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Alcohol drinking and risk of subsequent hospitalisation with pneumonia

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ABSTRACT: The dose–response relationship between alcohol consumption and pneumonia risk in healthy individuals is poorly understood.

We examined 22,485 males and 24,682 females from Denmark who were aged 50–64 yrs. Subjects were without major chronic diseases at baseline and had a median follow-up of 12 yrs for first-time hospitalisation with pneumonia.

1,091 (males) and 944 (females) had pneumonia-related hospitalisation. Among males, the risk of pneumonia was increased for alcohol abstainers and those who drank large weekly amounts. The adjusted hazard ratios (HRs) for 0, 7–20, 21–34, 35–50 and >50 drinks·week^{-1} were 1.49 (95% CI 1.00–2.21), 0.88 (95% CI 0.76–1.03), 0.87 (95% CI 0.72–1.05), 1.15 (95% CI 0.93–1.44) and 1.81 (95% CI 1.40–2.33), respectively, compared with 1–6 drinks·week^{-1}. The association between high alcohol intake and pneumonia persisted after controlling for subsequent chronic diseases. Among females, HRs for 0, 7–20, 21–35 and >35 drinks·week^{-1} were 1.26 (95% CI 0.89–1.79), 1.01 (95% CI 0.88–1.17), 1.10 (95% CI 0.88–1.37) and 0.54 (95% CI 0.29–1.01), respectively. For the same moderate to high weekly alcohol amount, infrequent intake yielded higher pneumonia HRs than more regular intake in both sexes.

Regular moderate alcohol intake is not associated with increased risk of hospitalisation for pneumonia. High weekly alcohol consumption in males and infrequent heavy drinking in both sexes may increase pneumonia risk.

KEYWORDS: Alcohol drinking, chronic diseases, epidemiologic study, pneumonia, risk

Pneumonia is a major clinical and public health problem and a leading cause of death worldwide. Over the past two decades, hospitalisations with pneumonia have increased by 20–50% in ageing European and US populations [1–5].

Alcohol abuse has been associated with a two- to nine-fold higher risk of pneumonia [6–10], and alcohol consumption is high in Western populations [11]. Abuse of alcohol may increase susceptibility to pneumonia for several reasons. For example, alcohol intake may cause alterations in neutrophil and macrophage function and abnormalities in ciliary and surfactant functioning in the lung [12]. Alcohol overuse also can increase the risk of aspiration and suppress the normal cough reflex [12]. Finally, chronic alcohol intake is closely associated with malnutrition [12] and other chronic diseases that may affect pneumonia risk [13].

However, data are sparse on how the amount and frequency of alcohol intake are associated with increased pneumonia risk in apparently healthy individuals [10, 14–16]. A recent meta-analysis [10] based on only three studies [14–16] found that individuals who consumed alcohol in amounts corresponding to 14, 35 and 70 drinks per week had relative risks for pneumonia of 1.1 (95% CI 1.0–1.2), 1.3 (95% CI 1.1–1.7) and 1.8 (95% CI 1.1–2.8), respectively, compared with nondrinkers. Inadequate adjustment for smoking and other potential confounders may have affected these findings, and the studies also did not address whether the relationship resulted from alcohol consumption *per se* or from acquired chronic diseases. Moreover, frequency of alcohol consumption (*i.e.* regular *versus* binge drinking) has been shown to affect health differently [17, 18], but the effect of drinking frequency on pneumonia risk remains unknown. Finally, important sex differences in alcohol pharmacokinetics have been reported [19], and few studies on alcohol intake and pneumonia have examined this interaction [15, 16].

In-depth studies of these issues are needed to improve our understanding of the relationship between alcohol consumption and pneumonia risk. In this prospective cohort study, we examined the association between amount and frequency

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of alcohol intake and risk of subsequent pneumonia-related hospitalisation among apparently healthy middle-aged males and females who were free from major chronic diseases at baseline.

MATERIALS AND METHODS

Study population

From December 1993 to May 1997, a total of 160,725 people (80,996 males and 79,729 females) were invited to participate in the Danish study entitled Diet, Cancer and Health. The study has been described in detail elsewhere [20, 21]. Eligible participants were aged 50–64 yrs, were born in Denmark, were residents of Copenhagen or Aarhus (both Denmark) and did not have a record of cancer in the Danish Cancer Registry. Potential participants were identified from the computerised records of the Civil Registration System in Denmark, which has records dating from 1968 on all Danish residents. Information maintained by the Civil Registration System includes name, address, vital status and a unique personal identification number encoding sex and date of birth. A total of 57,053 people (27,178 males and 29,875 females) agreed to participate in the Danish Diet, Cancer and Health Study. All participants completed a detailed food frequency questionnaire [22, 23] and a second baseline questionnaire concerning lifestyle factors.

For this study, we excluded 840 people who had experienced a hospitalisation for pneumonia before enrolment, 6,851 people who had other major chronic diseases diagnosed before enrolment (see below), 366 people with a missing baseline questionnaire or missing variables, and 1,829 people with inconsistent information (*i.e.* who reported no alcohol intake at all together with a reported alcohol drinking frequency greater than zero, or *vice versa*). Thus, data for a total of 47,167 people (22,485 males and 24,682 females) were included in our analysis. The study was approved by regional ethics committees in Copenhagen and Aarhus and by the Danish Data Protection Agency.

Data on alcohol intake and drinking patterns

In the lifestyle questionnaire, participants reported their usual frequency of alcohol intake using one of seven possible response categories: ''never'', ''less than once per month'', ''one to three times per month'', ''once a week'', ''two to four times per week'', ''five to six times per week'', and ''daily'' [18].

In the food frequency questionnaire, participants were asked to state their average quantity of alcohol consumed during the past year, in terms of intake of specific amounts of each beverage: light, normal and strong beer (number of bottles); red, white and fortified wine (number of glasses); and spirits (number of drinks). The possible response categories (for bottles of beer, glasses of wine or drinks of spirits) were: ''no alcohol intake'', ''less than one per month'', ''one per month'', ''two to three per month'', ''one per week'', ''two to four per week'', ''five to six per week'', ''one per day'', ''two to three per day'', ''four to five per day'', ''six to seven per day'', and ''eight or more per day''. Based on the ethanol content of the different beverage types, these exposure categories were converted into number of standard drinks (12 g alcohol) per week and then added to yield an average measure of total weekly alcohol intake [18]. We defined abstainers as participants who reported never drinking in both questionnaires.

For a supplementary analysis, we obtained information from the lifestyle questionnaires on abstainers' previous alcohol intake.

Identification of first-time hospitalisation with pneumonia

Study participants who had a first-time pneumonia-related hospitalisation were identified by linking their civil registration number to the Danish National Registry of Patients. This registry has collected data on all hospitalisations in Denmark since 1977; its records include the civil registration number and up to 20 discharge diagnoses. Physicians coded diagnoses according to the International Classification of Diseases 8th revision (ICD-8) until the end of 1993, and 10th revision (ICD-10) thereafter. We identified all in-patients with the following diagnoses recorded between the date of enrolment into the cohort and April 10, 2008: pneumonia (J12.x-J18.x), ornithosis (A709.x) or legionellosis (A481.x) [3].

Data on major chronic diseases prior to enrolment

From the Danish National Registry of Patients, we obtained information on participants' major chronic diseases, defined as those included in the Charlson Comorbidity Index [24] (myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease (including asthma), connective tissue disease, ulcer disease, liver disease, diabetes, hemiplegia, renal disease, cancer and AIDS), as well as previous diagnoses of HIV infection, gastro-oesophageal reflux, hypertension and alcoholism-related diseases. We categorised these diseases as diseases directly related to alcoholism, cancer, cardiovascular diseases, chronic pulmonary diseases and other diseases (see the Appendix for the ICD-8 and ICD-10 codes).

Other potential confounders

At baseline, trained laboratory technicians recorded anthropometric measurements. Body mass index (BMI) was calculated as weight (kg) divided by height (m^2). Participants provided information on smoking, length of basic schooling and subsequent education in the baseline questionnaire.

Statistical analysis

We *a priori* categorised males and females according to total weekly alcohol intake (males: 0, 1–6, 7–20, 21–34, 35–50 and >50 drinks·week^{-1}; females: 0, 1–6, 7–20, 21–35 and >35 drinks·week^{-1}) and according to their weekly frequency of drinking alcohol (never, ⩽1 day, 2–4 days, 5–6 days, and 7 days a week) [17]. To ensure adjustment for confounding by age, we used age as the underlying time variable, with follow-up starting at participant age at recruitment. Follow-up extended until age on April 10, 2008, or until age at pneumonia diagnosis, death, or migration, whichever came first.

We computed pneumonia incidence rates by dividing the number of events by the accumulated person-time of follow-up within the groups defined by alcohol intake, separately for males and females. Cox's regression was used to compute hazard ratios (HRs) as measures of relative risk for hospitalisation with pneumonia according to alcohol intake level. Participants who consumed 1–6 drinks·week^{-1} served as the reference group. We also controlled for baseline BMI (<22.5, 22.5–24.9, 25.0–29.9, 30.0–34.9 and >35 kg·m^{-2}) and smoking status (never, former and current; <15, 15–<25 or ⩾25 g tobacco·day^{-1}).

In a supplementary analysis, we adjusted for length of basic schooling (7, 8–10 and >10 yrs) and higher education (no higher education or short-, mid- or long-term higher education). Next, we examined the impact of chronic diseases diagnosed during follow-up, by including categories of diseases diagnosed during follow-up and before first pneumonia-related hospitalisation as time-dependent binary variables in the regression model. All analyses were repeated using frequency of alcohol consumption as the exposure (with those who consumed alcohol no more than one day per week serving as the reference). Finally, we computed HRs of pneumonia-related hospitalisation for different combinations of amount of alcohol consumption and drinking frequency. Data were analysed using Stata Statistical Software (Release 11 SE; Stata Corporation, College Station, TX, USA).

RESULTS

Descriptive data

A total of 1,091 males and 944 females had their first pneumonia-related hospitalisation during median follow-up periods of 11.8 and 11.9 yrs, respectively. The corresponding incidence rates of hospitalisation with pneumonia were 4.25 and 3.28 per 1,000 person-yrs for males and females, respectively. Table 1 summarises participant baseline characteristics. At enrolment, median alcohol intake was 12 drinks·week^{-1} (5th to 95th percentiles: 1–47 drinks·week^{-1}) among males and 6 drinks·week^{-1} (5th to 95th percentiles: 1–25 drinks·week^{-1}) among females. In total, 338 (1.5%) males and 644 (2.6%) females were alcohol abstainers. Among male abstainers, 152 (45.0%) reported having had a previous alcohol intake of >21 drinks·week^{-1} at some time prior to enrolment in the Danish Diet, Cancer and Health Study, whereas 93 (14.4%) of the female abstainers reported having had a previous alcohol intake of >14 drinks·week^{-1}.

TABLE 1 Baseline characteristics among females and males in the Danish cohort followed for pneumonia hospitalisations

	Females	Males
Participants n	24682	22485
Age yrs	56 (51–64)	56 (51–64)
Alcohol intake drinks·week^{-1}	6 (1–25)	12 (1–47)
Body mass index kg·m^{-2}	24.7 (20.0–33.2)	26.1 (21.5–32.7)
Education %		
Basic schooling		
⩽7 yrs	29.3	33.0
8–10 yrs	51.1	42.1
>10 yrs	19.6	24.9
After basic schooling		
No education	17.7	9.1
Short term	31.6	13.7
Mid term	38.9	42.1
Long term	11.9	35.2
Smoking status %		
Never smoked	45.1	27.0
Formerly smoked	23.4	34.4
Current smoker		
<15 g tobacco·day^{-1}	14.9	10.5
15–<25 g tobacco·day^{-1}	14.1	17.0
⩾25 g tobacco·day^{-1}	2.4	11.2

Data are presented as median (5th–95th percentiles), unless otherwise stated.

Risk of hospitalisation with pneumonia among males and females according to alcohol intake

Among males, no alcohol intake at all and an intake >50 drinks·week^{-1} were associated with a higher risk of pneumonia-related hospitalisation compared to the reference consumption of 1–6 drinks·week^{-1} (tables 2 and 3). The corresponding adjusted HRs were 1.49 (95% CI 1.00–2.21, p=0.05) for abstainers and 1.81 (95% CI 1.40–2.33, p<0.001) for those consuming >50 drinks·week^{-1}, after adjustment for smoking status and BMI. Moderate alcohol consumption was associated with adjusted pneumonia HRs <1. Further adjustment for length of basic schooling and higher education yielded virtually identical HRs (data not shown). When chronic diseases diagnosed during follow-up were added to the model, the adjusted HR for pneumonia associated with an intake of >50 drinks·week^{-1} was 1.45 (1.11–1.90, p=0.01). Among females, alcohol abstinence was associated with an adjusted pneumonia HR of 1.26 (95% CI 0.89–1.79, p=0.19), whereas high consumption of >35 drinks·week^{-1} was associated with an adjusted HR of 0.54 (95% CI 0.29–1.01, p=0.06).

Risk of hospitalisation with pneumonia according to weekly frequency of alcohol consumption

Among males, drinking alcohol 2–6 days·week^{-1} was associated with pneumonia hospitalisation HRs <1, compared with those drinking no more than 1 day·week^{-1} (table 4). The adjusted HRs were 0.82 (95% CI 0.69–0.97, p=0.02) for drinking 2–4 days·week^{-1}, 0.82 (95% CI 0.67–1.01, p=0.06) for 5–6 days·week^{-1} and 1.05 (95% CI 0.88–1.24, p=0.59) for 7 days·week^{-1}. Similar to males, females who consumed alcohol more often had a lower pneumonia risk than females who drank no more than 1 day·week^{-1} (table 4).

Risk of hospitalisation with pneumonia according to combinations of drinking frequency and alcohol intake

Table 5 lists the HRs of hospitalisation with pneumonia for different combinations of alcohol amount and drinking frequency. Within each category of drinking frequency, males who drank the largest amounts generally had the highest risk. Among males consuming >20 drinks·week^{-1}, HRs were generally higher for infrequent intake than for frequent intake within similar categories of amount. Similar results were observed for females (table 5).

DISCUSSION

In this large cohort study conducted among middle-aged Danes with no hospital-diagnosed chronic diseases at enrolment, we found that both total alcohol abstinence and high alcohol consumption were associated with a higher risk of pneumonia-related hospitalisation among males, but not among females. The increased risk conferred by heavy alcohol use in males was not exclusively explained by development of other chronic diseases during follow-up. Drinking frequency influenced the relationship between alcohol intake and pneumonia risk, *i.e.* for the same moderate to high average amount of alcohol intake, infrequent intake was associated with higher pneumonia risk than was frequent intake.

TABLE 2 Hospitalisation rates for pneumonia among males according to alcohol intake, Denmark 1993–2008

	Drinks·week^{-1}					
	0	1–6	7–20	21–34	35–50	>50
Males n	338	5346	9637	4469	1894	801
Pneumonia diagnosis n	26	272	406	193	114	80
Incidence rate per 1000 person-yrs	7.02	4.45	3.67	3.79	5.34	9.16
Crude HR (95% CI)#	1.61 (1.08–2.39) p=0.02	1.0 (ref.)	0.86 (0.74–1.00) p=0.05	0.89 (0.74–1.07) p=0.22	1.30 (1.05–1.62) p=0.02	2.28 (1.77–2.93) p<0.001
Adjusted HR (95% CI)¶	1.49 (1.00–2.21) p=0.05	1.0 (ref.)	0.88 (0.76–1.03) p=0.11	0.87 (0.72–1.05) p=0.14	1.15 (0.93–1.44) p=0.20	1.81 (1.40–2.33) p<0.001
Adjusted HR (95% CI)+	1.40 (0.93–2.12) p=0.11	1.0 (ref.)	0.94 (0.80–1.10) p=0.42	0.90 (0.75–1.09) p=0.30	1.14 (0.91–1.43) p=0.24	1.45 (1.11–1.90) p=0.01

HR: hazard ratio; CI: confidence interval; ref.: reference. #: calculated using Cox's regression, with age as the underlying time variable; ¶: based on the crude model with additional adjustment for smoking status and body mass index; +: based on the crude model with additional adjustment for smoking status, body mass index and major chronic diseases.

The strengths of our study include its large size, the ability to adjust for related lifestyle factors such as smoking and BMI, and the virtually complete follow-up for pneumonia-related hospitalisations. Regarding weaknesses, similar to other cohort studies on this topic, we based our information on self-reported alcohol use at the time of enrolment, and we cannot exclude misclassification stemming from inaccurate reporting. Underreporting of alcohol intake or drinking frequency could have led to overestimation of the relative risks. Alcohol consumption was estimated based on the type of drink and, because drinks can vary in their alcohol content, some misclassification may have occurred. Moreover, drinking habits among study participants may have changed over time.

Another potential limitation is the study's reliance on discharge diagnoses, which were not independently confirmed. However, the estimated positive predictive value of a pneumonia diagnosis in the Danish National Registry of Patients is 90% (95% CI 82%–95%) [3].

Another concern is that physicians may be more likely to hospitalise patients with infection if they are known to have high alcohol intake. Such bias would cause overestimation of the relative risks associated with high alcohol intake. However, a generally increased surveillance could probably not explain the observed differences in risk estimates between males and females. Conversely, persons with high alcohol intake and potentially associated socioeconomic or psychological problems may be less likely to seek medical advice and treatment [25], which would cause a bias in the opposite direction. We can only speculate about whether such detection bias may have been disproportionally strong among alcohol-drinking females *versus* males in our study. Finally, despite the relatively large size of our study, we had a limited ability to evaluate the risk of pneumonia-related hospitalisation for different combinations of alcohol amount and drinking frequency.

In the context of previous reports, our finding of a sex difference in the relationship between alcohol intake and pneumonia risk

TABLE 3 Hospitalisation rates for pneumonia among females according to alcohol intake, Denmark 1993–2008

	Drinks·week^{-1}				
	0	1–6	7–20	21–35	>35
Females n	644	12686	8854	2111	387
Pneumonia diagnosis n	35	472	329	98	10
Incidence rate per 1000 person-yrs	4.72	3.18	3.19	4.03	2.25
Crude HR (95% CI)#	1.40 (0.99–1.98) p=0.05	1.0 (ref.)	1.05 (0.91–1.20) p=0.53	1.33 (1.07–1.65) p=0.01	0.80 (0.43–1.50) p=0.49
Adjusted HR (95% CI)¶	1.26 (0.89–1.79) p=0.19	1.0 (ref.)	1.01 (0.88–1.17) p=0.87	1.10 (0.88–1.37) p=0.41	0.54 (0.29–1.01) p=0.06
Adjusted HR (95% CI)+	1.17 (0.82–1.68) p=0.38	1.0 (ref.)	1.03 (0.89–1.19) p=0.70	1.08 (0.86–1.36) p=0.50	0.48 (0. 25–0.93) p=0.03

HR: hazard ratio; CI: confidence interval; ref.: reference. #: calculated using Cox's regression, with age as the underlying time variable; ¶: based on the crude model with additional adjustment for smoking status and body mass index; +: based on the crude model with additional adjustment for smoking status, body mass index and major chronic diseases.

TABLE 4 Hospitalisation rates for pneumonia among males and females according to frequency of alcohol consumption, Denmark 1993–2008

	Frequency of alcohol consumption days·week^{-1}				
	Never	⩽1	2–4	5–6	Daily
Males					
Subjects n	338	3996	7993	3965	6193
Pneumonia diagnosis n	26	219	321	161	364
Incidence rate per 1000 person-yrs	7.02	4.81	3.49	3.53	5.22
Crude HR (95% CI)#	1.48 (0.99–2.21) p=0.06	1.0 (ref.)	0.77 (0.65–0.91) p=0.002	0.78 (0.64–0.96) p=0.02	1.09 (0.92–1.29) p=0.31
Adjusted HR (95% CI)¶	1.41 (0.94–2.10) p=0.10	1.0 (ref.)	0.82 (0.69–0.97) p=0.02	0.82 (0.67–1.01) p=0.06	1.05 (0.88–1.24) p=0.59
Adjusted HR (95% CI)+	1.35 (0.89–2.05) p=0.16	1.0 (ref.)	0.88 (0.74–1.06) p=0.17	0.88 (0.71–1.08) p=0.23	1.06 (0.89–1.27) p=0.51
Females					
Subjects n	644	9039	8657	2863	3479
Pneumonia diagnosis n	35	388	269	94	158
Incidence rate per 1000 person-yrs	4.72	3.68	2.65	2.81	3.96
Crude HR (95% CI)#	1.23 (0.87–1.74) p=0.24	1.0 (ref.)	0.78 (0.66–0.91) p=0.002	0.81 (0.65–1.02) p=0.08	1.08 (0.89–1.29) p=0.44
Adjusted HR (95% CI)¶	1.14 (0.80–1.61) p=0.48	1.0 (ref.)	0.81 (0.70–0.95) p=0.01	0.79 (0.63–0.99) p=0.04	0.90 (0.75–1.09) p=0.29
Adjusted HR (95% CI)+	1.06 (0.74–1.52) p=0.76	1.0 (ref.)	0.82 (0.70–0.97) p=0.02	0.78 (0.62–0.99) p=0.04	0.90 (0.74–1.09) p=0.28

HR: hazard ratio; CI: confidence interval; ref.: reference. #: calculated using Cox's regression, with age as the underlying time variable; ¶: based on the crude model with additional adjustment for smoking status and body mass index; +: based on the crude model with additional adjustment for smoking status, body mass index and major chronic diseases.

accords with the results of a Spanish case–control study [16]. Based on 1,336 pneumonia cases and 1,336 age-, sex- and primary health centre-matched controls, ALMIRALL *et al*. [16] found in crude analyses that an increasing amount of alcohol intake was associated with increasing risk of pneumonia in males but not in females. Unlike our study, however, the Spanish study did not examine whether smoking influenced results. Among US males from the Health Professionals' Follow-up Study and females from the Nurses' Health Study II, BAIK *et al*. [15] found no association between low or moderate alcohol intake and risk of pneumonia either in males after 6 yrs of follow-up or in females after 2 yrs of follow-up. Because their study population had a much lower reported alcohol intake than our Danish population, BAIK *et al*. [15] had limited power to observe the effect of heavy drinking. In addition to sex-based differences in alcohol pharmacokinetics, the sex difference observed in our study could be the result of chance because relatively few females (1.6%) had an average consumption >35 drinks·week^{-1}. Also, in Denmark,

TABLE 5 Hospitalisation with pneumonia according to drinking frequency and alcohol intake

Alcohol intake drinks·week^{-1}	Frequency of drinking alcohol days·week^{-1}				
	Never	⩽1	2–4	5–6	Daily
Males					
0	1.38 (0.92–2.07) p=0.12				
1–6		1.0 (ref.)	0.78 (0.60–1.01) p=0.06	1.41 (0.72–2.78) p=0.31	0.61 (0.16–2.34) p=0.47
7–20		0.81 (0.56–1.17) p=0.27	0.81 (0.66–0.99) p=0.04	0.78 (0.60–1.01) p=0.06	0.88 (0.68–1.14) p=0.34
21–34		1.85 (0.78–4.41) p=0.16	0.65 (0.42–0.99) p=0.5	0.68 (0.49–0.94) p=0.02	0.89 (0.70–1.12) p=0.31
35–50			1.04 (0.47–2.29) p=0.93	1.10 (0.70–1.72) p=0.68	1.08 (0.84–1.40) p=0.54
>50		2.57 (0.31–21.55) p=0.38	2.80 (0.99–7.92) p=0.05	0.98 (0.36–2.66) p=0.98	1.70 (1.29–2.24) p<0.001
Females					
0	1.16 (0.82–1.66) p=0.40				
1–6		1.0 (ref.)	0.75 (0.60–0.93) p=0.01	0.84 (0.43–1.64) p=0.61	0.50 (0.13–2.03) p=0.35
7–20		1.28 (0.90–1.82) p=0.18	0.87 (0.72–1.06) p=0.18	0.81 (0.62–1.06) p=0.12	1.02 (0.81–1.29) p=0.86
21–35		2.15 (0.80–5.81) p=0.13	1.36 (0.82–2.26) p=0.24	0.90 (0.58–1.39) p=0.63	0.96 (0.73–1.27) p=0.77
>35		10.11 (1.55–65.75) p=0.02	2.66 (0.65–10.83) p=0.17		0.42 (0.20–0.88) p=0.02

Data are present as hazard ratio (95% CI). The hazard ratio was calculated using Cox's regression, with age as the underlying time variable and with adjustment for smoking status and body mass index. Ref. reference.

females in the highest socioeconomic classes tend to drink considerably more alcohol than females in the lower socioeconomic classes, and these differences according to socioeconomic status are reportedly larger than among males [26]. Although we were able to adjust for length of schooling and subsequent education, lack of adjustment for socioeconomic status may thus have led to social confounding associated with high alcohol intake among females more than among males. The previously mentioned earlier studies did not explore the association between drinking patterns and pneumonia risk.

Biological mechanisms underlying higher pneumonia risk among males with high alcohol intake may include development of chronic diseases. Excess alcohol consumption can lead to liver disease, including liver cirrhosis, which is characterised by a defect in innate immunity and a high susceptibility to infections [27]. Overconsumption of alcohol also contributes to cancers of the breast, oral cavity, larynx, pharynx and oesophagus [13], which may increase the likelihood of pneumonia. Other medical conditions associated with alcoholism that also could increase susceptibility to pneumonia include cardiomyopathy, hypertension, and malnutrition with vitamin deficiency [13, 28]. Nevertheless, after we added chronic diseases to the regression model, the association between high alcohol intake and pneumonia risk among males weakened but remained. Thus, our data show that chronic diseases alone do not explain the association. Other mechanisms may include the detrimental effects of chronic alcohol exposure *per se* on systemic and local immune responses [10, 12].

As other studies have done previously, we determined drinking patterns by combining information on average quantity with usual drinking frequency [18, 29]. Our findings suggest that infrequent heavy drinking is particularly harmful concerning pneumonia risk. For the same amount of alcohol intake, an infrequent drinking pattern compared to a frequent drinking pattern would lead to a higher alcohol concentration in the gastrointestinal tract and in the blood which, in turn, could lead to an escalation of the harmful effects of alcohol [18]. It is plausible that infrequent excessive alcohol consumption leads to episodes of decreased consciousness, vomiting, immobility and body cooling. Our study's long-term follow-up design prevented examination of the effects of acute alcohol exposure on pneumonia risk.

Among males, moderate alcohol consumption tended to have a small, statistically nonsignificant protective effect against pneumonia, compared with drinking less. It has been suggested that moderate consumption of alcohol may enhance immune function through a positive effect on lymphocyte count and on pro-inflammatory cytokine cascades [30]. Components such as polyphenols, antioxidants and vitamins that are present in beer or wine may also have beneficial effects on immunity [30]. TAKKOUCHE *et al.* [31] found that consumption of wine, in particular red wine, was inversely associated with the risk of common cold among Spanish university faculty staff, with an adjusted incidence rate ratio for drinkers of >14 glasses of wine per week of 0.6 (95% CI 0.4–0.8) compared with nondrinkers. Similarly, among 391 persons intentionally exposed to respiratory virus and 26 persons given saline, COHEN *et al*. [32] showed that moderate consumption of alcohol was associated with decreased risk of developing clinical colds.

An additional finding was our observation that male alcohol abstainers had a higher pneumonia risk than males who drank 1–6 drinks·week^{-1}. However, there are few total abstainers in the Danish Diet, Cancer and Health Study, and many of these have reported a previously high alcohol intake. Similarly, a British study showed that middle-aged, male nondrinkers are likely to be ex-drinkers, older and have higher prevalence of a wide range of diseases and drug treatments compared to light or moderate drinkers [33].

In conclusion, our data show that consumption of >50 alcoholic drinks per week among males and infrequent heavy drinking are positively associated with risk of pneumonia-related hospitalisation. In contrast, moderate alcohol intake had no detrimental effect on pneumonia risk.

APPENDIX

International Classification of Diseases (ICD) codes for major chronic diseases are shown in table 6. The codes were used both to exclude people with major chronic diseases at baseline and to control for chronic diseases diagnosed during follow-up.

SUPPORT STATEMENT

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TABLE 6 International Classification of Diseases (ICD) codes for major chronic diseases

Disease category	ICD-8	ICD-10
Diseases related directly to alcoholism	571.09, 571.10; 577.10	G31.2; G62.1; G72.1; I42.6; K29.2; K70; K86.0
Cancer	140-207; 275.59	C00-C85; C88; C90-C96
Cardiovascular diseases	400-404; 410; 427.09-427.11; 427.19; 428.99; 430-438; 440-445; 782.49	G45; G46; I10-I15; I21-I23; I50; I60-I69; I70-I74; I77
Chronic pulmonary diseases	490-493; 515-518	J40-J47; J60-J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3
Other	070.00; 070.02; 070.04; 070.06; 070.08; 079.83; 135.99; 249; 250; 290.09-290.19; 293.09; 344; 446; 456.0; 571.11; 571.19; 571.99; 530.91; 530.98; 530.99; 531-534; 573.00; 573.01; 573.04; 580-584; 590.09; 593.19; 712; 716; 734; 753.1; 792	B20-B24; B15.0; B16.0; B16.2; B18; B19.0; D86; E10-E14; F00-F03; F05.1; G30; G81; G82; H36.0; I85; K21; K22.1; K25-K28; K71-K73; K74; K76.0; K76.6; M05; M06; M08; M09; M30-M36; N00-N05; N07; N11; N14; N17-N19; O24.0-O24.3; O24.5-O24.9; Q61

STATEMENT OF INTEREST

None declared.

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