

Article

# Alcohol Consumption and Inpatient Health Service Utilization in a Cohort of Patients With Alcohol Dependence After 20 Years of Follow-up

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## Abstract

**Aims:** To examine the association between drinking levels and inpatient health service utilization in people with a lifetime diagnosis of alcohol dependence.

**Methods:** A longitudinal prospective study was conducted in a cohort of patients with alcohol dependence who had undergone treatment in 1987. Current results refer to the association between drinking patterns at 20-year follow-up and subsequent inpatient health service utilization. At 20 years after baseline, 530 of 850 patients were alive with administrative data available. Follow-up interview was conducted on 378 patients. There were 88 refusals and 64 could not be traced. Three categories of alcohol consumption were established (abstainers, moderate drinkers and heavy drinkers) depending on the pattern of alcohol use during the last year prior to the evaluation. Health service utilization was based on official statistics, including admissions to general, rehabilitation and psychiatric hospitals. The time period analysed was 5 years after the assessment of drinking patterns.

**Results:** Admission rates were lowest for abstainers compared to people with moderate and heavy drinking. With respect to hospital days, heavy drinking was associated with significantly higher adjusted rates than both abstainers and moderate drinkers. Alcohol-related diagnoses in hospital admissions were more frequent for both moderate and heavy drinkers.

**Conclusion:** Abstinence and moderate alcohol consumption were both associated with lower hospitalization in people with a lifetime diagnosis of alcohol dependence. Thus, not only abstinence-oriented treatment strategies but also those to reduce alcohol intake would reduce inpatient hospitalizations.

**Short Summary:** Abstinence and reduced drinking in lifetime alcohol-dependent patients were associated with lower health care utilization compared to heavy drinking. Alcohol treatment strategies for alcohol-dependent patients have a positive impact on the reduction in health care utilization. An increase in treatment rate for alcohol use disorders will consequently have marked population health improvements.

## INTRODUCTION

Alcohol consumption, in particular heavy consumption, has been associated with an elevated risk of morbidity and mortality for >200 disease and injury categories (Dawson *et al.*, 2008; Rehm *et al.*, 2010). Interventions that had success in reducing drinking levels including, but not limited to, alcohol dependence treatment have been associated with reduced morbidity and mortality (Magill and Ray, 2009; Rosner *et al.*, 2010a, 2010b; McQueen *et al.*, 2011) and a reduction of health utilization costs. (Holder, 1998; Popova *et al.*, 2011) It is well known that treatment for alcohol use disorders decreases health care utilization after 6–12 months (Holder, 1998), but how drinking patterns in treated people with alcohol dependence impacts on health care utilization, has not been established over longer periods of time. The prospective longitudinal study conducted in Catalonia (Multi20) started in 1987 provides a unique opportunity to analyse the impact of drinking on the use of health care resources, specifically hospital admissions. Throughout this study, and at the follow-up at 20 years, three patterns of drinking were distinguished: abstaining, moderate and heavy drinking. This classification has proven useful in prior studies in identifying predictors of early death, morbidity and emergency room visits, with heavy drinking being associated with more detrimental results on almost all indicators compared to abstaining or moderate drinking, and abstaining often showing the best results. (Gual *et al.*, 1989, 1999, 2004, 2009) These studies had limitation in that data on health resources utilization were obtained through self-report, which potentially could lead to bias. (Rhodes and Fung, 2004)

Several studies have shown that the more alcohol consumption is reduced, the better the mortality and morbidity outcomes (for overviews see Rehm and Roerecke (2013); Roerecke *et al.* (2013) and the meta-analyses on treatment outcomes for different modalities cited above). Moreover, given the exponential nature between level of drinking and mortality/morbidity (see Rehm *et al.* (2010) for an overview; see Rehm and Roerecke (2013); Roerecke *et al.* (2013) for the most important lethal outcome of heavy drinking and alcohol dependence: liver cirrhosis), relatively higher gains are expected from reducing the heaviest levels of drinking (Rehm and Roerecke, 2013).

Using administrative data regarding the use of inpatient health resources, the current article tries to confirm previous findings based on self-reported information with the following hypothesis: Heavy drinking will incur higher hospital utilization compared to abstaining (lowest utilization) or moderate drinking.

## METHODS

### Sample

A multicentre longitudinal prospective study was originally initiated in 1987, and 850 patients with alcohol dependence were followed up for >20 years. At baseline, patients had attended treatment in 8 out of 48 outpatient specialized Catalan centres for substance dependence. Centres participating in the study were chosen based

on the global number of new patients who attended during the previous year to the study initiation and their geographical distribution. The centres participating in the study were representative of the Catalan Addiction Treatment Network created in the early 1980s. This treatment network has expanded to a total of 64 outpatient centres spread all over Catalonia (Spain), providing evidence-based universal treatment free of charge. The sample constitutes the 76.5% of the total number of new treatments for alcohol dependence initiated in Catalonia during the period studied. The inclusion criteria comprised fulfilling alcohol dependence DSM-III criteria, being 16–55 years old, agreeing to undergo outpatient treatment, having a family member with a stable home address and giving informed consent to participate in the study. Recruitment happened between 1987 and 1988. Patients received psychosocial and/or pharmacological treatment to achieve abstinence as the treatment goal. The patient population and further sociodemographic characteristics have been described in detail elsewhere (Gual *et al.*, 1989, 1999, 2004, 2009; Bravo *et al.*, 2013).

Of note, 81% of the subjects were male and at baseline on average 39 (SD 9) years old. Of the 850 patients who participated at baseline, at the follow-up 20 years later, 285 (33.5%) patients had died, 28 (3.3%) had left Catalonia and data for 7 (0.8%) patients were lost in CMBD data. This left a net sample of 530 subjects for the study, for which inpatient health services utilization records were available. For 378 of these subjects (71.3%), data on consumption during the previous year at the time of assessment (Year 20) could be secured (88 patients (16.6%) refused to be interviewed and 64 patients (12.1%) were lost to follow-up).

### Assessment

Sociodemographic information, mortality, age at first consumption, number of years of alcohol dependence, drinking pattern during the previous 12 months in terms of quantity (amounts drunk per drinking day expressed in standard drinks (one standard drink = 10 g of pure alcohol)) and frequency (never, <1 occasion per month, 1 or more occasion per month, 1–6 occasion per week or daily) were measured at Year 20 (Gual *et al.* 2009). In total, 101 patients were interviewed in the treatment setting, 13 at home and 319 were contacted by telephone. Drinking behaviour was assessed with a quantity frequency questionnaire specifically designed for this study and considering different time frames (week, month and year). Participants were classified into three groups: abstainers, moderate drinkers and heavy drinkers based on the following criteria: abstainers were those who drank less than once a month and did not consume five or more drinks on their drinking occasion. Moderate drinkers were those who drank less than five drinks on average on their drinking occasions and between once per month and <7 days a week. All others were classified as heavy drinkers. If the patient had changed his pattern of alcohol consumption during the 12 months prior to assessment, it was systematically classified into the higher drinking category. Drinking categories proved to be quite stable

over time: 97.4% of abstinent patients drank zero grams per day during the previous 12 months, 72.4% of moderate drinkers and 70.7% of heavy drinkers maintained the same pattern of alcohol consumption during the previous year.

Inpatients' health service utilization indicators were collected from the central register for health services ("Conjunt Mínim de Bases de Dades—CMBD") provided by the Catalan Health Service, from the last visit at the Year 20 follow-up to the 31 December 2012. Time at risk was defined as the time between the last follow-up visit and whatever event happened first: death, the patient leaving Catalonia or 31 December 2012. Data on acute and chronic hospitalizations, including psychiatric admissions by the Catalan Health Service (Catalut) were analysed using two indicators: number of admissions and hospital days, defined as the number of days stayed in any hospital. Three types of hospitals are included in the administrative system: general (acute), rehabilitation (skilled nursing facilities) and psychiatric hospital. The patient's diagnosis at admission was also registered. Using the same categories as Jones and colleagues, we distinguished between entry diagnosis wholly attributable to alcohol (e.g. alcohol dependence or alcoholic liver cirrhosis), entry diagnosis partly attributable (acute and chronic) or not related to alcohol (Jones *et al.*, 2008). The quality and consistency of the central Catalan register is very good with a built-in validation to detect problems and inconsistencies between variables. In addition, the system is periodically externally validated to ensure quality of data, as these data are used to control payment to service providers. The study was performed according to the ethical standards given in the Declaration of Helsinki and approved by the ethics committee of the hospital.

### Statistical analysis

Descriptive analyses of sociodemographic and clinical data were carried out. Analysis of variance was used to compare continuous data and chi-square analysis for categorical variables. Bonferroni correction was used for multiple comparisons. A probability level of 5% or less was considered as statistically significant. After testing the assumptions, Poisson regression was used to analyse the relationships between the total number of admissions per 100 persons per year, the number of hospital days per 100 persons per year and the number of hospitalizations due to alcohol-attributable conditions, and the pattern of alcohol consumption (groups distinguished: abstaining, moderate drinking, heavy drinking, not located, refused to be interviewed), the independent variable, adjusted for age and sex. The number of admissions was analysed as a rate in order to take into consideration population at risk during the 5 years after alcohol consumption assessment. Sensitivity analyses with negative binomial regression were carried out as well. Marital status and employment were not included as co-variables, as data at Year 20 were not available and no baseline sociodemographic differences were detected between respondents and those patients who were lost at the 20-year follow-up or refused to be interviewed. Data were analysed with SPSS statistical software version 20.0.

## RESULTS

Of note, 530 patients of 850 had at least health services utilization records and thus could be evaluated at the 20-year follow-up (most people had died in the meantime; see in the Methods section). Of these 530 patients evaluated at Year 20, 77.7% were men. At baseline 74.9% were employed, the majority (68.9%) had finished

primary school and 25.7% completed high school or had a university degree. Of note, 70.1% of the total sample were married, 19.1% were single, 9.8% divorced and 0.9% widowed; 50.9% of individuals had an alcohol dependence of <10 years and 15.7% had an alcohol dependence of >10 years; 57.0% of patients started alcohol consumption between the age of 10 and 20 years, 34.7% before the age of 10 years and 8.3% when they were older than 20 years; 75.5% consumed tobacco and 20.2% other drugs.

Even though there were more men than women in all three groups based on drinking patterns, at the 20-year follow-up, the percentage of women in the group of abstainers (27.7%) was significantly higher compared to moderate (10.3%) and heavy (12.2%) drinkers ( $P = 0.04$  and  $0.004$ , respectively). Table 1 gives an overview of the sample and key characteristics at the 20-year follow-up. During the period analysed, from the day of the interview at Year 20 until the end of 2012, 12.8% of the sample had died; 36.9% were attending treatment, 27.2% gave up and 35.9% were discharged.

Table 2 describes the number and rate of hospital admissions and hospital days by pattern of consumption. Abstainers had the lowest ratio of hospitalizations (26.6 per 100 person/year, 95% CI: 24.1–29.4), significantly lower than moderate and heavy drinkers (40.9 per 100 person/year, 95% CI: 31.2–53.7 and 39.3, 95% CI: 32.8–47.2), respectively. These differences remained significant after adjusting for age and sex (Table 3). The group of individuals that refused to be interviewed and were lost to follow-up at Year 20 had similar rates of total admissions than abstainers (Tables 2 and 3).

Heavy drinkers spent more days hospitalized than moderate drinkers or abstainers (618.5 days/100 person and year, 455.5 and 425.7, respectively). The differences remained significant after adjustment (vs abstaining: Relative Risk (RR) = 1.42, 95% CI: 1.36–1.49; vs moderate drinking: RR = 1.52, 95% CI: 1.47–1.57).

Table 4 shows the reasons why individuals were admitted to hospital and the number of admissions wholly attributable, partly attributable or not attributable to alcohol consumption. After adjusting for sex and age, heavy and moderate drinking were associated with significantly higher risk of being admitted for wholly attributable alcohol conditions compared with abstaining (RR = 2.95, 95% CI: 1.54–5.64; RR = 2.98, 95% CI: 1.17–7.60, respectively). Furthermore, heavy drinkers had also significantly higher risk than abstainers for hospital admission due to partly alcohol-attributable conditions (heavy drinkers: RR = 2.51, 95% CI: 1.77–3.58). No significant differences between the three groups were observed for hospitalization of non-related causes.

## DISCUSSION

The results not only clearly indicated that abstainers and moderate drinkers had lower inpatient health care utilization in terms of hospital days compared to heavy drinkers but also that people who refused to participate in the assessment for alcohol consumption had lower utilization as well. People lost to follow-up had a lower number of admissions but spent on average a higher number of days in hospital similar to heavy drinkers. This indicated that we had self-selection of people who were relatively well-off.

The key result expands knowledge on how changes on the pattern of alcohol consumption after treatment and even after a very long follow-up period influence inpatient health care utilization. Our findings state that for people with lifetime alcohol use disorder, not only abstinence but also moderate drinking is associated with positive consequences such as reduced inpatient health care

**Table 1.** Sociodemographic and clinical characteristics of the total sample at Year 20 follow-up

	Abstinent	Moderate	Heavy	Refused	Not located	Total	<i>P</i>
N	267	29	82	88	64	530	
Men (%)	72.3 <sup>a*,b**</sup>	89.7	87.8	80.7	78.1	77.7	0.016
Age (years)							
Mean (SD)	56.8 (8.6) <sup>b*</sup>	55.9 (9.2)	53.4 (8.4)	56.7 (9.0)	53.9 (9.0)	55.9 (8.8)	0.008
35-49 (%)	23.6	24.1	37.8	26.1	32.8	27.4	0.34
50-59 (%)	36.7	34.5	35.4	33.0	40.6	36.2	
60-69 (%)	30.3	37.9	20.7	30.7	18.8	27.9	
>69 (%)	9.4	3.4	6.1	10.2	7.8	8.5	
Vital status at 31 December 2012							
Alive (%)	87.3	79.3	82.9	77.3	81.3	83.8	0.5
Died (%)	10.1	13.8	13.4	19.3	14.1	12.8	
Left Catalonia (%)	2.6	6.9	3.7	3.4	4.7	3.4	
Civil status							
Single	13.1 <sup>b**</sup>	10.3	14.6			13.2	0.018
Married	67.0	69.0	51.2			63.8	
Divorced	6.0	6.9	20.7			9.3	
Widowed	5.2	3.4	3.7			4.8	
Unknown	8.6	10.3	9.8			9.0	
Employment							
Employed	57.3	37.9	50.0			54.2	<0.001
Not employed	17.2	17.2	32.9			20.6	
Retired	24.7	34.5	14.6			23.3	
Unknown	0.7	10.3	2.4			1.9	
Medical illness	52.6	68.0	60.8			55.4	0.2
Psychiatric illness	3.0	24.0	50.0			14.2	<0.001
Time of risk (years) (mean (SD))	5.3 (1.0)	5.1 (1.2)	5.2 (1.2)	5.0 (1.5)	5.0 (1.7)	5.2 (1.3)	0.117
Grams of pure alcohol consumed per drinking occasion (mean (min-max))	0.6 (0-40)	22.3 (10-40)	84.9 (10-450)				<0.001

\**P* < 0.05, \*\**P* < 0.01.<sup>a</sup>Abstinent vs moderate.<sup>b</sup>Abstinent vs heavy.**Table 2.** Use of hospitalization resources by pattern of alcohol consumption

	Abstinent	Moderate	Heavy	Refused	Not located	Total	<i>P</i>
Number of hospital admissions (crude rate per 100 person/year)							
General	311 (21.9) <sup>b*</sup>	42 (28.6)	131 (30.7)	114 (25.9)	94 (29.6)	692 (25.1)	0.002
Psychiatric	38 (2.7) <sup>a*</sup>	12 (8.2) <sup>c,*</sup>	12 (2.8)	6 (1.4)	8 (2.5)	76 (2.8)	0.001
Skilled nursing facilities	29 (2.0) <sup>b**</sup>	6 (4.1)	25 (5.9)	11 (2.5)	9 (2.8)	80 (2.9)	<0.001
Total admissions	378 (26.6) <sup>a,b*</sup>	60 (40.9)	168 (39.3)	131 (29.8)	111 (34.9)	848 (30.8)	<0.001
Number of hospital days (crude rate per 100 person/year)							
General	1,886 (132.8) <sup>b**</sup>	274 (186.8)	995 (232.9)	675 (153.5)	813 (255.8)	4,643 (168.7)	<0.001
Psychiatric	1,050 (73.9) <sup>a*</sup>	284 (193.7) <sup>c,*</sup>	191 (44.7)	51 (11.6)	145 (45.6)	1,721 (62.5)	0.001
Skilled nursing facilities	3,111 (219.0)	110 (75.0)	1,056 (340.9)	521 (118.4)	1,006 (316.5)	7,866 (225.4)	0.23
Total number of days of stay	6,047 (425.7)	668 (455.5)	2,642 (618.5)	1,247 (283.5)	1,964 (617.9)	12,568 (456.7)	0.09

\**P* < 0.05, \*\**P* < 0.001.<sup>a</sup>Abstinent vs moderate.<sup>b</sup>Abstinent vs heavy.<sup>c</sup>Moderate vs heavy.

utilization in addition to reduced mortality, (Rehm and Roerecke 2013; Roerecke et al. 2013) morbidity or other health-related outcomes (Mann et al., 2013).

It is important to note that our results are about people with lifetime alcohol dependence. In the general population, the relationship between level and patterns of alcohol consumption and health

services utilization is not that clear, and usually abstainers have a higher use of health services than moderate drinkers and sometimes even than heavy drinkers. (Armstrong et al., 1998; Rice et al., 2000; Baumeister et al., 2006) However, many of these studies did not control for former heavy drinking in abstainers, and results were often based on one-time measures of drinking status. Unfortunately, self-reports about drinking status and especially about lifetime abstinence are quite unreliable (Rehm et al., 2008), and the repeated assessment of drinking status and patterns in our study is definitely an advantage leading to more reliable data.

**Table 3.** Multivariate analyses of total number of admissions and total days of stay by pattern of consumption

	RR	95% CI
Total number of hospital admissions (100 persons/year)		
<i>Gender</i>		
Male	1	—
Female	0.58	0.46–0.71
<i>Age</i>		
35–49	1	—
50–59	1.20	0.99–1.46
60–69	1.28	1.04–1.58
>69	2.13	1.64–2.76
<i>Level of alcohol consumption</i>		
Abstainers	1	—
Moderate	1.52	1.14–2.04
Heavy	1.46	1.20–1.79
Not located	1.22	0.96–1.55
Refuse survey	0.97	0.78–1.22
Total number of hospital days		
<i>Gender</i>		
Male	1	—
Female	0.34	0.32–0.36
<i>Age (years)</i>		
35–49	1	—
50–59	1.65	1.57–1.73
60–69	2.05	1.95–2.16
>69	2.51	2.35–2.68
<i>Level of alcohol consumption</i>		
Abstainers	1	—
Moderate	0.94	0.87–1.02
Heavy	1.42	1.36–1.49
Not located	1.52	1.44–1.60
Refuse survey	0.65	0.61–0.69

**Implications for behavioural health**

Alcohol dependence and alcohol use disorders in general are prevalent in Europe, affecting an estimated 23 million in the European Union alone. (Rehm et al., 2005, 2014) Heavy drinking is one of the main characteristics of alcohol use disorders (Rehm et al., 2015a, 2015b); it has even been recently suggested to define such disorders by heavy drinking over time (Li et al., 2007; Rehm et al., 2013a), even though both standard classification systems have not included this as criterion. As the results of our cohort study show to avoid health services utilization, it seems imperative to reduce drinking levels in heavy drinkers, including in people with persistent alcohol use disorders. This can be achieved via alcohol policy, for instance, via taxation increases or restrictions of availability, which have been shown to reduce not only overall consumption but also heavy drinking (Anderson et al., 2009). In addition, individual-level interventions have shown public health impact (Babor, 2010). There is sufficient evidence for effectiveness in brief interventions in different settings (Kaner et al., 2007; McQueen et al., 2011), with some indication that even minimal feedback on the screening test is sufficient (Kaner et al., 2013). Thus, screening tests could be implemented including referral to formal treatment if a screening test like the Alcohol Use Disorder Identification Test (AUDIT) so indicates (for the AUDIT, see [http://whqlibdoc.who.int/hq/2001/who\\_msd\\_msb\\_01.6a.pdf](http://whqlibdoc.who.int/hq/2001/who_msd_msb_01.6a.pdf)). From a population health perspective, it is also important to increase the current treatment rate, which has been ~10% in Europe (Rehm et al., 2013a), with Spain being no exception (Rehm et al., 2012). Alcohol use disorders thus are the most undertreated mental disorder (Alonso et al., 2004; Kohn et al., 2004), which

**Table 4.** Hospital admissions attributable to alcohol consumption

	n	Number of admissions (100 persons/year)				Crude rate				RR			
		Wholly	Partly	NR	Total	Wholly	Partly	NR	Total	Wholly	Partly	NR	Total
<i>Gender</i>													
Male	412	50	174	501	725	2.36	8.22	23.67	34.2	1	1	1	1
Female	118	6	25	92	123	0.94	3.94	14.48	19.4	0.59	0.52**	0.62**	0.59**
<i>Age</i>													
35–49	145	29	49	125	203	3.73	6.30	16.08	26.1	1	1	1	1
50–59	192	18	75	223	316	1.73	7.21	21.45	30.4	0.51*	1.26	1.38**	1.23*
60–69	148	6	55	161	222	0.81	7.42	21.73	30.0	0.25**	1.45	1.43**	1.27*
>69	45	3	20	84	107	1.55	10.30	43.26	55.1	0.46	1.88*	2.75**	2.27**
<i>Level of alcohol consumption</i>													
Abstainers	267	18	72	288	378	1.27	5.07	20.28	26.6	1	1	1	1
Moderate	29	6	13	41	60	4.09	8.86	27.96	40.9	2.98*	1.60	1.32	1.45**
Heavy	82	20	56	92	168	4.68	13.11	21.54	39.3	2.95**	2.51**	1.06	1.44**
Not located	64	3	35	73	111	0.94	11.01	22.97	34.9	0.63	2.23**	1.18	1.35**
Refused	88	9	23	99	131	2.05	5.23	22.51	29.8	1.47	1.01	1.09	1.09

\*P < 0.05; \*\*P < 0.01; NR: not related with alcohol.

certainly has to do with the high stigma attached (Schomerus *et al.*, 2010). Increasing treatment rates is especially important, as the treatment gap is generally wider in mental health compared to other disease conditions such as hypertension (Elliott, 2003; Ortiz Marron *et al.*, 2011). An increase in treatment rate for alcohol use disorders will consequently have marked population health improvements (Rehm *et al.*, 2013a, 2013b). This increase in treatment rate for people with alcohol use disorders can only be achieved if stigma is reduced (Schomerus *et al.*, 2010), if treatment is also possible in primary care settings and if it includes reduced drinking as a therapy option as this option is sought by ~50% of the people with alcohol use disorders. (Heather *et al.*, 2010)

Some limitations should be considered. We were limited firstly by the small sample size, especially for the group of moderate drinkers. Secondly, we were limited by the specificity of the sample, as we could only generalize to people with alcohol dependence at a certain time period, which may limit interpretations. In Catalonia the number of patients entering treatment has increased during the last 20 years (Anon, 2011), but even though medical services are free, just a minority of alcohol-dependent patients seek treatment (Drummond *et al.*, 2011). However, our conclusion about hospitalization utilization of moderate drinking and abstinence vs heavy drinking seem to be valid for this group of people with severe lifetime alcohol dependence who sought treatment (in other words, for people with considerable heavy drinking over time) (Rehm *et al.*, 2014). A third limitation concerned the lack of any data on the evolution of drinking patterns after patients were interviewed at the 20-year follow-up. Even though drinking patterns in this sample have shown a high stability over time (Gual *et al.*, 2009), especially in the later periods of the follow-up, it is quite likely that some patients who may have changed their drinking habits and shifted drinking category in the 60 months to the end of the follow-up remain unnoticed. A fourth limitation that should be considered is that in some cases the amount of alcohol consumed by some individuals in the group category “moderate drinkers” should exceed drinking limits stated in the most recent guidelines. This would be the case of women drinking four standard units almost daily; however, the number of women included in this group is relatively small ( $n = 4$ ) and would not bias the results. Also, we should notice that the way we gathered information on frequency of alcohol consumption does not allow us to state the number of drinking occasions per month drunk for each participant.

A major strength of the study was the low attrition rate (0.6% per year). In patients with alcohol dependence, any rate of <1% of dropouts per year can be considered as good (Vaillant *et al.*, 1983). Another strength concerned the fact that we were able to obtain valid health services utilization data for all members of the sample living in Catalonia.

The results of this study are also encouraging because they show that a relevant percentage of the patients who initiated treatment 25 years ago have reduced their alcohol consumption in a long lasting way and that those who reduce or abstain are using less health resources.

## AUTHORS' CONTRIBUTIONS

The second, third and fourth authors designed the original study. The first and the third authors undertook all statistical analyses reported here. The first draft of this report was produced by the first and the last author and led the redrafting, to which all authors contributed. All authors provided critical revision and approved the paper for submission.

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## CONFLICT OF INTEREST STATEMENT

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