, separately, was obtained by summing across all beverage types and converting to the number of standard drinks, each containing 16 ml (12.8 gms) of pure ethanol.

Country-level drinking pattern

The country-level drinking pattern was determined based on a country's detrimental drinking pattern (DDP) score as an indicator of "detrimental impact" on health and other drinking-related harms at a given level of alcohol consumption. This measure ranges in scoring from 1 (least detrimental) to 4 (most detrimental) and was developed and validated by WHO from indicators of heavy drinking occasions, drinking with meals and drinking in public places (19, 20). DDP was included in these analyses since prior ED studies have found it to be a strong predictor of alcohol-related injury (18, 21).

Data analysis

Data were analyzed using case-crossover analysis in which injured patients' alcohol consumption within six hours prior to injury is compared to their own alcohol consumption during the same time period the previous week (22, 23), a method which reduces confounding of the

alcohol-injury relationship by controlling for stable risk factors. Conditional logistic regression was used to estimate ORs and 95% CIs for risk of injury from drinking.

Fractional polynomial modeling (24) was used to model the relationship between continuous volume of consumption and the odds of injury, using the conditional logistic model: $\text{logit}(\text{Prob}(\text{injury}))=b_0+b_1x^p+b_2x^q$ (or $b_0+b_1x^p+b_2x^p(\ln x)$ if $p=q$) where p and q are chosen from -2, -1, -0.5, 0, 0.5, 1, 2 and 3 ($x^0=\ln(x)$) and x is volume consumed in standard drinks, shifted to the right by adding 1 so that the function is still estimable when the respondent reports zero drinks. The best fit is determined for the model producing the largest maximized likelihood function. The 2-degree model was chosen as it provides both flexibility and stability by choosing from 36 possible models (produced from all possible combinations of p and q), and has been found to sufficiently represent a large range of commonly observed epidemiologic relationships (25). All models were fitted using the STATA version 13 (26) `fracpoly` command. ORs and CIs are compared between the fractional polynomial and step-function approaches (Table 2).

As CIs in the fractional polynomial approach may be too narrow due to uncertainty resulting from the estimation of p and q (24), bootstrap CIs are also generated based on 1000 replications involving both re-sampling and re-estimating the fractional polynomial function form, and results compared with analytically derived CIs (Figure 1).

Given sparse data at high consumption levels which may be subject to recall bias, ORs for up to 30 drinks only are shown in sub-group analysis. Point-wise testing of differences in risk estimates, as opposed to testing of overall curve differences, were conducted via comparisons of CIs produced from analytically-derived standard errors (results not shown). To inform inferences regarding the shape of the dose-response relationship, point-wise estimates of the slope of the risk

curve function and its test of significance were derived from the derivative (with respect to consumption) of the fractional polynomial function (results not shown).

RESULTS

Table 1 shows characteristics of the 37 EDs in the combined 18-country sample.

[Table 1 about here]

Table 2 shows estimated ORs (and 95% CIs) of injury risk by levels of consumption, using both the categorical step-function and the fractional polynomial approaches. For the step-function approach, narrower volume confidence intervals are found at lower levels, as 74% of those who drank before injury and 80% who drank the previous week reported 10 or fewer drinks. Average volume for each interval of the disjoint volume partition is also shown in Table 2. For the fractional polynomial approach, although volume of consumption is treated as a continuous measure in the model, ORs and 95% CIs are shown only for selected volume levels.

Overall, a consistent dose-response risk pattern was observed both for categorical step-function estimates and the estimated fractional polynomial model. Visual inspection of the injury risk effect size for both approaches suggested an increasing relationship between volume and injury risk up to about 20-30 drinks, above which risk appeared to drop. From the fractional polynomial model estimated, the OR was estimated as 2.3 for one drink, and increased to 10.3 for 10 drinks, peaking at nearly 14 for 30 drinks. Estimates from the categorical step-function approach appeared to be more variable, particularly at higher volume categories, with larger CIs compared to the fractional polynomial model. Restricting the sample to those reporting 30 or fewer drinks, the estimated derivative of the fractional polynomial regression model indicated that the consumption risk slope increased up to 19 drinks.

[Table 2 about here]

Bootstrap CIs for the fractional polynomial OR estimates were generated based on 1000 replications and compared to analytically derived CIs (shown in Figure 1). Up to about 10 drinks, CIs produced from the two methods were very similar; above 10 drinks differences increased, with the bootstrap method indicating proportionally larger intervals.

[Figure 1 about here]

Sub-group comparisons of the dose-response relationship

Fractional polynomial risk estimates were similar for males and females up to three drinks, above which risk appeared to increase more rapidly for females, doubling and tripling in magnitude at higher volume levels (Table 3). This diverging trend is further emphasized by the non-overlapping point-wise confidence intervals at higher consumption levels. No significant risk differences were seen for those aged 18-30 compared to those older; however, above 10-15 drinks, injury risk appeared to continue to increase for those over 30 while estimates leveled off for those younger.

[Table 3 about here]

A dose-response relationship was evident for traffic, fall and violent injuries, but was weaker for injuries from other causes (Table 4). Risk was largest for violence-related injuries and was significant up to 15 drinks compared to traffic injuries and up to 8 drinks compared to falls. Risk of injury from falls and traffic was similar up to 3 drinks and then appeared to increase more rapidly for falls, although not significant.

[Table 4 about here]

Up to approximately 5 drinks, injury risk was greatest for DDP-4 countries, followed by DDP-3 countries (Table 5). Above 5 drinks, risk for DDP-4 countries appeared to plateau while

risk for DDP-3 countries continued to climb to 15-20 drinks, with non-overlap of point-wise confidence intervals above approximately 9 drinks. Risk for DDP-2 countries was significantly lower compared to DDP-3 countries up to 15-20 drinks.

[Table 5 about here]

DISCUSSION

The RR of injury from alcohol consumption is one important component in estimating the AAF for non-fatal injury. The present study sought to update previous estimates and to extend analyses to include dose-response risk estimates by gender, age, cause of injury and country-level drinking pattern, not previously reported in the literature and highly important for refining AAF of injury morbidity in the GBD. Visual inspection of effect size estimates suggested an increasing relationship between alcohol and injury up to about 20-30 drinks, at which point injury risk appeared to drop with further increasing volume. This visual indication of an observed decline in risk may be real (e.g., assuming that at extremely large quantities of alcohol intake one may be too incapacitated to incur an injury), or may be a result of unstable estimates at the higher end of consumption due to sparse data, or an artifact of measurement error in reported quantity consumed. While step-function findings here are not directly comparable to Borges et al. (6)), due to dissimilar volume categories, injury risk was found to increase three-fold with only one drink within the six hours prior to injury in both studies, and this was similar to the overall increase in risk of injury for any drinking within the six-hour period (OR=2.79) in the Zeisser et al. (4) meta-analysis.

Injury risk was similar for males and females up to three drinks prior to injury, but then appeared to increase more rapidly for females and estimates diverged at higher volume levels. A greater risk of injury (OR =1.7) has been found at a lower consumption level (40 grams) for

females compared to males (60 grams) (27), and risk has also been found to be greater for females compared to males at the same level of consumption (28). These data suggest that assuming a uniform risk for males and females may not be appropriate in estimating AAF for injury morbidity.

The dose-response relationship suggested no significant differences in injury risk for those aged 18-30 compared to those older. While younger individuals may have personality dispositions (e.g., greater propensity for risk taking) putting them at an elevated risk of injury (27), this does not appear to be an important factor in risk of injury here. Further research is needed to determine the effect of age on the dose-response relationship between alcohol and injury.

Risk for violence-rated injury was consistently larger than risk for traffic, falls, and other causes, supporting heterogeneity found in the dose-response relationship for injury by type and cause in prior studies (29-31). Violence-related injuries have shown a steeper dose-response relationship than non-intentional injury in other studies (32-34) as also found here, and these data suggest that assuming a uniform risk across all causes of injury may not be appropriate in estimating AAF for injury morbidity, an area that requires additional research.

Countries with the highest detrimental pattern of drinking (DDP-4), exemplified by heavy episodic drinking, were found to be at greater risk of injury at lower levels of consumption, but were surpassed by DDP-3 countries at higher volume levels, while risk for DDP-3 countries was greater at all volume levels compared to DDP-2 countries. Countries with similar DDP often cluster in a given region or area; for example, those of Central or Eastern Europe and those in Central America tend to exhibit more detrimental patterns of drinking than those in Western Europe, and this variation in DDP may be correlated with and reflect regional variation in risk of injury. DDP has been found to predict alcohol-related injury in other ED studies (18, 21), and findings here

suggest that country-level drinking pattern may be important to consider in estimating AAF for GBD estimates.

A secondary focus of this paper, linked to extending and refining analysis of RR of injury from alcohol to subgroups of patients, was examining the validity and efficiency of the fractional polynomial approach to modeling the dose-response relationship, comparing it to the traditional categorical step-function approach, and to standard error estimates from the bootstrap approach. Highly consistent estimates were found between the fractional polynomial and categorical step-function approaches, and CIs for the analytically-derived fractional polynomial risk estimates were also found to be validated against results from bootstrap analyses. Compared to the categorical step-function approach, the fractional polynomial method generated smoother estimates with smaller confidence intervals, allowing risk estimation and cross-group comparisons at arbitrary consumption levels, especially important since volume intake varies greatly between groups (e.g., between males and females). While the fractional polynomial approach has previously been applied in a meta-analysis (5), this is the first time it has been used to model the alcohol-injury relationship using individual-level data, and findings here suggest it is a valid and efficient approach to estimating the dose-response relationship between alcohol consumption and injury. Future research should focus on the sensitivity of the fractional polynomial approach at higher consumption volumes.

Limitations

While patient samples in all studies are representative of their respective EDs, they are not necessarily representative of a broader area or jurisdiction. The combined sample consists of an unbalanced number of respondents across countries or regions, and variation in individual and country characteristics may not be fully represented. For example, the DDP-4 region is dominated

by countries in the Americas, with representation absent from large countries such as Russia. Subgroup analyses (gender and age) assume a constant effect for the population within the subgroup, ignoring potential heterogeneity, for example, differences in the composition of injuries within the subgroup. However, sample size did not permit analysis of demographic subgroups by cause of injury or DDP, and this is also an important focus of future research.

Estimates of a dose-response relationship were derived from case-crossover analysis, which controls characteristics not varying over time such as demographics, but this method is not without potential bias. For example, findings have been mixed in terms of recall of one's drinking the previous week (35, 36), and potential bias may also arise from the context of drinking in the injury event compared to the previous week (37, 38).

As the case-crossover design assesses exposure during case and control periods on the same individual, models must account for the corresponding respondent-level fixed effects to obtain unbiased risk estimates, here using conditional logistic regression models. However, it should be noted that the data represent nesting of patients within EDs and EDs within country, representing a design consideration that, due to the lack of available methodological tools, was not taken into account when modeling.

Despite these limitations, data here provide new estimates of the dose-response relationship of drinking and risk of injury, important for refining the AAF of injury morbidity to inform the GBD. These data underscore the fact that uniform estimates of the risk of injury due to alcohol cannot be assumed for subgroups (e.g., gender), for all injury causes, or across countries or regions with differing drinking patterns. Further research is necessary in refining AAF of injury morbidity.

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Table 1. Characteristics of ED samples by study to be used for alcohol-injury risk estimation (n=13,119)

Studies and year	# of EDs	Response rate	Valid n[5]	% 6-hour drinking	% male	% age 18-30	DDP[6]
Argentina							
Mar Del Plata 2001	1	97%	429	23.3	66.6	48.6	2
Belarus							
Minsk 2001	1	96%	455	30.1	58.9	39.8	4
Brazil							
São Paulo 2001	1	95%	477	11.5	66.3	53.6	3
Canada							
Orangeville (ON) 2002	1	78%	220	5.9	60.0	29.7	2
Vancouver 2009	2	59%	239	21.3	61.5	39.1	2
China							
Changsha (Hunan) 2001	1	100%	418	9.3	65.1	50.5	2
5 cities[1] 2009	5	89%	2,318	14.6	63.2	44.4	2
Cezch Republic							
Prague 2001	1	93%	466	6.0	53.9	41.4	2
Dominican Republic							
Santa Domingo 2010	1	99%	450	16.0	81.0	56.9	2
Guatemala							
Guatemala City 2011	1	85%	505	21.2	68.9	50.5	4
Guyana							
Georgetown 2011	1	91%	445	20.2	71.9	46.2	3
India							
Banglore 2001	1	85%	492	15.4	73.7	58.9	3
Ireland							
5 cities[2] 2003-04	6	84%	2,049	21.9	64.6	47.7	3
Korea							
Bucheon/Uijeongbu 2007	2	75%	97	29.9	54.6	23.7	3
4 cities[3] 2009	4	73%	1,858	22.3	60.7	31.2	3
Mexico							
Mexico City 2002	1	94%	371	20.8	66.8	57.7	4
New Zealand							
Auckland 2000	1	60%	127	41.7	67.7	49.6	2
Nicaragua							
Managua 2010	1	96%	469	19.2	66.3	53.9	4
Panama							
3 cities[4] 2010	3	91%	451	19.3	68.5	46.1	3
Sweden							
Malmö 2001	1	84%	467	13.5	54.2	30.3	3
Switzerland							
Lausanne 2006-07	1	69%	316	23.7	66.5	41.3	1

[1] Beijing, Changsha, Chengdu, Hangzhou and Hengyang
[2] Dublin (2), Galway, Letterkenny, Sligo and Waterford
[3] Seoul, Suwon, Chuncheon and Donggu
[4] La Chorrera, Colon and Veraguas

[5] Have valid data for drinking both before injury and the same time last week
[6] Country detrimental drinking pattern, obtained for the year the ED study was conducted.

Table 2. Odds Ratios (OR) and 95% Confidence Intervals (CI) for Risk of Injury Related to Drinking from Conditional Logistic Regression Comparing the Categorical Step-function and Fractional Polynomial Estimations (18 countries, n=13,119)

Step function estimation					Fractional Polynomial estimation			
Alcohol intake in drinks	Mean volume	OR[2]	LO[2]	HI[2]	Alcohol intake in drinks	OR[2]	LO[2]	HI[2]
(0, 1] [1]	0.8	**2.7**	2.0	3.6	1	**2.3**	2.1	2.4
(1, 2]	1.6	**2.8**	2.2	3.6	2	**3.5**	3.2	3.9
(2, 3]	2.6	**4.1**	3.1	5.4	3	**4.6**	4.1	5.2
(3, 4]	3.5	**3.9**	2.9	5.3	4	**5.7**	5.0	6.5
(4, 5]	4.6	**6.9**	5.1	9.4	5	**6.7**	5.8	7.6
(5, 6]	5.7	**7.3**	4.8	11.0	6	**7.5**	6.5	8.7
(6, 7]	6.4	**5.4**	3.8	7.8	7	**8.3**	7.2	9.7
(7, 8]	7.5	**12.6**	7.5	21.1	8	**9.0**	7.8	10.5
(8, 9]	8.6	**8.1**	4.8	13.5	9	**9.7**	8.3	11.3
(9, 10]	9.5	**9.8**	6.8	14.0	10	**10.2**	8.7	12.0
(10, 15]	12.5	**13.1**	9.4	18.1	15	**12.3**	10.2	14.9
(15, 20]	17.4	**18.5**	11.7	29.2	20	**13.4**	10.7	16.8
(20, 30]	24.1	**21.4**	11.1	41.2	30	**13.9**	10.1	19.0
(30, 45]	36.6	**8.3**	3.6	19.1	45	**12.7**	8.1	20.0
(45, 60]	54.0	**10.4**	2.3	46.6	60	**10.9**	6.1	19.6
>60	98.3	**3.4**	1.1	10.1	80	**8.6**	4.1	18.1

[1] (a,b] means ≤b and >a

[2] OR: odds ratio; LO, HI: lower and higher limits of the 95% confidence interval

Table 3. Odds Ratios (OR) and 95% Confidence Intervals (CI) for Risk of Injury Related to Drinking from Conditional Logistic Regression Fractional Polynomial Estimations, by Gender and by Age Separately

	Male			Female			Age 18-30			Age 31+		
Alcohol intake in drinks	OR[1]	LO[1]	HI[1]	OR[1]	LO[1]	HI[1]	OR[1]	LO[1]	HI[1]	OR[1]	LO[1]	HI[1]
1	**2.2**	2.1	2.4	**2.2**	1.9	2.4	**2.3**	2.1	2.6	**2.2**	2.0	2.4
2	**3.4**	3.1	3.9	**3.4**	2.8	4.1	**3.6**	3.1	4.2	**3.3**	2.9	3.9
3	**4.6**	4.0	5.2	**4.7**	3.7	5.9	**4.8**	4.1	5.7	**4.5**	3.8	5.3
4	**5.6**	4.8	6.5	**6.0**	4.5	7.9	**5.9**	4.9	7.1	**5.5**	4.6	6.6
5	**6.5**	5.6	7.6	**7.3**	5.4	10.0	**6.8**	5.6	8.3	**6.5**	5.4	7.9
6	**7.3**	6.3	8.6	**8.7**	6.2	12.2	**7.7**	6.3	9.4	**7.5**	6.1	9.1
7	**8.1**	6.9	9.5	**10.1**	7.0	14.4	**8.4**	6.8	10.3	**8.3**	6.8	10.3
8	**8.8**	7.4	10.4	**11.5**	7.8	16.8	**9.0**	7.3	11.2	**9.2**	7.4	11.4
9	**9.4**	7.9	11.1	**12.9**	8.6	19.2	**9.6**	7.7	11.9	**10.0**	7.9	12.5
10	**9.9**	8.3	11.8	**14.3**	9.4	21.7	**10.0**	8.0	12.5	**10.7**	8.5	13.6
15	**11.8**	9.6	14.5	**21.5**	13.3	34.8	**11.4**	8.8	14.7	**13.8**	10.3	18.5
20	**12.8**	10.1	16.3	**28.6**	16.8	48.9	**11.8**	8.8	15.9	**16.1**	11.2	23.2
25	**13.2**	9.9	17.6	**35.4**	19.6	63.9	**11.6**	8.2	16.4	**17.8**	11.5	27.7
30	**13.2**	9.5	18.4	**41.5**	21.2	81.0	**11.1**	7.4	16.5	**19.1**	11.3	32.1

[1] OR: odds ratio; LO, HI: lower and higher limits of the 95% confidence interval

Table 4. Odds Ratios (OR) and 95% Confidence Intervals (CI) for Risk of Injury Related to Drinking from Conditional Logistic Regression Fractional Polynomial Estimations, by Cause of Injury

	Traffic			Violence			Fall			Other injuries		
Alcohol intake in drinks	OR[1]	LO[1]	HI[1]	OR[1]	LO[1]	HI[1]	OR[1]	LO[1]	HI[1]	OR[1]	LO[1]	HI[1]
1	**1.8**	1.6	2.0	**3.5**	3.0	4.0	**1.8**	1.6	1.9	**2.2**	2.0	2.5
2	**2.5**	2.1	3.0	**6.0**	4.8	7.4	**2.6**	2.3	3.0	**3.2**	2.6	3.8
3	**3.2**	2.5	4.0	**8.3**	6.5	10.7	**3.5**	2.9	4.2	**3.8**	3.1	4.8
4	**3.9**	2.9	5.0	**10.4**	7.9	13.7	**4.5**	3.6	5.5	**4.4**	3.5	5.5
5	**4.5**	3.3	6.1	**12.3**	9.1	16.5	**5.5**	4.3	7.0	**4.8**	3.7	6.1
6	**5.1**	3.7	7.1	**13.9**	10.2	19.1	**6.5**	5.1	8.5	**5.1**	4.0	6.6
7	**5.7**	4.0	8.1	**15.5**	11.2	21.4	**7.6**	5.8	10.0	**5.4**	4.1	7.0
8	**6.3**	4.4	9.1	**16.9**	12.1	23.5	**8.7**	6.5	11.6	**5.6**	4.3	7.3
9	**6.9**	4.7	10.1	**18.1**	12.9	25.5	**9.7**	7.1	13.2	**5.7**	4.3	7.5
10	**7.5**	5.0	11.2	**19.3**	13.6	27.4	**10.7**	7.8	14.7	**5.8**	4.4	7.7
15	**10.2**	6.4	16.3	**24.0**	16.5	35.0	**15.0**	10.3	22.0	**6.1**	4.5	8.3
20	**12.9**	7.8	21.5	**27.6**	18.6	40.8	**17.6**	11.2	27.7	**6.0**	4.3	8.6
25	**15.6**	9.0	26.9	**30.4**	20.3	45.5	**18.3**	10.7	31.5	**5.8**	3.9	8.7
30	**18.3**	10.3	32.6	**32.9**	21.8	49.6	**17.5**	9.2	33.6	**5.5**	3.5	8.8

[1] OR: odds ratio; LO, HI: lower and higher limits of the 95% confidence interval

Table 5. Odds Ratios (OR) and 95% Confidence Intervals (CI) for Risk of Injury Related to Drinking from Conditional Logistic Regression Fractional Polynomial Estimations, by Country Detrimental Drinking Pattern[1]

	DDP = 2			DDP = 3			DDP = 4		
Alcohol intake in drinks	OR[2]	L[21]	HI[2]	OR[2]	LO[2]	HI[2]	OR[2]	LO[2]	HI[2]
1	**1.9**	1.7	2.0	**2.2**	2.1	2.4	**4.9**	3.9	6.3
2	**2.6**	2.3	3.1	**3.6**	3.1	4.0	**6.6**	4.9	8.9
3	**3.4**	2.8	4.1	**4.9**	4.2	5.8	**7.4**	5.4	10.1
4	**4.1**	3.3	5.0	**6.3**	5.3	7.6	**7.7**	5.6	10.6
5	**4.7**	3.8	5.9	**7.7**	6.3	9.4	**7.9**	5.7	11.0
6	**5.4**	4.2	6.8	**9.1**	7.4	11.3	**8.1**	5.8	11.2
7	**5.9**	4.6	7.7	**10.5**	8.4	13.1	**8.2**	5.9	11.3
8	**6.5**	5.0	8.5	**11.8**	9.3	14.9	**8.2**	5.9	11.4
9	**7.0**	5.3	9.3	**13.1**	10.2	16.7	**8.3**	5.9	11.5
10	**7.5**	5.6	10.1	**14.3**	11.1	18.3	**8.3**	6.0	11.5
15	**9.7**	6.9	13.5	**19.0**	14.3	25.2	**8.4**	6.0	11.6
20	**11.3**	7.7	16.6	**21.3**	15.5	29.4	**8.4**	6.0	11.7
25	**12.5**	8.1	19.4	**21.1**	14.4	31.1	**8.4**	6.0	11.7
30	**13.4**	8.2	22.0	**19.0**	11.6	31.0	**8.4**	6.1	11.8

[1] Switzerland was the only country with a DDP of 1, and with a relatively small sample size, was excluded.
[2] OR: odds ratio; LO, HI: lower and higher limits of the 95% confidence interval

Figure 1. Comparing 95% confidence intervals (Cis) generated analytically and through 1000 replication bootstrap,

Showing the odds ratio (OR) and lower and higher limits of the 95% CIs