The contribution of alcohol-related deaths to the life-expectancy þÿ g a p b e t w e e n p e o p l e w i t h a n d w i t h o u t d e p r e s s i o n cross-country comparison

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The contribution of alcohol-related deaths to the life-expectancy gap between people with and without depression – a cross-country comparison

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ABSTRACT

Background: Alcohol-related deaths may be among the most important reasons for the shorter life expectancy of people with depression, yet no study has quantified their contribution. We quantify the contribution of alcohol-related deaths to the life-expectancy gap in depression in four European countries with differing levels of alcohol-related mortality.

Methods: We used cohort data linking population registers with health-care and death records from Denmark, Finland, Sweden and Turin, Italy, in 1993–2007 (210,412,097 person years, 3046,754 deaths). We identified psychiatric inpatients with depression from hospital discharge registers in Denmark, Finland, and Sweden and outpatients with antidepressant prescriptions from prescription registers in Finland and Turin. We assessed alcohol-related and non-alcohol-related deaths using both underlying and contributory causes of death, stratified by sex, age and depression status. We quantified the contribution of alcohol-related deaths by cause-of-death decomposition of the life-expectancy gap at age 25 between people with and without depression.

Results: The gap in life expectancy was 13.1–18.6 years between people with and without inpatient treatment for depression and 6.7–9.1 years between those with and without antidepressant treatment. The contribution of alcohol-related deaths to the life-expectancy gap was larger in Denmark (33.6%) and Finland (18.1–30.5%) – i.e., countries with high overall alcohol-related mortality – than in Sweden (11.9%) and Turin (3.2%), and larger among men in all countries. The life-expectancy gap due to other than alcohol-related deaths varied little across countries.

Conclusions: Alcohol contributes heavily to the lower life expectancy in depression particularly among men and in countries with high overall alcohol-related mortality.

1. Introduction

The excess mortality of people with depressive disorders is well established (Walker et al., 2015; Wulsin et al., 1999). The gap in life expectancy between people with and without depression has been estimated to range between three to 17 years depending on the setting (Jia et al., 2018; Laursen et al., 2016; Lawrence et al., 2013; Nordentoft et al., 2013; Steensma et al., 2016). Although, the mechanisms producing the excess mortality remain debated (Machado et al., 2018), previous studies have suggested excessive alcohol consumption among people with depression to be a potentially important mechanism (Miloyan and Fried, 2017; Wulsin et al., 1999). The association between depression and alcohol consumption may be bidirectional (Swendsen and Merikangas, 2000), although recent genetic evidence from

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Mendelian randomization studies supports a causal effect of depression on alcohol dependence, but not of alcohol use on depression (Köhler et al., 2018; Polimanti et al., 2019; Treur et al., 2021).

Surprisingly, empirical studies indicate that controlling for self-reported alcohol-use has little impact on the excess mortality among people with depression (Gilman et al., 2017; Miloyan and Fried, 2017; Oude Voshaar et al., 2021), which may reflect methodological issues such as underreporting of alcohol use and non-response among heavy drinkers (Gray et al., 2013). Another way to assess the importance of alcohol use is to quantify the contribution of specific alcohol-related causes to the excess mortality among people with depression. This method does not rely on self-reports and captures the actual deaths attributable to alcohol use. While it does not identify causal mechanisms or assess the temporal ordering of depression and alcohol use, it gives a direct quantification of how much of the overall excess mortality among people with depression is alcohol-related. An Australian study found that liver cirrhosis and chronic liver disease, the main causes of alcohol-related disease deaths, only accounted for three percent of the excess deaths of depressed in- and outpatient men and one percent among women (Lawrence et al., 2013). In contrast, substantially larger contributions were observed in a Finnish study, that used a more comprehensive measure for alcohol-related mortality (Moustgaard et al., 2013). When including all deaths where an alcohol-related disease, alcohol poisoning, or alcohol intoxication was either an underlying or a contributory cause of death, alcohol-related causes of death accounted for as much as 50 % of the excess mortality of depressed in- and outpatients among men and around 30 % among women (Moustgaard et al., 2013).

These differences in prior evidence indicate two important issues: First, the comprehensiveness of the measure for alcohol-related deaths is likely to have a major impact on results. Alcohol is a causal factor in many deaths where the underlying cause of death is not an alcohol-related disease such as alcoholic liver cirrhosis. Quantifying the contribution of alcohol-related deaths comprehensively thus requires assessing both the underlying and the contributory causes of death where possible. Second, the country context may play an important role. Comparing the contexts of the two previous studies conducted in Finland and Australia, alcohol-related mortality overall is at a much higher level in Finland with around three-fold liver cirrhosis mortality rates compared to Australia (World Health Organization, 2018). Alcohol-related deaths may thus contribute more strongly to the mortality of people with depression in contexts where alcohol-mortality is higher overall. To the best of our knowledge, no study has compared the contribution of alcohol-related deaths to the gap in life expectancy between individuals with and without depression across countries with differing levels of alcohol-related mortality.

Our aim was to quantify the contribution of alcohol-related deaths on the gap in life expectancy between people with and without depression by using administrative population data from four European countries: Denmark, Finland, Sweden, and Italy (city of Turin). During our study period (1993–2007) these countries differed relatively little in per-capita alcohol consumption (Sweden: steady below European average; Italy: decreasing below European average; Denmark, Finland: steady around European average) (OECD, 2012; World Health Organization, 2018). However, per-capita consumption may not reflect how consumption is distributed within the population or the prevalence of binge drinking. Notably, the countries also differ in alcohol drinking patterns (Turin: Mediterranean daily; Denmark, Finland, Sweden: Northern binge) (Mäkelä et al., 2006, 2001), and alcohol-related mortality (Turin: low; Sweden: middle; Denmark, Finland: high) (Mackenbach et al., 2015; Ramstedt, 2002). We hypothesized that alcohol-related deaths have a larger contribution to the life-expectancy gap in countries with Northern binge drinking patterns, and high alcohol-related mortality.

2. Methods

We used cohort data from population registers from Denmark, Finland, Sweden, and the city of Turin (Italy), with full individual-level linkage to healthcare and death records. The samples, study periods, and measurements in each country (and the municipality of Turin) are described in more detail in Table 1. All measurements and the study design were harmonized across the datasets. The specific diagnoses, drug types, and causes of death used for the measurements are listed in Table 2.

Depression was measured in the years preceding the baseline of each one-year mortality follow-up. Two separate measures were used, depending on the availability of data in each country. (1) For Denmark, Finland and Sweden, inpatient treatment with a diagnosis of depressive disorders in the preceding five years was used to indicate severe depression requiring hospital care. These persons were classified as *depressed psychiatric inpatients*. (2) For Finland and Turin, having a prescription or purchase of antidepressants in the preceding three years was considered an indication of milder depression. These persons were named *antidepressant-treated outpatients*. Because data on both measures were not available for all countries, these groups were not mutually exclusive: depressed psychiatric inpatients could have antidepressant treatment and antidepressant-treated outpatients could have inpatient treatment. With the Finnish data, where both measures were available, we ran sensitivity analyses excluding depressed psychiatric inpatients from the antidepressant-treated outpatients (Supplementary Table 1). The antidepressant data contained no information on diagnoses, so we could not ascertain that the antidepressants were prescribed for depression. Although depression is the main indication for antidepressants, antidepressants are also prescribed for other psychiatric indications such as anxiety disorders as well as for non-psychiatric indications such as chronic pain (Gardarsdottir et al., 2007). Thus, the results regarding outpatients must be interpreted with caution.

Alcohol-related mortality included (1) deaths where an alcohol-related disease or alcohol poisoning was the underlying cause of death, and (2) deaths where an alcohol-related disease or alcohol intoxication was a contributory cause of death (Table 2). The latter included suicides and other accidental and violent deaths where the coroner considered alcohol intoxication to be a contributory causal factor in the events leading to death. In Supplementary Table 2, we present the results separately for alcohol-related suicides, other accidents and violence, and diseases. For Turin, contributory causes of death were not available, thus only underlying causes of death were assessed. To gain a more comprehensive measure for Turin, we additionally calculated alcohol-attributable deaths by weighing each underlying cause of death (defined at the level of the fourth digit in the International Classification of Diseases) by the corresponding alcohol attributable fraction as defined by Single et al. (Single et al., 2000) and updated in 2015 by the Centers for Disease Control and Prevention (Centers for Disease Control and Prevention, 2022).

All-cause and cause-specific death rates were calculated from 1-year mortality follow-ups pooled over 15 study-years 1993–2007 by age (5-year groups), sex, and depression status. The study-years for the analyses on antidepressant-treated outpatients were restricted to 2000–2007 due to data availability. Directly age-standardized death rates and their 95% confidence intervals (CIs) were calculated with the 'dstdize' operation in Stata version 16 (StataCorp, 2019), using the European Standard Population 2013 (Eurostat et al., 2013). All-cause death rates were used to calculate life expectancy at age 25 for each group. To assess the contribution of alcohol-related deaths, the life-expectancy gap between those with and without depression was decomposed by cause of death using the Arriaga decomposition method (1984). Abridged period life tables an decomposition were calculated using Stata version 16 (StataCorp, 2019), adapting the decomposition syntax provided by Auger et al. (2014). The 95% confidence intervals were calculated by bootstrapping.

Table 1
Datasets used in the study.

	Denmark	Finland	Sweden	Turin (Italy)
Data source	National population register linked to hospital discharge register	National population register linked to hospital discharge register and prescription register	National population register linked to hospital discharge register	Municipal census linked to prescription register
Sample coverage	100%	100%	100%	100%
Analyses on depressed psychiatric inpatients[a]				
Follow-up years (pooled)	1993–2007	1993–2007	1993–2007	NA
Person-years	53 512 338	53 301 989	97 849 111	NA
Deaths	862 797	722 319	1 384 234	NA
% of person-years by depressed psychiatric inpatients				
Men	0.2	0.6	0.3	NA
Women	0.4	0.8	0.5	NA
Analyses on antidepressant-treated outpatients[b]				
Follow-up years (pooled)	NA	2000–2007	NA	2000–2007
Person-years	NA	28 927 285	NA	5 748 659
Deaths	NA	383 084	NA	77 404
% of person-years by antidepressant-treated outpatients				
Men	NA	8.0	NA	6.0
Women	NA	13.1	NA	11.7

[a] Hospital diagnosis of depression in preceding 5 years
[b] Antidepressant purchase in preceding 3 years

All procedures contributing to this work comply with the ethical standards of the Helsinki Declaration of 1975, as revised in 2008. The use of these data was approved by the Danish Data Protection Agency (permit 514–0230/18–3000) in Denmark, Boards of Ethics of Statistics Finland (permit TK-53–1490–18) and Findata (permit THL/2180/14.02.00/2020) in Finland, and Karolinska Institutet regional ethics committee (permit 02–481) in Sweden. The use of data from the Turin Longitudinal Study for statistical purposes is allowed under the National Program of Statistics. The data were collected for routine administrative registration purposes and, therefore, informed consent of the participants was not obtained. All data were pseudonymised prior to providing them to researchers.

3. Results

Age-standardized alcohol-related mortality was higher in Denmark and Finland than in Sweden and Turin, and higher among men than among women (Table 3). Among Finnish men, mortality for deaths with an alcohol-related disease or alcohol poisoning as the underlying cause of death was 70.4 per 100,000 person-years (95 % confidence interval 69.4–71.5), and 54.5 (53.6–55.5) among Danish men, whereas in Sweden and Turin these rates were only 20.5 (20.0–20.9) and 6.9 (5.9–8.0) respectively. The differences were similar among women, although rates were lower, and highest in Denmark. Further including deaths where an alcohol-related disease or alcohol intoxication was a contributory cause of death more than doubled alcohol-related mortality rates among men and nearly doubled them among women.

The gap in life expectancy at age 25 between people with and without psychiatric inpatient treatment for depression was 19 years in Denmark, 16 years in Finland, and 13 years in Sweden (Table 4). The gap was larger among men than women in all countries. The total contribution of alcohol-related deaths (both underlying and contributory) to the lower life expectancy among depressed psychiatric inpatients was larger in Denmark (34 %) and Finland (31 %) than in Sweden (12 %) and larger among men than among women in all countries. Contributory alcohol-related causes of death had a larger contribution to the life-expectancy gap than underlying alcohol-related causes, particularly in Sweden. Among Finnish women, however, the contributions of the underlying and contributory causes were of equal magnitude. The life-expectancy gap attributable to other than alcohol-related causes of deaths was very similar (around 10–13 years) in all countries and among men and women.

The gap in life expectancy at age 25 between those with and without antidepressant purchases was nine years in Finland and seven years in Turin. Again, the life-expectancy gap was larger among men than women in both countries. The total contribution of alcohol-related deaths to the lower life expectancy of antidepressant-treated outpatients in Finland was 26%. No data on contributory causes of death for Turin were available so we could only assess the contribution of alcohol as an underlying cause. This was substantial in Finland (14%) and negligible in Turin (0.5%). Also the contribution of deaths calculated from alcohol-attributable fractions was larger in Finland (18%) than in Turin (3%). The between-country differences in the life-expectancy gap were primarily due to alcohol-related deaths. However, the between-sex differences in the gap in both countries remained large even for other than alcohol-related deaths.

The sensitivity analysis excluding depressed psychiatric inpatients from the antidepressant-treated outpatients in the Finnish data yielded highly similar results: a life-expectancy gap of 8 years, and a 25 % contribution of all alcohol-related deaths (Supplementary Table 1). When excluding all alcohol-related suicides from alcohol-related deaths, the contribution of alcohol-related mortality to the life-expectancy gap decreased but was still considerable: 30 % among Danish inpatients, 22 % among Finnish inpatients and outpatients, and 8 % among Swedish inpatients (Supplementary Table 2).

4. Discussion

4.1. Main findings and their significance

We used population data from administrative registers in Denmark, Finland, Sweden, and Turin, to quantify the contribution of alcohol-related mortality to the lower life expectancy of people with depression. The lower life-expectancy of depressed psychiatric inpatients is well established and our estimates (19 years in Denmark, 16 in Finland, and 13 in Sweden) were in accordance with earlier studies from the Nordic countries (Laursen et al., 2016; Nordentoft et al., 2013) and West Australia (Lawrence et al., 2013). Less is known about the life-expectancy of depressed people outside specialized psychiatric treatment settings. We showed that the life-expectancy gap was much smaller for antidepressant-treated outpatients (nine years in Finland and seven in Turin), and closer to the three-to-four-year gap observed among a general-population sample of Canadians with clinically assessed depression (Steensma et al., 2016). This is a valuable contribution to the

Table 2
Diagnoses, medication types, and causes of death used to identyfy exposure and outcome measures.

	Classification			
	ICD10	ICD9	ICD8	ATC
Years for which each classification was applied in the study				
Denmark	1994–2007	NA	1987–1993	NA
Finland	1996–2007	1987–1995	NA	1997–2007
Sweden	1997–2007	1993–1996	1987–1992	NA
Turin	NA	2000–2007	NA	1997–2007
Hospital diagnoses for depressive disorders	F32, F33, F34.1, F38.1	296.1, 298.0, 300.4, 311	296.0, 296.2, 298.0, 300.4	
Antidepressant purchases				N06A
Alcohol-related underlying causes of death				
Alcohol-related mental and behavioural disorders	F10	291, 303, 3050	291, 303	
Degeneration of nervous system due to alcohol	G31.2			
Epileptic seizures related to alcohol	G40.51			
Alcoholic polyneuropathy	G62.1	357.5		
Alcoholic myopathy	G72.1			
Alcoholic cardiomyopathy	I42.6	425.5		
Alcoholic gastritis	K29.2	535.3		
Alcoholic liver disease	K70	571.0–571.3	571.0	
Alcohol-induced pancreatitis	K86.0, K85.2			
Accidental alcohol poisoning	X45	E860	E860	
Alcohol-related contributory causes of death (in addition to those listed above)				
Toxic effect of alcohol	T51			
Alcohol poisoning, intentional	X65			
Alcohol poisoning, undetermined intent	Y15	980	980	

ICD International Classification of Diseases
ATC Anatomical Therapeutic Chemical Classification

Table 3
Age-standardised death rates[a] by cause with 95% confidence intervals among men and women aged 25 + .

	Men			Women		
Deaths by cause	Rate	95% CI		Rate	95 % CI	
Denmark[b]						
All deaths	2475.2	2467.7	2482.7	1687.4	1682.6	1692.1
All alcohol-related causes of deaths	116.4	115.0	117.8	36.8	36.0	37.5
Alcohol-related underlying causes of death	54.5	53.6	55.5	18.6	18.1	19.1
Alcohol-related contributory causes of death	61.9	60.9	62.9	18.2	17.7	18.7
Finland[b]						
All deaths	2414.1	2405.5	2422.7	1488.5	1483.9	1493.1
All alcohol-related causes of deaths	166.1	164.5	167.8	29.4	28.8	30.1
Alcohol-related underlying causes of death	70.4	69.4	71.5	16.2	15.7	16.7
Alcohol-related contributory causes of death	95.7	94.5	97.0	13.2	12.8	13.6
Sweden[b]						
All deaths	1816.9	1812.7	1821.1	1207.1	1204.3	1209.8
All alcohol-related causes of deaths	49.5	48.9	50.2	12.0	11.6	12.3
Alcohol-related underlying causes of death	20.5	20.0	20.9	5.2	5.0	5.4
Alcohol-related contributory causes of death	29.0	28.5	29.5	6.7	6.5	7.0
Turin[c]						
All deaths	1940.5	1920.7	1960.3	1166.2	1155.2	1177.2
All alcohol-related causes of deaths	NA			NA		
Alcohol-related underlying causes of death	6.9	5.9	8.0	2.1	1.6	2.6
Alcohol-related contributory causes of death	NA			NA		

CI Confidence Interval; NA Not Available
[a] Per 100,000 person-years, European standard population 2013 as standard
[b] 1993–2007
[c] 2000–2007

earlier literature, which has mainly assessed patients in specialized care (Laursen et al., 2016; Lawrence et al., 2013; Nordentoft et al., 2013). The setting (inpatient, specialized outpatient, primary care, general population) is likely related to depression severity and thus conclusions on the life-expectancy gap should not be based on data from specialized psychiatric treatment settings alone. Since antidepressants are most often prescribed by general practitioners, our analysis provides a more comprehensive picture on the role of alcohol in the mortality of people with depression across different treatment settings. While the life-expectancy gap in Finland was smaller among antidepressant-treated outpatients, the relative contribution of alcohol-related deaths was similar to that among depressed psychiatric inpatients.

We assessed the contribution of alcohol-related deaths in various ways: by (1) the observed number of deaths where alcohol was the underlying cause (all countries), (2) the observed number of deaths where alcohol was the underlying or contributory cause (Denmark, Finland, and Sweden), and (3) the estimated number of alcohol-attributable deaths based on alcohol-attributable fractions (Finland and Turin). When only considering deaths with alcohol as an underlying cause – i.e. the least comprehensive measure of alcohol-related mortality – the contribution to the life-expectancy gap was smallest, around 15 % in Denmark, 13–14 % in Finland, 2.5 % in Sweden, and 0.5 % in Turin. The Danish and Finnish figures correspond to a recent register-study from Denmark showing that of the excess life-years lost among those with any mood disorder, around 19% among men and 11 % among women were due to deaths with alcohol misuse as the underlying cause (Plana-Ripoll et al., 2019). These results are, however, not fully comparable to ours since they include other mood disorders such as bipolar disorder, for which mortality may be higher than for unipolar depressive

Table 4
The contribution of alcohol-related deaths to the gap in life-expectancy at age 25 between people with and without depression.

	Men				Women				Both			
	Years	95% CI		%	Years	95% CI		%	Years	95% CI		%
Depressed psychiatric inpatients, 1993–2007												
Denmark												
Gap in life expectancy at age 25	20.5	19.4	21.8	100.0	17.6	16.7	18.4	100.0	18.6	17.9	19.3	100.0
All alcohol-related causes of death	8.1	6.9	9.4	39.6	4.7	4.0	5.4	26.5	6.3	5.6	6.9	33.6
Underlying causes of death	3.9	3.0	4.7	18.8	2.0	1.6	2.4	11.2	2.9	2.4	3.3	15.3
Contributory causes of death	4.3	3.4	5.2	20.9	2.7	2.2	3.3	15.4	3.4	2.9	3.9	18.3
All other causes of death	12.4	10.4	14.4	60.4	12.9	11.7	14.0	73.5	12.4	11.3	13.5	66.4
Finland												
Gap in life expectancy at age 25	18.3	17.8	18.9	100.0	13.6	13.1	14.2	100.0	16.0	15.6	16.4	100.0
All alcohol-related causes of death	7.0	6.4	7.6	38.1	2.4	2.0	2.7	17.3	4.9	4.6	5.2	30.5
Underlying causes of death	2.7	2.4	3.0	14.5	1.2	1.0	1.4	8.7	2.0	1.8	2.2	12.6
Contributory causes of death	4.3	3.9	4.8	23.6	1.2	1.0	1.4	8.6	2.9	2.6	3.1	17.9
All other causes of death	11.4	10.5	12.3	61.9	11.3	10.5	11.9	82.7	11.1	10.6	11.7	69.5
Sweden												
Gap in life expectancy at age 25	15.3	14.8	16.0	100.0	11.7	11.2	12.2	100.0	13.1	12.7	13.4	100.0
All alcohol-related causes of death	2.1	1.8	2.5	13.9	1.1	0.9	1.3	9.4	1.6	1.4	1.7	11.9
Underlying causes of death	0.6	0.4	0.7	3.6	0.1	0.1	0.2	1.2	0.3	0.3	0.4	2.5
Contributory causes of death	1.6	1.3	1.9	10.3	1.0	0.8	1.2	8.1	1.2	1.1	1.4	9.3
All other causes of death	13.2	12.5	14.0	86.1	10.6	10.0	11.1	90.6	11.5	11.1	11.9	88.1
Antidepressant-treated outpatients, 2000–2007												
Finland												
Gap in life expectancy at age 25	12.3	12.1	12.5	100.0	7.3	7.1	7.4	100.0	9.1	8.9	9.2	100.0
All alcohol-related causes of death	4.2	4.0	4.4	34.1	1.1	1.0	1.1	14.7	2.3	2.2	2.4	25.8
Underlying causes of death	2.1	2.0	2.2	17.2	0.6	0.6	0.7	8.7	1.2	1.2	1.3	13.7
Contributory causes of death	2.1	1.9	2.2	16.9	0.4	0.4	0.5	6.0	1.1	1.0	1.2	12.1
All other causes of death	8.1	7.8	8.4	65.9	6.2	6.0	6.4	85.3	6.7	6.6	6.9	74.2
Weighted alcohol-related deaths[a]	2.7	2.5	2.8	21.9	0.9	0.8	1.0	12.5	1.6	1.6	1.7	18.1
All other causes of death	9.6	9.3	9.9	78.1	6.4	6.2	6.5	87.5	7.4	7.3	7.6	81.9
Turin												
Gap in life expectancy at age 25	9.5	8.8	10.1	100.0	5.9	5.5	6.3	100.0	6.7	6.3	7.0	100.0
All alcohol-related causes of death		NA				NA				NA		
Underlying causes of death	0.07	0.00	0.16	0.7	0.03	0.00	0.07	0.6	0.04	0.00	0.08	0.5
Contributory causes of death		NA				NA				NA		
All other causes of death		NA				NA				NA		
Weighted alcohol-related deaths[a]	0.4	0.2	0.6	4.1	0.2	0.1	0.3	2.8	0.2	0.1	0.3	3.2
All other causes of death	9.1	8.4	9.7	95.9	5.8	5.3	6.1	97.2	6.5	6.1	6.8	96.8

CI Confidence Interval; NA Not Available

[a] Calculated from underlying causes of death by weighing each cause by corresponding alcohol attributable fraction (Centers for Disease Control and Prevention, 2022; Single et al., 2000)

disorders (Walker et al., 2015). Our results for Sweden and Turin correspond to those for West Australia (Lawrence et al., 2013). The contribution of weighted alcohol deaths was around 13 % in Finland and around three percent in Turin. For the most comprehensive, and arguably the best measure of alcohol-related deaths (Trias-Llimós et al., 2018), the observed underlying and contributory causes combined, the contribution was as large as 34 % in Denmark, 26–31 % in Finland, and 12 % in Sweden. This is less than in a prior Finnish study showing that all alcohol-related deaths accounted for 50 % of the excess mortality of depressed in- and outpatients at ages 40–74 among men and around 30% among women. This is likely due to the different age-spans. We assessed life expectancy at age 25, which is heavily influenced by deaths occurring at younger ages. As mortality to alcohol-related causes peaks between ages 40–74 (Mäkelä, 1998), its contribution was larger in the previous Finnish study.

Of the deaths where alcohol was a contributory cause, around half in Finland and around 20 % in Denmark and Sweden were deaths were the underlying cause of death was suicide, violence or accident. For these deaths, the coroner considered alcohol intoxication to be a causal factor in the events leading to death, and thus mere alcohol intoxication at the time of death was not sufficient for a death to be classified as alcohol related. However, it can be argued that an alcohol-related suicide could have taken place even without alcohol and including them would inflate the contribution of alcohol-related deaths in the lower life expectancy of people with depression. This would be further emphasized by the fact that deaths occurring at young ages, such as suicides, contribute heavily to the gap in life expectancy because of the large number of life-years lost. However, even after excluding all alcohol-related suicides from the alcohol-related deaths the contribution remained large: 30% among Danish inpatients, around 22 % among Finnish inpatients and outpatients, and around 8% among Swedish inpatients.

The contribution of alcohol-related causes of death to the lower life expectancy in depression was much larger in Denmark and Finland than in Sweden and Turin. This may partly relate to measurement issues (see methodological considerations for further discussion), and thus comparisons across countries must be done with caution. However, differences in social, cultural and treatment factors may also influence the role of alcohol in depression. People with depression likely experience other social vulnerabilities, such as low socioeconomic position and living alone, that are associated with a higher mortality, and controlling for these has been shown to attenuate the excess all-cause mortality of people with depression (Markkula et al., 2012). It is also plausible that between-country differences in the contribution of alcohol-related deaths reflect social inequalities in alcohol-related mortality more widely. Correspondingly, larger social inequalities in alcohol-related mortality have been found in Finland and Denmark than in Sweden and Italy (Mackenbach et al., 2015). In this study using aggregated data and life-table methodology, we were unable to assess the importance of socio-demographic factors other than gender in alcohol-related mortality among people with depression. Future cross-national studies using regression or mediation-based methods are needed to disentangle the role of other socio-demographic factors in the alcohol-related mortality of people with depression.

Overall, the contribution of alcohol-related deaths to the life-

expectancy gap between people with and without depression seemed larger in contexts with higher population-level alcohol-related mortality. Furthermore, alcohol-related causes mostly accounted for the larger life-expectancy gap in Denmark and Finland as well as for men as compared to women. In terms of policy, this suggests leverage for reducing the mortality of people with depression. The life-expectancy gap attributable to causes other than alcohol is still substantial (around 7–12 years), but alcohol-related deaths can be considered preventable by public health measures and thus their large contribution particularly in countries with high overall alcohol-related mortality warrants attention.

What kind of policy measures should, then, be taken to reduce alcohol-related mortality in depression? The evidence on the effectiveness of targeted interventions to reduce substance abuse among people with severe mental disorders, is weak and inconclusive, mostly due to engagement problems (Liu et al., 2017). Population-level interventions focused at reducing overall alcohol-related mortality may thus be warranted. A large body of evidence shows alcohol pricing to be an effective policy tool for reducing population alcohol consumption and related morbidity and mortality (Brand et al., 2007; Elder et al., 2010; Wagenaar et al., 2010). Moreover, in Finland, a large alcohol price reduction in 2004 raised the level of alcohol-related morbidity and mortality particularly in high risk groups, including the unemployed and people living alone (Herttua et al., 2011, 2008), and the same might be true for people with depression. Interventions targeting the pricing of alcohol might thus prove effective also in reducing the alcohol-related mortality of depressed people. However, further research is needed to evaluate the effects of alcohol policy and pricing specifically among people with depression.

4.2. Methodological considerations

Our study carried considerable strengths for assessing the contribution of alcohol to the lower life expectancy in depression. We used routinely collected administrative register data on total populations in four different alcohol-mortality contexts. These data had reliable individual-level linkage to death and hospital records, and prescription data (Phillips et al., 2014; Sund, 2012). The data avoid problems related to non-response, attrition, and misreporting, all common limitations particularly when studying depression and alcohol-use (Fischer et al., 2001; Gray et al., 2013). Specifically, we assess alcohol-related deaths instead of alcohol use, thus directly capturing and quantifying the harm caused by alcohol. We used various indicators of depression and alcohol-related mortality to obtain a comprehensive view of the contribution of alcohol-related deaths. We were also able to harmonize measurement and design across different country contexts (three national and one municipal), making comparisons more informative.

Some limitations should also be acknowledged. First, the recording of alcohol as a causal factor on the death certificate may differ considerably across countries. Cross-country differences must therefore be interpreted with caution (Ramstedt, 2002). However, the findings were similar in the comparison between Finland and Turin when using alcohol-attributable fractions, a measurement less affected by the coding of alcohol on death certificates. We thus believe the contribution of alcohol-related causes truly differs across country contexts and is larger in countries with higher overall alcohol-related mortality.

Second, our measures of depression have their limitations. Inpatient psychiatric treatment captures the most severe cases for whom mortality is very high (See Section 4.1). Additionally assessing antidepressant treatment gives a more complete picture of mortality among people with depression as it captures less severe cases. However, although depression is the main indication for antidepressant prescriptions, we likely also captured mortality among people using antidepressants for indications other than depression, including anxiety, sleep disorders, and pain (Gardarsdottir et al., 2007). Furthermore, depressed people with no registered inpatient or antidepressant treatment were classified as non-depressed, which may result in an underestimation of the life-expectancy gap. Future studies would benefit from a linkage of death registers to large population-based surveys with clinical assessment of depression.

Third, using administrative register data and life-table methods we were unable to control for important confounders such as socio-demographic factors, comorbidities, or other health behaviours. According to prior evidence, controlling for self-reported health behaviours has little impact on the excess mortality among people with depression (Miloyan and Fried, 2017), but controlling for socio-demographic factors (Markkula et al., 2012) and psychiatric comorbidity (Markkula et al., 2012; Miloyan and Fried, 2017; Moustgaard et al., 2013) may be more important. For alcohol-related mortality, comorbid alcohol use disorders are particularly relevant. As we could not ascertain the temporal ordering of depression and problematic alcohol use, we may have partly captured alcohol-related mortality among depressed persons with comorbid or pre-existing alcohol use disorders. In a previous Finnish study, controlling for comorbid substance use disorders attenuated the excess alcohol-related mortality of people with depression by about 25–80% (Moustgaard et al., 2013). This suggests that had we controlled for (or excluded people with) comorbid disorders, the life-expectancy gap and the contribution of alcohol-related deaths would have been smaller. For establishing a causal effect of depression on mortality, accounting for confounding by comorbid disorders would be appropriate. However, our aim was to provide a quantification of the contribution of alcohol-related deaths to the shorter life expectancy of people with depression overall, and thus controlling for comorbidities or using them as exclusion criteria would have led to an underestimation of the contribution among the total depressed population. Irrespective of the precise aetiology, our results indicate that this contribution is indeed large.

Finally, the period life-table method estimates life expectancy at age 25 for people with and without depression with the assumption that they will remain in these same states throughout their lifespan. It answers the hypothetical question of what the life expectancy of a depressed person at age 25 would be if they experienced the age-specific death-rates of depressed people throughout their life – and correspondingly for non-depressed people. While this is standard methodology for calculating life expectancy, it is unlikely to fully reflect reality. Many depressed persons recover while healthy persons develop depression, and this may affect their future mortality. Our estimates, as well as others based on lifetables, should thus be considered an upper limit for the life-expectancy gap between those with and without depression.

4.3. Conclusions

As the first study to quantify the total contribution of alcohol-related deaths to the life-expectancy gap between people with and without depression, we showed that alcohol is a major factor in the lower life expectancy of people with depression in contexts with high overall alcohol-related mortality, such as Denmark and Finland. This suggests a possibility for narrowing the gap by preventing alcohol-related mortality.

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Contributors

HM and LT conceived the study. PM, OÖ and GC acquired the data. HM analysed the data and prepared the first draft. All authors reviewed the results and the manuscript for important intellectual content. All authors approved the final version.

Conflict of Interest

No conflict declared.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.drugalcdep.2022.109547.

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