

# Alcohol consumption and COVID-19 in Europe: how the pandemic hit the weak

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## Abstract

**Introduction.** The COVID-19 pandemic came along with several health and social unprecedented emergencies, among which handling people with substance use disorder issues.

**Methods.** In this work, data from a cross-sectional online survey conducted among more than 40,000 adults in 21 European countries during the spring of 2020 are analyzed. The survey recorded participants drinking habits during the year preceding the survey and the changes in alcohol consumption during lockdown. The analyses focused on alcohol consumers' type, investigating on the behavioral change in people who already had a problematic alcohol consumption attitude.

**Results and conclusion.** The results show how subjects with risky or hazardous use of alcohol increased both drinking quantity and frequency in most European countries, underlining the urge to establish regulations on online and home delivered alcoholic beverages availability and reinforcing and restructuring health care services.

## Key words

- alcohol consumption
- COVID-19
- Europe
- hazardous drinking

## INTRODUCTION

The global outbreak of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2, henceforth: COVID-19) at the beginning of 2020 led to an unprecedented worldwide health, social and economic crisis. On March 11, 2020 World Health Organization (WHO) declared COVID-19 to be a pandemic disease, and reports, as of October 7<sup>th</sup> 2021, over 235 million confirmed cases and almost 5 million deaths [1]. In order to halt the spread of the virus many countries have dramatically curbed public life, often with nationwide lockdowns. Particularly in Europe, across the months of March and April, most of the region's population was suddenly confined at home, often facing a number of personal and social consequences [2, 3].

It has been reported how the COVID-19 pandemic increased the levels of stress, depression and anxiety, implying a very strong psychological impact on the global population [4, 5]. Among the several consequences on society, change in alcohol consumption is one of these: social isolation is a major risk factor for alcohol misuse, while social support is a protective factor against it [6, 7]. It follows that the effects of forced home isolation added to the lack of support from social services have been detrimental, especially for the populations subgroups that already had a hazardous alcohol consumption. To mention one example, data from a survey

conducted in Italy between April and June 2020 reports that social isolation during the SARS-CoV-2 pandemic a noteworthy increase in sedentariness, tobacco smoking and alcohol consumption [8]. A similar scenario has been observed in Germany [9] and Belgium [10].

Changes in alcohol consumption attitudes are undoubtedly one of the detrimental social consequences of the COVID-19 restrictive measures [11]. Every year alcohol consumption contributes to 3 million deaths and to the disabilities and poor health of millions of people all over the world. Harmful use of alcohol is responsible for 5.1% of the global burden of disease and alcohol is the leading risk factor for premature mortality and disability in people from 15 to 49 years old: it accounts for 10 percent of all deaths in this age group [12]. The higher rates of alcohol-related death and hospitalization affect especially disadvantaged and vulnerable populations [13].

As recently reported, the pandemic and necessary public health response have exacerbated individual-level and population-level substance use problems [14, 15]. Dramatic increases in alcoholic beverages sales were recorded [16], for instance in the US online sales increased 262% from 2019 [17]. Some evidences show how there has been an increase in alcohol consumption frequency, quantity and risky behavior such as binge drinking [18-25], while a reduction in use support for

alcohol reduction by high-risk drinkers has been reported [26]. On April 14th WHO warned on alcohol harm during the pandemic and encouraged governments to enforce measures which limit alcohol consumption [27].

Several surveys have been carried out during the past year since the beginning of the pandemic, with the scope to retrieve information on people's alcohol and substance use behavior [10, 28-32]. The results from such studies are to be interpreted cautiously because of the many biases that surveys may imply, such as sample collection and self-reporting bias [33, 34]. Nevertheless, some useful and precious information may be extrapolated if properly analyzed and interpreted.

Between April 24 and July 22 of 2020 a cross-sectional online survey was conducted among more than 40,000 adults in 21 European countries [35-37]. The survey recorded participants drinking habits during the last year and the changes in alcohol consumption during the last month (*i.e.*, during lockdown), specifically in their drinking frequency, the quantity they consumed, and incidence of heavy episodic drinking events. As previously shown [36, 38], data collected from the survey globally shows that, since the beginning of the pandemic, alcohol consumption has decreased on average and that the decline is primarily due to a reduction in heavy episodic drinking occasions. However, in the present study, we propose a different perspective analysis, approaching the data with a focus on drinking behaviors, particularly analyzing subjects that already had a hazardous alcohol consumption. We aim at investigating alcohol consumption change during lockdown in subjects with a hazardous drinking behavior, compared to low-risk drinkers. In fact, we hypothesize that people mostly affected from lockdown measures in terms of alcohol consumption have been those with previous hazardous drinking patterns, which suddenly found themselves without social connections, deprived of all the support instruments that were usually available for alcohol related issues, and with a high availability of online alcoholic products for sale. Furthermore, while for those who were used to "social drinking" the lockdown could have represented a deterrent for alcohol consumption, those who had the dangerous tendency to drink alone found themselves with unprecedented occasions to drink [39, 40], without a social context that would usually hold them back from drinking. A further element in support of our hypothesis is the fact that many people – once more those from the lower socioeconomic status – found themselves temporarily laid off, if not unemployed, lacking therefore of another strong deterrent from drinking.

## METHODS

This study fully complies with the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) statement [41].

### Data

A cross-sectional online survey was developed to investigate on changes in alcohol consumption among European adults during the first COVID-19 emergency period. Answers were collected between April 24 and July 22 of 2020. The survey used fixed standard ques-

tions, and researcher-led outcome measures, to ensure comparability across countries and to other studies.

The questionnaire was written in English, and then translated into 20 languages and disseminated in 21 European countries. In some countries a targeted sampling was used to ensure sufficient representation across gender, age, and educational attainment (*e.g.*, via paid ads on social media websites) [35].

The survey section of interest for the present work regards the questions on the consumer type – *i.e.*, alcohol consumption attitudes of the respondent during the 12 months prior to completing the questionnaire – and the change in alcohol consumption during the lockdown experience – *i.e.*, in the month prior to completing the questionnaire. The questions related to the former are the ones from the AUDIT-C test [42], while for the latter are the following: "Did you drink alcohol less or more often in the past month?", "Did the amount of alcohol you usually drink on each drinking occasion (*i.e.*, the volume of alcohol consumed) change in the past month?". The answer was in a scale from 1 to 5 as follows: 1 "much less", 2 "slightly less", 3 "no change", 4 "slightly more", 5 "much more". The consumer type questions regard alcohol frequency, quantity and binge drinking, and the results are summed into a final score. Participants that did not respond to all three AUDIT-C questions were considered as non-responders, therefore, they were not included in the final analysis.

### Summary of study protocol

The cross-sectional online survey consisted of five sections covering: (i) sociodemographics; (ii) the AUDIT-C; (iii) perceptions of measures employed to contain the pandemic; (iv) changes in personal alcohol consumption; and (v) changes in the personal use of other substances. The target population was adults aged 18 years or over and there were no further inclusion or exclusion criteria. Participation was voluntary and fully anonymous. Respondents could select not to answer any of the questions and opt to terminate participation in the survey at any time. The survey was designed to take a maximum of 10 minutes to complete, and participants could complete the survey in any of the languages provided, irrespective of their location. The current country of residence was recorded in a separate question. The survey was conducted using the open source survey tool LimeSurvey [43]. Anonymity of respondents was ensured by not collecting data such as the referral URL, HTTP cookies, internet protocol (IP) address, or the exact time of completing the survey. Sampling procedures differed between countries: decentralized snowball technique was used to reach as many people as possible. Amongst the channels used for dissemination of the surveys were alcohol research and policy networks, social media, web pages, press releases, and institutional or interest group mailing lists. Further details about the study design and implementation can be found elsewhere [35].

### Definitions

*Standard alcohol unit*: in the questionnaire, one standard alcohol unit is defined as 11 grams of pure alcohol

based on the average of the most widely used definitions in Europe, except for those countries where a different definition is employed: Czech Republic (16 grams), Denmark and Sweden (12 grams), Slovenia (10 grams) and the UK (8 grams), for further details see [35].

**Alcohol consumer:** participants that declared to have consumed at least one standard alcohol unit within the 12 months prior compiling the questionnaire.

**Consumer type:** the hazardous alcohol consumer has an AUDIT-C sum score higher or equal to 5 for males and higher or equal to 4 for females. Conversely, we defined low-risk consumer the responder with an AUDIT-C sum score below 5 and 4 for males and females, respectively.

**Non-responder:** participants that did not respond to all three the AUDIT-C questions, and therefore when it was not possible to compute the AUDIT-C sum score, where classified as non-responders.

**Change in alcohol consumption:** participants that responded 1 or 2 (“much less” or “slightly less”) to the questions about alcohol consumption change in the month prior compiling the questionnaire (*i.e.* the lockdown period) where grouped into the “decrease” category, while participants that responded 4 or 5 (“much more” or “slightly more”) where grouped into the “increase” category.

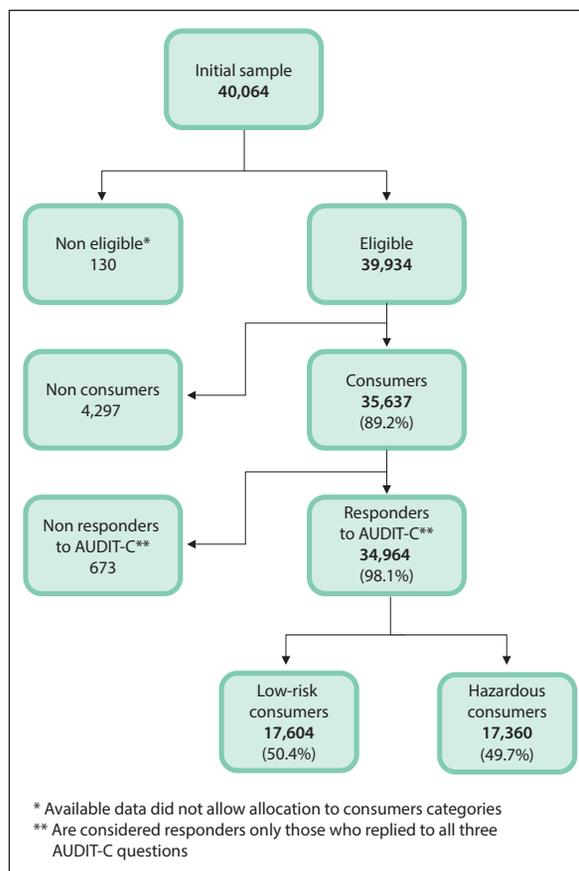
### Statistical analyses

We analyzed the data for each of the European countries involved in the study. Non-consumers and non-responders (see above definitions) were not included in the analysis (see flow chart reported in Figure 1). In order to investigate whether people that were already showing an inappropriate drinking behavior increased their consumption during lockdown, we grouped consumers in “Hazardous” and “Low risk” as described above. We investigated, in the two identified groups, if there has been an increase or decrease in alcohol consumption quantity or in alcohol consumption frequency during lockdown. Change in alcohol consumption was grouped into “Decrease” (1 or 2) and “Increase” (4 or 5), no change was not included in the analysis.

We implemented a logistic regression model, where change in alcohol consumption (quantity or frequency) is the dependent variable, and hazardous, sex and age are the independent variables. Survey weight were used to account for the respective population distributions of each country, weights computation has been described elsewhere [38]. Statistical analyses were performed in R version 3.6.1 [44].

## RESULTS

A total of 40,064 people participated to the survey, the sample numerosity is described in the flowchart in Figure 1, while data for each participating country are reported in Table 1. 130 subjects were not eligible for the analyses as data was not sufficient to compute their consumer type. Final survey population resulted in 39,934 (11,800 males and 28,134 females) with an average of 41.13 years of age. Alcohol consumers (at least one consumption in the last 12 months) in Europe are 35,637 (89.2%). Non-responders to AUDIT-



**Figure 1** Flowchart describing numerosity of the sample.

C among consumers were 673, and responders are 34,964. Overall hazardous consumers are 17,360 and low-risk consumers are 17,604 (see Table 1). During lockdown, alcohol consumption quantity decreased for 9,921 responders and increased for 5,362, while alcohol consumption frequency decreased for 10,865 and increased for 8,345. For 19,481 and 15,123 responders there was no change for quantity nor frequency, respectively.

In Table 2 changes in alcohol consumption quantity and frequency for each country and for alcohol consumption groups are reported, as well as the Bonferroni adjusted p-value for each logistic regression model implemented. Change in alcohol consumption quantity during lockdown (increase *vs* decrease) was found to be positively significantly correlated with consumer type (hazardous *vs* low risk), after correcting for sex and age and adjusting for multiple testing ( $p < 0.001$ ) for 15 out of 21 countries (except for Albania, Iceland, Ireland, Slovakia, Slovenia and the United Kingdom). Similarly, change in alcohol consumption frequency during lockdown was positively significantly correlated with consumer type (hazardous *vs* low risk) for 16 out of 21 countries (except for France, Slovakia, Slovenia, United Kingdom and Ukraine). Figure 2 illustrates, for each country, the percentage increase in alcohol quantity (2A) and frequency (2B) for hazardous (red) and low-risk (green) consumers. It can be observed how the

**Table 1**

Participants details by country. In the column indicating the percentage of hazardous consumers, the highlighted cells indicate whether hazardous consumers are more than half of the responders

Country	N	Consumers	% Consumers	Non responders*	% Non responders* (% among consumers)	Hazardous	% Hazardous (% among consumers who responded)	Low-risk	% Low-risk (% among consumers who responded)
Albania	574	201	35.02%	34	16.92%	29	17.37%	138	82.63%
Czechia	1,552	1,431	92.20%	33	2.31%	729	<b>52.15%</b>	669	47.85%
Denmark	2,556	2,427	94.95%	50	2.06%	1542	<b>64.87%</b>	835	35.13%
Finland	3,761	3,437	91.39%	50	1.45%	1713	<b>50.58%</b>	1,674	49.42%
France	389	312	80.21%	8	2.56%	150	49.34%	154	50.66%
Germany	1,644	1,502	91.36%	35	2.33%	774	<b>52.76%</b>	693	47.24%
Greece	553	529	95.66%	15	2.84%	184	35.80%	330	64.20%
Hungary	544	433	79.60%	16	3.70%	155	37.17%	262	62.83%
Iceland	601	477	79.37%	7	1.47%	166	35.32%	304	64.68%
Ireland	541	480	88.72%	12	2.50%	296	<b>63.25%</b>	172	36.75%
Italy	990	686	69.29%	18	2.62%	184	27.54%	484	72.46%
Norway	17,061	15,497	90.83%	158	1.02%	7821	<b>50.99%</b>	7,518	49.01%
Poland	1,145	1,087	94.93%	19	1.75%	638	<b>59.74%</b>	430	40.26%
Portugal	704	607	86.22%	13	2.14%	161	27.10%	433	72.90%
Russia	815	698	85.64%	32	4.58%	251	37.69%	415	62.31%
Slovakia	506	453	89.53%	13	2.87%	187	42.50%	253	57.50%
Slovenia	560	497	88.75%	9	1.81%	145	29.71%	343	70.29%
Spain	3,135	2,769	88.33%	94	3.39%	1154	43.14%	1,521	56.86%
Sweden	807	720	89.22%	10	1.39%	245	34.51%	465	65.49%
Ukraine	537	477	88.83%	16	3.35%	150	32.54%	311	67.46%
United Kingdom	959	917	95.62%	31	3.38%	686	<b>77.43%</b>	200	22.57%
Europe	39,934	35,637	89.24%	673	1.89%	17,360	49.65%	17,604	50.35%

\*Consumers that did not respond to one or more AUDIT C questions.

increase is almost always higher for the hazardous consumers compared to the low-risk.

## DISCUSSION AND CONCLUSIONS

With the COVID-19 outbreak, and in particular during the lockdown period, managing healthcare and prevention, among the others, became one of the most problematic issues of everyday life. All of the common activities aimed at detecting, preventing, responding and recovering from all of the acute and chronic diseases, became extremely complicated, not only as reported by the scientific literature but mainly as testified by people themselves [45, 46]. Many have been the missed prevention opportunities due to a blocked health system, trying to ensure the COVID cases management as the main Public Health priority endangering controls, screening and diagnosis of a number of chronic and acute conditions [47]. The impact of this has been experienced particularly by the most fragile patients always in need for a very sensitive, usually hardly planned management in the treatment of problematic mental health disorders and addictions, who experienced a dis-

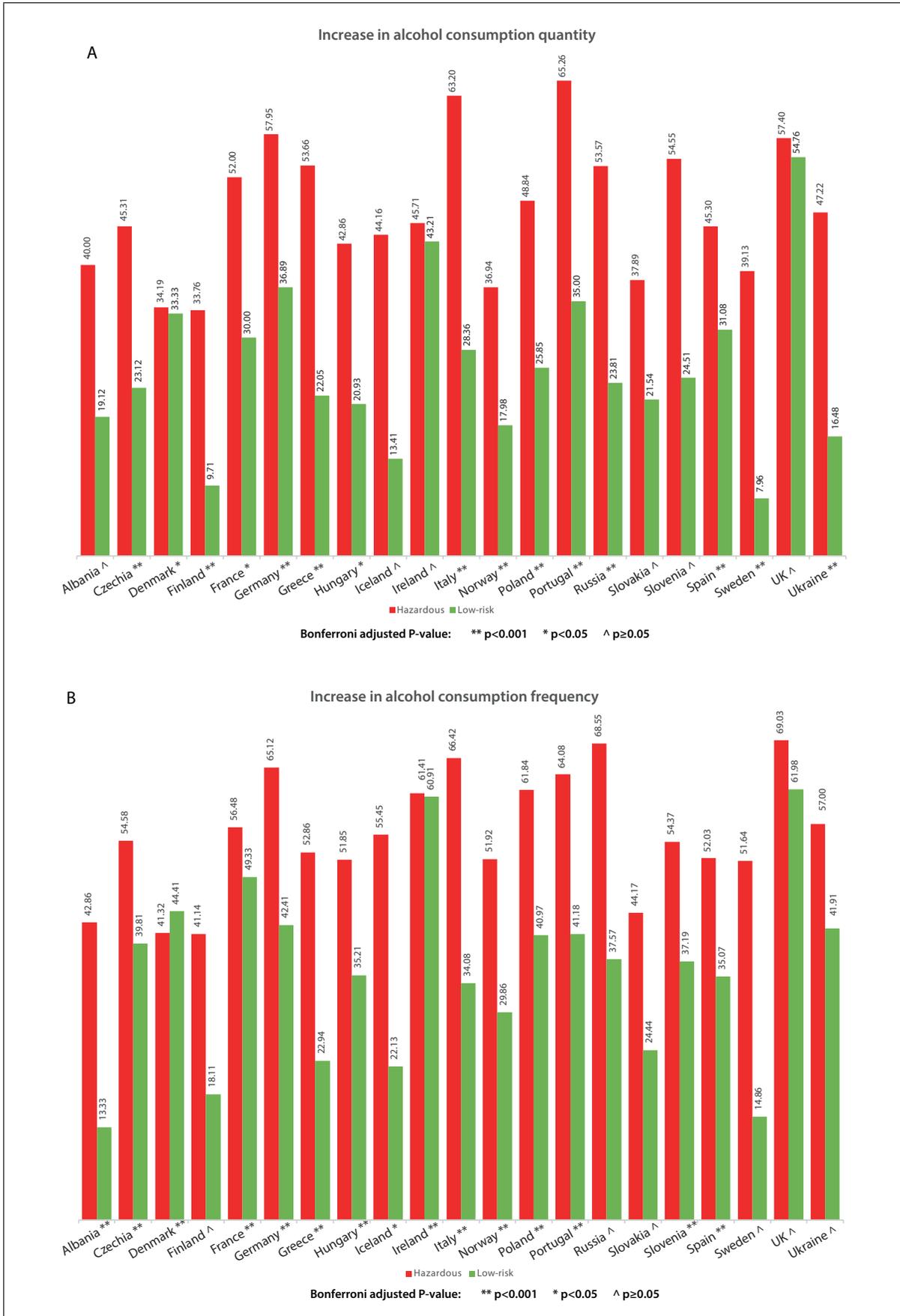
ruption in the continuity of care, due to closures of specialized treatment services during lockdown [48, 49].

In particular, people with alcohol addiction issues found themselves without psychological and motivational support and without the opportunity for a correct pharmacological treatment and lack of symptoms control, such as craving [50]. During a period in which loneliness, pressure by not easy social dynamics, difficult working and family conditions may have influenced mental health and led to behavioral changes, lack of self-control, pushing people into a new, unrealistic dimension where progress towards the final goal of abstinence was lost. Loneliness has been identified as a health concern during the pandemic, and its association with alcohol consumption has been investigated, although it is not yet very well understood. For example, a pilot study conducted in the USA during the 2020 summer of the COVID-19 pandemic – in which restrictions were in place – reported that adults who felt lonelier on average across 30 days consumed more alcohol each day [51]. Loneliness can be a factor that triggers or increases mental health frailty, and it has indeed

**Table 2**

Change in alcohol consumption quantity and frequency during lockdown. The table shows, for each country, the number and percentage of hazardous or low-risk consumers who increased or decreased alcohol consumption and frequency. Bonferroni adjusted p-value refers to the output of the logistic regression model, where significance ( $p < 0.05$ ) indicates that change in alcohol consumption (quantity or frequency) depends on the consumer type (hazardous or low risk), after correction for sex and age and multiple testing. In the columns indicating the percentages of increase in alcohol consumption (quantity and frequency), the highlighted cells indicate whether consumers that increased consumption are more than half

Country	Consumer type	Change in alcohol consumption quantity					Change in alcohol consumption frequency				
		Increase		Decrease		Bonferroni adjusted P-value <sup>a</sup>	Increase		Decrease		Bonferroni adjusted P-value
		n	%	n	%		n	%	n	%	
Albania	Hazardous	8	40.00%	12	60.00%	P=0.4329	9	42.86%	12	57.14%	P=0.0067
	Low-risk	13	19.12%	55	80.88%		10	13.33%	65	86.67%	
Czechia	Hazardous	174	45.31%	210	54.69%	P<.001	262	<b>54.58%</b>	218	45.42%	P<.001
	Low-risk	46	23.12%	153	76.88%		123	39.81%	186	60.19%	
Denmark	Hazardous	306	34.19%	589	65.81%	P=0.0017	500	41.32%	710	58.68%	P<.001
	Low-risk	73	33.33%	146	66.67%		159	44.41%	199	55.59%	
Finland	Hazardous	319	33.76%	626	66.24%	P<.001	469	41.14%	671	58.86%	P<.001
	Low-risk	40	9.71%	372	90.29%		121	18.11%	547	81.89%	
France	Hazardous	52	<b>52.00%</b>	48	48.00%	P=0.0053	61	<b>56.48%</b>	47	43.52%	P=1
	Low-risk	15	30.00%	35	70.00%		37	49.33%	38	50.67%	
Germany	Hazardous	266	<b>57.95%</b>	193	42.05%	P<.001	351	<b>65.12%</b>	188	34.88%	P<.001
	Low-risk	83	36.89%	142	63.11%		137	42.41%	186	57.59%	
Greece	Hazardous	66	<b>53.66%</b>	57	46.34%	P<.001	74	<b>52.86%</b>	66	47.14%	P<.001
	Low-risk	28	22.05%	99	77.95%		39	22.94%	131	77.06%	
Hungary	Hazardous	27	42.86%	36	57.14%	P=0.0207	42	<b>51.85%</b>	39	48.15%	P<.001
	Low-risk	9	20.93%	34	79.07%		25	35.21%	46	64.79%	
Iceland	Hazardous	34	44.16%	43	55.84%	P=1	56	<b>55.45%</b>	45	44.55%	P=0.001
	Low-risk	11	13.41%	71	86.59%		27	22.13%	95	77.87%	
Ireland	Hazardous	96	45.71%	114	54.29%	P=0.0608	148	<b>61.41%</b>	93	38.59%	P=0.0024
	Low-risk	35	43.21%	46	56.79%		67	60.91%	43	39.09%	
Italy	Hazardous	79	<b>63.20%</b>	46	36.80%	P<.001	91	<b>66.42%</b>	46	33.58%	P<.001
	Low-risk	57	28.36%	144	71.64%		76	34.08%	147	65.92%	
Norway	Hazardous	1,551	36.94%	2,648	63.06%	P<.001	2,679	<b>51.92%</b>	2,481	48.08%	P<.001
	Low-risk	357	17.98%	1,629	82.02%		905	29.86%	2,126	70.14%	
Poland	Hazardous	169	48.84%	177	51.16%	P<.001	269	<b>61.84%</b>	166	38.16%	P<.001
	Low-risk	38	25.85%	109	74.15%		93	40.97%	134	59.03%	
Portugal	Hazardous	62	<b>65.26%</b>	33	34.74%	P<.001	66	<b>64.08%</b>	37	35.92%	P<.001
	Low-risk	42	35.00%	78	65.00%		63	41.18%	90	58.82%	
Russia	Hazardous	60	<b>53.57%</b>	52	46.43%	P<.001	109	<b>68.55%</b>	50	31.45%	P<.001
	Low-risk	30	23.81%	96	76.19%		71	37.57%	118	62.43%	
Slovakia	Hazardous	36	37.89%	59	62.11%	P=1	53	44.17%	67	55.83%	P=1
	Low-risk	14	21.54%	51	78.46%		22	24.44%	68	75.56%	
Slovenia	Hazardous	42	<b>54.55%</b>	35	45.45%	P=0.0531	56	<b>54.37%</b>	47	45.63%	P=1
	Low-risk	25	24.51%	77	75.49%		45	37.19%	76	62.81%	
Spain	Hazardous	405	45.30%	489	54.70%	P<.001	486	<b>52.03%</b>	448	47.97%	P<.001
	Low-risk	267	31.08%	592	68.92%		330	35.07%	611	64.93%	
Sweden	Hazardous	36	39.13%	56	60.87%	P<.001	63	<b>51.64%</b>	59	48.36%	P<.001
	Low-risk	9	7.96%	104	92.04%		22	14.86%	126	85.14%	
United Kingdom	Hazardous	287	<b>57.40%</b>	213	42.60%	P=1	390	<b>69.03%</b>	175	30.97%	P=1
	Low-risk	46	54.76%	38	45.24%		75	61.98%	46	38.02%	
Ukraine	Hazardous	34	47.22%	38	52.78%	P<.001	57	<b>57.00%</b>	43	43.00%	P=1
	Low-risk	15	16.48%	76	83.52%		57	41.91%	79	58.09%	



**Figure 2** Increase in alcohol consumption quantity (A) and frequency (B) for hazardous and low-risk consumers.

been reported as the quarantine, during the COVID-19 pandemic, has affected mental health indicators, such as anxiety symptoms, depression, and various measures of psychological distress: all factors that have been associated with alcohol misuse [14, 52].

In the present study we highlight that, in a pan-European survey with more than 40 thousand participants, the majority of alcohol consumers that already were hazardous consumers before the pandemic outbreak, increased their alcohol intake during lockdown, both in terms of quantity and frequency. In fact, despite the general decrease in alcohol consumption that was detected from the survey data analyzed as a whole [36, 38], this tendency is mostly driven from those consumers that are classified as low-risk. In fact, giving a deeper look at the data, the story to be told is different [53, 54]: the percentage of hazardous drinkers who increased alcohol consumption quantity and frequency is higher than those who decreased it in 8 and 17 – respectively for quantity and frequency – out of 21 European countries where the survey was conducted. In Ireland and the United Kingdom also low-risk drinkers increased alcohol consumption quantity (only UK) and frequency. If we consider that in Europe half (49.65%, see *Table 1*) of the consumers that responded to the survey are hazardous consumers (more than half in Czech Republic, Denmark, Finland, Germany, Ireland, Norway, Poland and United Kingdom), this analysis sheds light on the very critical situation that emerged during the COVID-19 pandemic. Vulnerable subjects, that already had a dangerous attitude towards drinking for their health, increased alcohol intake, especially frequency, as being isolated at home, with no social and medical support, and often without an occupation, increased the occasions for drinking. To support our results, one recent Italian study [55] based on hair samples of 30 subjects with drug and/or alcohol disorders, showed that consumption of benzodiazepines and alcohol increased. Interestingly, the trend was opposite compared to heroin, cocaine, MDMA and cannabis, all of which decreased during the lockdown and went back to pre-lockdown levels after the period of confinement. Both the number of benzodiazepine-positive samples and the level of alcohol consumption increased and remained high, even at the end of the lockdown: during home isolation, people with substance use disorder shifted toward what was more easily accessible, used as self-medication for negative feelings and to alleviate the effects of abstinence from drugs that were no longer readily available, producing significant changes in substance use patterns [55].

The herein presented results shed light on the urgent need to take action on two main fronts: regulations on online and home delivered alcoholic beverages availability and reinforcing and restructuring health care services for people with alcohol use issues [56]. Increases in alcoholic beverages sales have been reported widely since the outbreak of the pandemic – not to mention unrecorded alcohol consumption [57] – partner in crime the ease in purchasing alcohol online and having it home delivered [58-60], new habits where regulations are not yet established. For this reason it is essential that evidence-based restrictions on alcohol prices, avail-

ability and marketing are introduced, such as increases in taxation coupled with minimum unit pricing [61, 62]. On the other end, much is to be accomplished for health services: first of all, care should be warranted and systems should for no reason be interrupted, remote health delivery is to be structured and fine-tuned and individualized practices planned [63, 64]. Nonetheless the overall decrease in the frequency and volume of alcohol consumption – as detected by the survey – the increase in the frequency of hazardous drinkers, those who were already in a need-for-treatment situation, represents the most relevant and neglected result to be reported, whereas the decrease of drinkers not at risk, represents an empty prize.

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#### Authors' contribution

Alice Matone: methodology, software, data curation, formal analysis, writing - original draft preparation, vi-

sualization; Silvia Ghirini: data curation, methodology, validation, writing, review and editing, visualization; Claudia Gandin: writing, review and editing, visualization; Emanuele Scafato: conceptualization, writing, review and editing, visualization, supervision, project administration.

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#### Conflict of interest statement

All the Authors of the manuscript have no conflict of interest to declare.

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