

Mortality risk among individuals treated for alcohol use disorders: results of a longitudinal study from 1978 to 2016 in Northern Italy

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Abstract. – **OBJECTIVE:** The aim of this study was to examine the mortality trends and causes of death in Northern Italy in a cohort of a population of individuals treated for alcohol use disorder (AUD) over a 38-year follow-up period (1978-2016).

MATERIALS AND METHODS: 6,198 patients attending eighteen centres for addiction treatment (CATs) for AUD were recruited.

RESULTS: During the follow-up period, 19.5% of the whole cohort died. The crude mortality rates (CMRs) were elevated (21.34 x 1000 person-years [PY]), higher for men and increasing with age group. The CMRs were higher for all cancers, followed by digestive system diseases, diseases of the circulatory system, transport accidents, and suicide. The standardised mortality ratios (SMRs) were at least three times higher for women and for men, and they were more elevated in younger patients and have been falling since 2009. Multivariate analysis confirmed that the mortality risk was higher for males and increased with age and decreased over time.

The patients' main characteristics changed over time and, along with a greater presence of women and non-natives, fewer marginalised people and more socially integrated people turned to CATs.

CONCLUSIONS: The mortality risk in treated AUD is confirmed to be higher when compared with the general population, although it is decreasing. In addition, there is enough epidemiological data to assert that, independent of age and gender, the major causes of death in AUD patients are cancers, gastrointestinal disease, cardiovascular disease (CVD), and injuries.

Key Words:

Cohort study, Mortality risk, Alcohol use disorders, Alcoholic patients in treatment.

Introduction

Around two billion people worldwide consume alcoholic beverages. Alcohol consumption is responsible for 5.9% of all causes of death and for 5.1% of all causes of disease in the world¹. Globally, alcohol use was the seventh leading risk factor for both death and disability-adjusted life-years (DALYs) in 2016, accounting for 2.2% of age-standardised female deaths and 6.8% of age standardised male deaths². The chronic use of alcohol can lead to the onset of an alcohol use disorder (AUD) as defined in the new version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) which, with respect to previous editions, has eliminated the stigmatising terms of abuse and dependence³.

The prevalence of AUD ranges from 13% to 30% (about 20% of men and 10% of women) in most Western societies^{1,4}. In addition, up to 42% of patients admitted to general hospitals, one-third of patients admitted to hospital intensive care units⁵, and up to 50% of those hospitalised in psychiatric divisions, present an AUD^{1,6}.

Moreover, prospective studies carried out in different countries have reported that the mor-

tality risk among alcoholics was approximately two to five times greater than in controls or the general population, and was mainly attributed to major diseases, particularly liver cirrhosis (LC), cancers, cardiovascular diseases (CVD), coronary heart disease (CHD), and external causes including suicides and accidents^{7,8}, and was markedly higher for those < 40 years old⁹. Namely, the overall mortality of alcoholics treated for AUD has risen over time, and currently there are only a few published studies that have investigated this phenomenon¹⁰⁻¹³.

The aim of this study was to examine the mortality trends and causes of death in Northern Italy in a cohort of a population of alcoholic individuals treated for AUD (ATA) over a 38-year follow-up period (from 1978 to 2016). Our aims were to estimate overall crude mortality rates and excess mortality by age, gender, and calendar period.

Patients and Methods

Follow-Up

From 1 January 1978 to 31 December 2016, there were 6,198 patient residents in Emilia Romagna region (North Italy), attending 18 centres for addiction treatment (CATs) for AUD in the metropolitan area of Bologna, in the province of Parma, and in the territory of the Local Health Unit of Forlì that were recruited for this study. The data of subjects attending the 18 CATs were harvested from the digital social and health files in which the patients are distinguished by the date of first admission. The variables were date of birth, gender, country of birth, city of residence, level of education, marital status, living situation, professional condition, date of first and last contact with the CATs, substances of abuse, hepatitis C virus status, HIV status. Person-years (PY) were calculated from the first documented episode to 31 December 2016 or to the date of death. Patients lost to follow-up were included in the person-years until the date they moved out of their last known stable place of residence. Personal identifiers were used, following the rules of privacy regulation. Based on the ICD9 (until 2002) and ICD10 (from 2003) codes noted, mortality was checked at the registry offices of the municipality where the patients were living at the end of the study period (i.e., 31 December 2016) or at the time of their death. According to Italian privacy regulations, the study design was approved by the Local Research Ethics Committee (Cod. CE: 17084).

Diagnosis of AUD

All subjects were diagnosed as alcoholics according to the DSM III and DSM-IV criteria of alcohol abuse and alcohol dependence^{14,15} by physicians at the CATs from which the series is drawn. In order to investigate the number of drinking days and the amount of alcohol consumed, a quantity-frequency questionnaire and retrospective diary (timeline follow back [TLFB])¹⁶ were used. All the subjects also underwent the CAGE test¹⁷. In addition, the alcohol use disorders identification test (AUDIT) was employed¹⁸.

All these patients were offered free support and specific treatment within the framework of the regional health care system¹⁹. Treatment for AUD in Italy is multi-disciplinary and is based on pharmacological treatment, psycho-social-educational approach, and self-help groups, such as Alcoholics Anonymous and Clubs for Addiction Treatment^{20,21}. The prescribed drugs were sodium oxybate (gamma hydroxybutyrate), metadoxine, disulfiram, tiapride and chlordiazepoxide, naltrexone and acamprosate¹⁹⁻²².

Statistical Analysis

The continuous and categorical variables were analysed with Student's *t*-test and chi-squared test, respectively. Crude mortality rates (CMRs) per thousand PY and relative confidence intervals (CI) at 95% were calculated (Standard: Italia 2007). The year group (< 2000, 2001-2004, 2005-2008, 2009-2012, 2013-2016) was entered into a Poisson model adjusted for age group (< 25 years, 25-34 years, 35-44 years, > 44 years), and sex to determine the significance of trends in mortality over time. To compare the mortality rates of alcohol users with those of the general population, we calculated the SMRs, adjusted for age and calendar year (Standard: Emilia Romagna Region), and relative 95% confidence intervals specifically for cause, gender, calendar period, and age-group. A Poisson regression analysis was performed to analyse the combined effect of gender, age, and year group on mortality²³. Data analyses were performed using the STATA 15.1 statistical software program.

Results

Demographic Characteristics

The characteristics of the subjects at the time of admission to a CAT are shown in Table I. Thirty-three per cent of patients were >=

50 years old at time of admission to a CAT, three in five subjects had undertaken specific treatment after 2004, and 16% of patients were non-natives. As regards the non-native regions,

38% came from Eastern European countries, 30% from Africa, 13% from other European countries, and 10% from Latin America. Half of the patients were regularly employed, 25%

Table I. Socio-demographic data of patients treated in the eighteen Centers for Addiction Treatment (CATs) in Northern Italy from January 1978 to December 2016.

		Total (6198)	≤2000 (1262)	2001/2004 (1142)	2005/2008 (1162)	2009/2012 (1301)	2013/2016 (1331)	P	
Sex	% Female	26.6	21.2	26.9	29.1	25.8	30.1	<0.0001	
	Age at admission	Mean age	44.6	42.3	44.3	45.6	44.3	44.2	0.532
Age at admission	% <40 years	38.5	45.6	39.2	33.6	36.6	37.3	<0.0001	
	% 40-49 years	28.6	24.3	25.9	30.4	31.9	30.0	<0.0001	
	% ≥50 years	32.9	30.0	34.9	36.1	31.5	32.5	<0.0001	
	Country of Birth	% Non-natives	15.9	7.5	9.5	17.7	19.8	23.7	<0.0001
		Marital status	% Single	39.8	38.7	40.7	37.4	40.0	42.0
% Married	37.1		38.2	38.9	38.5	35.6	34.9	<0.0001	
% Widowed/ separated/ divorced	20.2		14.6	18.2	24.0	22.7	21.4	<0.0001	
Education level	% Elementary school	17.9	28.5	21.5	20.5	11.4	8.9	<0.0001	
	% Middle school diploma	51.7	47.5	52.4	50.8	54.1	53.4	<0.0001	
	% Secondary school exam certificate	19.2	12.8	15.8	19.9	23.2	23.9	<0.0001	
	% Graduate	5.6	2.6	4.3	6.0	7.2	7.5	<0.0001	
Employment status	% Work	50.4	44.6	53.8	53.3	50.1	50.5	<0.0001	
	% Not work	26.4	22.4	20.1	25.2	29.4	33.5	<0.0001	
	% Not professional	19.1	19.0	22.3	20.9	19.3	14.7	<0.0001	
Living situation	% Original family	29.1	56.9	36.8	17.2	18.6	16.9	<0.0001	
	% Acquired family	30.6	2.7	7.7	42.0	48.6	49.2	<0.0001	
	% Living alone	19.2	9.3	20.3	25.5	20.3	21.0	<0.0001	
Illegal substance use	% Yes	16.7	22.2	15.7	11.6	15.1	18.1	<0.0001	
Health situation	% HIV positive	1.5	2.7	1.3	0.7	1.6	1.1	0.001	
	% HCV positive	8.9	12.6	8.5	7.9	8.7	7.0	<0.0001	

The information was collected at the first contact. Marital status (2.9%), education level (5.7%), employment status (4.2) and living situation (21.1%) were missing data.

had a medium-high level of education, 37% were married, and 19% lived alone. Nine per cent were HCV positive, and 1.5% were HIV positive. Seventeen per cent had a secondary addiction to other psychoactive substances: heroin (8%), cannabinoids (7%), benzodiazepines (2.3%), and cocaine (2%).

As regards the temporal trends, there was an increasing number of new patients among which we observed a growing percentage of females and particularly of non-natives; the latter represent one new visit in four in the last period. The percentage of people that were unemployed, unmarried, or living alone rose throughout the study period. It should be noted that there was a growing number of patients with a medium-high education level, particularly graduates, who represented 8% of new patients in the last period. While the percentage of patients with hepatitis C or HIV positive ATA steadily fell, the percentage of patients with concomitant abuse of illegal substances has been increasing since 2001.

Follow-Up

The cohort was made up of 6,198 subjects (73% males) with an average age of 44.6 ± 12.8 years (mean age males 44.4, females 45.1 $p = 0.07$). Follow-up continued until 31 December 2016 for all the subjects or until the date of death (no subject was lost to follow-up), with 56,515 at-risk person-years (14,393 females, 42,122 males). The average follow-up period was 9.1 years, the average period of contact with CATs was 4.6 years, and the average time between the last contact with the CATs to the end of the follow-up was 4.5 years. By the end of the follow-up, 21% had an ongoing therapeutic programme, 32.2% had completed the treatment, 41.1% had given up, and 6.7% died during the treatment program.

Proportional Mortality

During the follow-up period, 1,206 patients (19.5% of the whole cohort) died [971 were male (21.3% of all males) with a mean age of 58.8 years and 235 were female (14.3% of all females) with a mean age of 53.6 years ($p = 0.653$). The main causes of death are shown in Table II. Cancers (except for breast cancer and neoplasm of the pancreas), road accidents, and suicide were the main causes of death in alcoholic men when compared with females (Table II). On the other hand, digestive disease (including liver cirrhosis) and accidental falls were the major causes of death in females when compared with males.

Mortality Rate

The CMRs for 1,000 PY were 21.34 (95% CI 20.17-22.58) and were higher for men and subjects aged over 64 years and fluctuated over time (Table III). As regards the causes of death, the CMR in both genders was higher for all cancers, followed by diseases of the digestive system, diseases of the circulatory system, and external causes of death, particularly transport accidents and suicide.

Standardised Mortality Ratios (SMRs)

Elevated and statistically significant SMRs were found in both genders, and they were higher in younger patients (< 45 years, SMR = 7.87, CI 95% 9.09-10.49; 45-64 years, SMR = 5.96, CI 95% 6.45-6.97; > 64 years, SMR = 1.58, CI 95% 1.74-1.92) and they decreased starting from 2009 (< 2000, SMR = 4.43, CI 95% 3.58-5.49; 2001-2004, SMR = 4.01, CI 95% 3.42-4.71; 2005-2008, SMR = 4.06, CI 95% 3.60-4.59; 2009-2012, SMR = 3.26, CI 95% 2.91-3.65; 2013-2016, SMR = 3.12, CI 95% 2.83-3.44).

In comparison with males, females had higher SMRs for diseases of the digestive system, external causes, diabetes mellitus, diseases of the nervous system, and endocrine diseases; in comparison with females, males had higher SMRs for all cancers, mental and behavioural disorders, and diseases of the circulatory system (Table IV). In particular, among males, higher SMRs were found for cancers (tumours of the lip, mouth, pharynx, digestive system organs, respiratory system organs, eye, brain and other parts central nervous system), diabetes mellitus, mental and behavioural disorders, hypertensive diseases, ischemic heart diseases, other forms of heart diseases, CVD, chronic diseases of the lower respiratory pathways, LC, transport accidents, accidental falls and intentional self-harm (Table III). Among females, there were higher SMRs for tumours of the organs of the digestive system or respiratory system, breast cancer, ischemic heart diseases, other forms of heart disease, CVD, chronic diseases of the lower respiratory pathways, LC, and intentional self-harm.

Poisson Regression Analysis

To analyse the combined effect of gender, age, and calendar period on mortality, five separate regression analyses were performed, using the Poisson method, for all causes of death, all cancers, diseases of the digestive system, diseases of the circulatory system, and injury. The variables inserted in the model were gender, age group (\geq

Table II. Proportional mortality.

	Total (1206)	%	Males (971)	%	Females (235)	%
All tumours	352	29.2	293	30.2	59	25.1
Malignant tumours of the lip, the mouth and the pharynx	50	4.1	44	4.5	6	2.6
Malignant tumours of the tongue	8	0.7	6	0.6	2	0.9
Malignant tumour of other and unspecified parts of the mouth	10	0.8	10	1.0	-	-
Malignant neoplasm of oropharynx	6	0.5	6	0.6	-	-
Malignant neoplasm of hypopharynx	6	0.5	5	0.5	1	0.4
Malignant neoplasm of other and ill-defined sites in the lip, oral cavity and pharynx	12	1.0	11	1.1	1	0.4
Malignant tumours of the organs of the digestive system	104	8.6	93	9.6	11	4.7
Malignant tumour of the oesophagus	16	1.3	15	1.5	1	0.4
Malignant tumour of the stomach	12	1.0	11	1.1	1	0.4
Malignant tumour of the colon	12	1.0	10	1.0	2	0.9
Malignant tumour of the rectum	5	0.4	4	0.4	1	0.4
Malignant tumour of the liver and the intrahepatic biliary ducts	47	3.9	44	4.5	3	1.3
Malignant neoplasm of pancreas	6	0.5	3	0.3	3	1.3
Malignant tumours of the organs of the respiratory system	122	10.1	104	10.7	18	7.7
Malignant neoplasm of larynx	16	1.3	13	1.3	3	1.3
Malignant tumour of the bronchi and the lung	103	8.5	88	9.1	15	6.4
Malignant breast tumour	15	1.2	1	0.1	14	6.0
Mental and behavioural disorders	60	5.0	49	5.0	11	4.7
Mental and behavioural disorders due to psychoactive substance use	32	2.7	26	2.7	6	2.6
Mental and behavioural disorders due to the use of alcohol	27	2.2	23	2.4	4	1.7
Diseases of the circulatory system	203	16.8	164	16.9	39	16.6
Hypertensive diseases	16	1.3	10	1.0	6	2.6
Ischemic heart diseases	74	6.1	61	6.3	13	5.5
Other forms of hearth diseases	60	5.0	51	5.3	9	3.8
Cerebrovascular diseases	41	3.4	33	3.4	8	3.4
Diseases of arteries, arterioles and capillaries	7	0.6	5	0.5	2	0.9
Diseases of the respiratory system	61	5.1	50	5.1	11	4.7
Influenza and pneumonia	9	0.7	6	0.6	3	1.3
Chronic diseases of the lower respiratory pathways	43	3.6	35	3.6	8	3.4
Diseases of the digestive system	211	17.5	163	16.8	48	20.4
Diseases of the oesophagus, the stomach and the duodenum	5	0.4	5	0.5	-	-
Other intestinal diseases	7	0.6	4	0.4	3	1.3

Table continued

Table II. (Continued). Proportional mortality.

	Total (1206)	%	Males (971)	%	Females (235)	%
Liver diseases (Cirrhosis)	186	15.4	143	14.7	43	18.3
Alcoholic liver disease	98	8.1	72	7.4	26	11.1
Hepatic fibrosis and cirrhosis	72	6.0	58	6.0	14	6.0
Disorders of gallbladder, biliary tract and pancreas	6	0.5	6	0.6	-	-
External causes	167	13.8	137	14.1	30	12.8
Transport accident	50	4.1	46	4.7	4	1.7
Accidental falls	15	1.2	9	0.9	6	2.6
Accidental poisoning by and exposure to noxious substances	29	2.4	23	2.4	6	2.6
Intentional self-arm	45	3.7	38	3.9	7	3.0

45 years, 45-64 years, and > 64 years), and calendar period (≤ 2000 , 2001-2004, 2005-2008, 2009-2012, and 2013-2016). The results are shown in Table V. The multivariate analysis showed a higher mortality risk for males (all causes and cancers), increasing with age, except for injury, where the relative risk (RR) was not statistically significant. Regarding the time period, the RR was statistically significantly higher before 2000 and decreased over time for all causes of death and diseases of the digestive system; it decreased in the period after 2008 for diseases of the circulatory system, all cancers, and injury.

Discussion

This is the first large cohort Italian study with the highest number of PY and the longest follow-up period showing the major causes of death in a population of subjects with AUD following treatment for alcohol addiction. Three important aspects emerged from this study: 1) the mortality risk and excess mortality compared with the general population are decreasing, 2) all cancers are the most common cause of death, and 3) the characteristics of the subjects accessing the public healthcare services treating AUD are changing.

As regards mortality, this was higher than values based on data on the risk of death in the general population; namely, the SMRs were at least three times higher for women and men and were more elevated in younger patients and have been falling since 2009. Multivariate analysis confirms the higher mortality risk for males, which

increased with age and decreased over time. The CMRs were elevated (21.34 x 1000 PY), they were higher for men and increased with increasing age groups. The rates were higher for all cancers, followed by digestive system diseases (particularly for LC), diseases of the circulatory system, external causes (particularly for transport accidents and suicide). The patients' main characteristics have changed over time and, along with a greater presence of women and non-natives, a complex situation can be observed, with an increasing number of lonely people (unmarried, living alone) with low (unemployed) or high (graduates) social position, and poly-drug users (concurrent abuse of illegal substances).

A recent meta-analysis has clearly shown the higher number of deaths in ATA when compared with the general population¹³. Like the general population, they are most likely to die of CVD. In contrast to the general population, gastrointestinal and unnatural deaths are the next most common causes of death. A more recent meta-analysis has shown that malignancy is the most common cause of death in the included AUD cohorts¹². An Italian cohort study²⁴ has shown that the major causes of death in a population treated for AUD were infections, cancers, CVD, respiratory and digestive system diseases, as well as violent causes. In addition, a Danish case-control study²⁵ showed that, compared with controls, alcohol-dependent men and women had statistically significantly higher risks of all disease groups and the majority of subgroups when analysed as disease events.

From the epidemiological point of view our study shows that cancers, digestive diseases (i.e.,

Table III. Crude Mortality Rates for most commons causes of death, time and age group.

	All cases (PY 56,515)		Males (PY 42,122)		Females (PY 14,393)	
	CMR	95% CI	CMR	95% CI	CMR	95% CI
All causes	21.34	20.17-22.58	23.05	21.65-24.55	16.33	14.37-18.55
Calendar period						
≤2000	16.07	12.98-19.90	18.70	14.98-23.35	5.68	2.55-12.64
2001/2004	20.83	17.75-24.44	22.53	18.89-26.86	15.30	10.42-22.48
2005/2008	23.56	20.87-26.60	24.40	21.26-28.01	21.06	16.31-27.18
2009/2012	20.79	18.58-23.26	21.99	19.36-24.97	17.38	13.65-22.12
2013/2016	22.14	20.09-24.40	24.65	22.13-27.47	15.49	12.40-19.33
	<i>p</i> <0.0001*		<i>p</i> <0.0001*		<i>p</i> <0.0001*	
Age group						
<45 years	7.92	6.86-9.15	8.34	7.11-9.79	6.54	4.72-9.07
45-64 years	23.55	21.77-25.47	25.36	23.21-27.71	18.66	15.75-22.10
>64 years	60.83	55.12-67.13	68.98	61.92-76.83	38.03	29.82-48.49
	<i>p</i> <0.0001*		<i>p</i> <0.0001*		<i>p</i> <0.0001*	
All tumors	6.23	5.62-6.91	6.96	6.20-7.80	4.10	3.18-5.29
Mental and behavioural disorders	1.06	0.82-1.37	1.16	0.88-1.54	0.76	0.42-1.38
Diseases of the Circulatory system	3.59	3.13-4.12	3.89	3.34-4.54	2.71	1.98-3.71
Diseases of the Respiratory system	1.08	0.84-1.39	1.19	0.90-1.57	0.76	0.42-1.38
Diseases of the Digestive system	3.73	3.26-4.27	3.87	3.32-4.51	3.34	2.51-4.43
External causes	2.96	2.54-3.44	3.25	2.75-3.85	2.08	1.46-2.98
Transport accidents	0.89	0.67-1.17	1.09	0.82-1.46	0.28	0.10-0.74
Accidental falls	0.27	0.16-0.44	0.21	0.11-0.41	0.42	0.19-0.93
Accidental poisoning by and exposure to noxious substances	0.51	0.36-0.74	0.55	0.36-0.82	0.42	0.19-0.93
Intentional self-arm	0.80	0.60-1.10	0.90	0.66-1.24	0.49	0.23-1.02

PY, Person Year; CMR, crude mortality ratio for 1000 PY; CI, confidence interval; * *p*-test for time trend.

LC), CVD, and traumatic episodes (including road accidents and suicides) were the prevalent causes of death, covering almost 80% of the total causes of death, with a higher prevalence of males dying for cancers in comparison with females. The pathophysiological causes are well explained. It has been demonstrated that chronic and heavy alcohol consumption is directly, and indirectly, toxic for the whole body through its metabolite acetaldehyde^{26,27}. Specifically, liver tissue inflammation with a progressive injury leads to steatosis, fibrosis and LC²⁸, the reduction of immune response, the malabsorption of macro and micro-nutrients, which leads to malnutrition²⁹, an increasing risk

of infections³⁰ and to the development of several cancers³¹; moreover, hypertension with increased blood levels of triglycerides and glycaemia leads to an increased risk of diabetes mellitus, metabolic syndrome^{32,33}, and CVD³⁴. Moreover, due to the increased risk of developing some life-threatening diseases, the implementation of a preventive strategy characterised by the results of laboratory and/or instrumental examinations to investigate the presence of malignancies, CVD, or gastro-intestinal diseases (including LC) also have to be pursued in the younger ATA (< 40 years old). Furthermore, a preventive strategy aimed at reducing the risk of injuries (i.e., traffic crashes), and a deeper investi-

Table IV. SMR.

	Total				Males				Females			
	O	E	SMR	95% CI	O	E	SMR	95% CI	O	E	SMR	95% CI
All causes	1206	344.3	3.50	3.31-3.71	971	276.5	3.51	3.30-3.74	235	67.8	3.47	3.05-3.94
All tumours	352	128.4	2.74	2.47-3.04	293	103.8	2.82	2.52-3.17	59	24.6	2.40	1.86-3.09
Malignant tumours of the lip, the mouth and the pharynx	50	0.3	171.0	129.6-225.6	44	0.3	169.3	126.0-227.5	6	0	184.3	82.77-410.1
Malignant tumours of the organs of the digestive system	104	4.2	24.73	20.41-29.98	93	3.5	26.64	21.74-32.65	11	0.7	15.40	8.53-27.82
Malignant tumours of the organs of the respiratory system	122	3.7	33.12	27.73-39.55	104	2.8	36.75	30.32-44.53	18	0.9	21.09	13.28-33.47
Malignant breast tumour	15	0.5	31.47	18.97-52.19	1	0	77.0	10.85-546.6	14	0.5	30.19	17.88-50.98
Malignant tumour of eye, brain and other parts central nervous system	11	0.4	24.98	13.84-45.11	9	0.4	25.33	13.18-48.68	2	0.1	23.55	5.89-94.14
Endocrine, nutritional and metabolic diseases	23	12.0	1.92	1.27-2.88	17	9.6	1.77	1.10-2.84	6	2.4	2.53	1.14-5.63
Diabetes mellitus	21	0.8	26.14	17.04-40.09	16	0.6	24.89	15.25-40.62	5	0.2	31.14	12.96-74.83
Mental and behavioural disorders	60	9.1	6.62	5.14-8.52	49	6.4	7.72	5.83-10.21	11	2.7	4.1	2.24-7.32
Diseases of the nervous system	17	10.0	1.7	1.06-2.74	12	7.6	1.58	0.90-2.78	5	2.4	2.08	0.86-4.99
Diseases of the circulatory system	203	104.1	1.95	1.70-2.24	164	82.6	1.99	1.70-2.31	39	21.5	1.82	1.33-2.48
Hypertensive diseases	16	1.1	14.87	9.11-24.27	10	0.8	13.13	7.06-24.39	6	0.3	19.09	8.56-42.50
Ischemic heart diseases	74	4.0	18.38	14.64-23.09	61	3.4	17.83	13.87-22.92	13	0.6	21.52	12.50-37.06
Other forms of hearth diseases	60	2.1	27.99	21.73-36.04	51	1.7	30.97	23.54-40.75	9	0.5	18.10	9.42-34.78
Cerebrovascular diseases	41	2.2	18.27	13.45-24.81	33	1.7	19.46	13.83-27.37	8	0.6	14.59	7.30-29.18
Diseases of arteries, arterioles and capillaries	7	0.6	12.39	5.91-25.98	5	0.5	10.46	4.36-25.14	2	0.1	22.92	5.73-91.64
Diseases of the respiratory system	61	21.8	2.79	2.17-3.59	50	17.9	2.80	2.12-3.69	11	4.0	2.78	1.54-5.02
Chronic diseases of the lower respiratory pathways	43	1.0	42.53	31.54-57.34	35	0.9	41.08	29.50-57.22	8	0.2	50.26	25.14-100.5
Diseases of the digestive system	211	13.4	15.72	13.74-17.99	163	10.9	14.93	12.80-17.40	48	2.5	19.19	14.47-25.47
Liver diseases (Cirrhosis)	186	0.6	301.0	260.7-347.6	143	0.5	268.8	228.2-316.7	43	0.1	500.8	371.4-675.2
External causes of morbidity and mortality	167	23.1	7.23	6.21-8.41	137	20.5	6.70	5.66-7.92	30	2.7	11.34	7.93-16.22
Transport accident	50	7.8	6.44	4.88-8.50	46	7.2	6.41	2.57-18.24	4	0.6	6.85	2.57-18.24
Accidental falls	15	4.2	3.54	2.13-5.87	9	3.4	2.68	1.39-5.14	6	0.9	6.87	3.09-15.29
Intentional self-arm	45	7.1	6.38	4.76-8.54	38	6.4	5.94	4.33-8.17	7	0.7	10.53	5.02-22.08

Table V. Rate ratio for all causes of death (Poisson multiple regression analyses).

		All causes (1206)		All cancers (352)		Digestive (211)		Circulatory (203)		Injury (167)	
		RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Sex	Females	1	Referent	1	Referent	1	Referent	1	Referent	1	Referent
	Males	1.37	1.19-1.58	1.70	1.29-2.25	1.13	0.82-1.56	1.38	0.97-1.96	1.45	0.97-2.15
Age group	≤45 years	1	Referent	1	Referent	1	Referent	1	Referent	1	Referent
	45-64 years	3.13	2.64-3.71	18.11	9.54-34.37	4.67	3.09-7.04	3.08	1.98-4.81	0.96	0.69-1.35
	>64 years	7.53	6.28-9.02	46.64	24.38-89.26	5.99	3.71-9.68	12.03	7.70-18.80	0.85	0.50-1.45
Calendar period	≤2000	1	Referent	1	Referent	1	Referent	1	Referent	1	Referent
	2001/2004	0.73	0.56-0.96	0.85	0.46-1.58	0.46	0.26-0.80	1.23	0.62-2.44	0.83	0.45-1.55
	2005/2008	0.56	0.43-0.71	0.71	0.40-1.27	0.31	0.18-0.52	0.64	0.33-1.26	0.61	0.34-1.10
	2009/2012	0.34	0.27-0.44	0.38	0.21-0.67	0.24	0.15-0.39	0.36	0.18-0.68	0.45	0.25-0.80
	2013/2016	0.28	0.22-0.36	0.39	0.22-0.67	0.15	0.09-0.24	0.33	0.17-0.63	0.33	0.18-0.59

gation of the psychiatric assessment of ATA aimed at reducing the risk of self-harm and homicides also need to be implemented.

As regards the fall in excess mortality, compared with the general population and the decrease in the death risk, the changes in the patients' characteristics must also be considered. In the last decade, fewer marginalised people and more and more socially integrated people have turned to CATs. This could have partly contributed to the improvement in the patients' health conditions thanks to the greater compliance with the proposed treatments and the greater awareness of having to undergo treatment and having to make lifestyle changes. From recent literature it has emerged that alcohol plays a crucial role in increases in premature mortality and decreased life expectancies in the general population, but a high proportion of this occurred in the lower socio-economic strata³⁵. Rates of alcohol-related mortality are higher in lower educational and occupational groups in all European countries^{36,37}. Unemployment is a significant risk factor for the development of alcohol use disorders, and it increases the risk of relapse after treatment³⁸. Countering increases in alcohol-related mortality in lower socioeconomic groups is essential for reducing inequalities in mortality, and future alcohol policies must take into consideration any differential effect on socioeconomic groups³⁹.

This study does have some limitations, however. Considering the retrospective evaluation of this cohort study, patients had no specific selection characteristics at the time of admission to the CATs. In addition, age at the first intake of alcoholic beverages, dietary habits, lifestyle, and tobacco consumption were not addressed. Hence, it is quite difficult to generalise some of our results. In particular, in regard to alcohol intake, an actual amount of alcohol has not been recorded, and a further stratification of risk according to these data was not performed. Additional research is required with specific studies in a targeted population of alcoholic patients undergoing treatment.

Conclusions

The mortality risk in treated AUD is observed to be higher when compared with the general population, although it is decreasing. In addition, there is enough epidemiological data to assert that, independently from age and gender, the major causes of death in AUD patients are cancers, gastrointestinal disease, CVD, and injuries. Therefore, it is stated

that the primary aim of professional work in the CATs is to help patients achieve and maintain alcohol abstinence through a multidisciplinary intervention; on the other hand, it is also true that planning a programme aimed at preventing diseases or conditions more at risk for death in AUD patient needs to be followed. A care network needs to be implemented, as CATs alone cannot govern this preventative strategy.

Conflict of Interests

The Authors declare that they have no conflict of interests.

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