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CLINICAL STUDY

Moderate alcohol consumption may protect against overt autoimmune hypothyroidism: a population-based case–control study

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Abstract

Objective: Alcohol consumption is an important protective risk factor for many autoimmune diseases. We wished to study the association between alcohol consumption and autoimmune hypothyroidism.
Design: Population-based, case–control study, 1997–2001, Denmark.
Methods: Patients with newly diagnosed autoimmune overt hypothyroidism ($n=140$) were prospectively identified in a population (2 027 208 person-years of observation), and their matched controls with normal thyroid function ($n=560$) were recruited simultaneously from the same population. Participants gave information on alcohol intake, smoking, previous diseases, education, and family history of hypothyroidism. The association between alcohol intake and development of hypothyroidism was analyzed in conditional regression models.
Results: Hypothyroid cases had reported a lower alcohol consumption than controls (median units of alcohol (12 g) per week: 3 vs 5, $P=0.002$). In a multivariate regression model, alcohol consumption was associated with a reduction in risk for development of overt autoimmune hypothyroidism. Odds ratios (95% confidence interval) compared with the reference group with a recent (last year) consumption of 1–10 units of alcohol per week were as follows: 0 units/week, 1.98 (1.21–3.33); 11–20 units/week, 0.41 (0.20–0.83); and ≥ 21 units/week, 0.90 (0.41–2.00). Similar results were found for maximum previous alcohol consumption during a calendar year. No interaction was found with type of alcohol consumed (wine vs beer), sex, or region of inhabitancy.
Conclusions: Alcohol consumption seems to confer considerable protection against development of overt autoimmune hypothyroidism irrespective of sex and type of alcohol consumed.

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Introduction

Alcohol consumption is associated with increased risk for development of various diseases. On the other hand, many studies have revealed that alcohol consumed in smaller amounts may protect from several non-autoimmune diseases such as ischemic heart disease (1), cerebral thrombosis (2), hypertension (3), upper respiratory infections (4), gallbladder and renal stones (5, 6), age-related macular degeneration (7), and dementia (8). Recently, it was shown that asthma incidence is also lower among moderate alcohol consumers compared with abstainers (9).

In terms of autoimmune disorders, moderate alcohol consumption is associated with lower frequency of rheumatoid arthritis (10, 11) and systemic lupus erythematosus (12, 13). The two major autoimmune thyroid disorders, primary autoimmune hypothyroidism and Graves' disease, are by far the most prevalent of all autoimmune disorders. Nevertheless, no studies have investigated the role of alcohol consumption for development of autoimmune hypothyroidism. Therefore, we used data collected as part of the monitoring of the Danish iodization program (14) to investigate the overall role of alcohol consumption for development of overt autoimmune hypothyroidism and to seek for any difference between the effect of wine and beer intake.

Materials and methods

The Danish Investigation of Iodine Intake and Thyroid Diseases (DanThyr) was established in 1997. Several

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part studies were implemented, including a registration of all patients newly diagnosed with overt hypothyroidism in a population by prospective monitoring of all thyroid function tests performed (2 027 208 person-years of observation). In the same population, we performed surveys in which randomly selected civilians were invited for investigation. From these studies, cases and controls for this study were included as detailed in Fig. 1.

Patients

We have previously described how the case identification system was developed and tested (15, 16), how patients with prior hypo- or hyperthyroidism were excluded, how the well-defined diagnostic criteria were used to identify patients with possible first time overt hypothyroidism, and how this diagnosis was verified and classified into various subtypes of disease (15). For this study, 147 patients newly diagnosed with overt hypothyroidism participated in a detailed investigation with sampling of blood and urine for further analyses and comprehensive questionnaires.

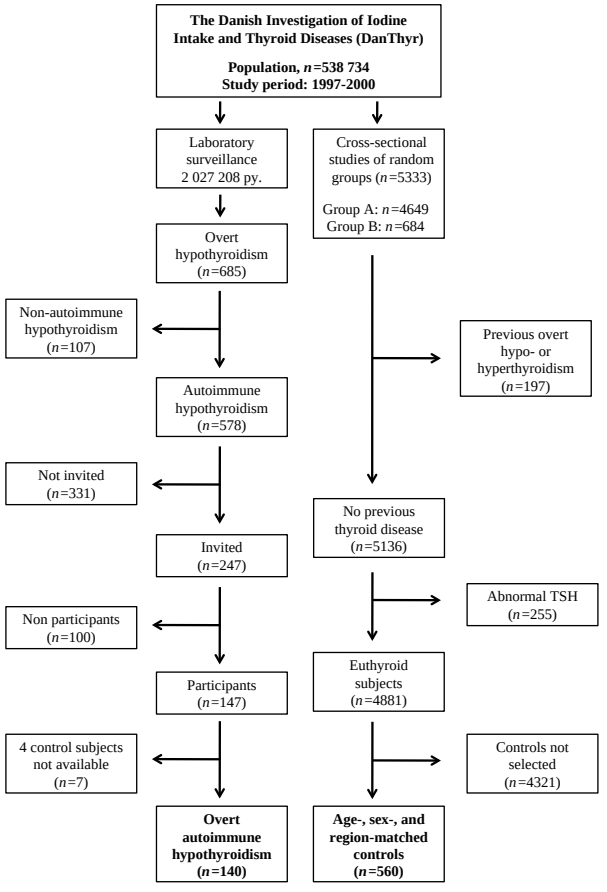

Figure 1 The selection of 140 hypothyroid cases and 560 controls (matched on age, sex, and region). During the registration period, funding was obtained to invite 247 randomly selected patients newly diagnosed with hypothyroidism. For seven of the 147 cases, we did not manage to find four matching controls among our survey participants. py, person-years of observation.

Controls

Controls were selected from the population survey performed during the same period and in the same geographic areas and were investigated by the same staff using identical methods. Lists were drawn at random from the Danish Civil Registration System in which all subjects living in Denmark are registered. In a cross-sectional study (DanThyr cohort, group A; $n=4649$; Fig. 1), women aged 18–22, 25–30, 40–45, and 60–65 years and men aged 60–65 years were investigated (17), and additional control subjects not falling into these age categories were invited and investigated during the same period (group B; $n=684$; Fig. 1). For this study, four control subjects were selected to match each patient on age, sex, and region of inhabitancy. Controls were excluded if they had abnormal serum TSH or if they had previously suffered from thyroid disease. We were able to find 560 controls matching 140 cases.

Questionnaires

Participants filled out questions on alcohol consumption (units/week, stratified on wine, beer, spirits, and liquor), both during the last year preceding hypothyroidism ('recent' consumption) and at maximum at any calendar year in the life ('maximum' consumption). A total alcohol consumption variable was introduced and calculated by adding the amount of each of the various beverages; one unit of alcohol was equivalent to one bottle of beer (33 cl, 4.6% alcohol by volume (ABV%), ~12 g of alcohol), a glass of wine (12 cl, 13 ABV%), a glass of spirits (3 cl, 45 ABV%), or a glass of liqueur (8 cl, 18 ABV%), almost similar to definitions from Klatsky *et al.* (18). Participants gave information on family history of hypothyroidism and of current and previous diseases and medication. For this study, we evaluated comorbidity in detail as cardiovascular (acute myocardial infarction, angina pectoris, cardiac arrhythmia, hypertension, and cerebral stroke) and non-cardiovascular disease (epilepsy, diabetes mellitus, asthma, chronic obstructive pulmonary disease, and gastrointestinal ulcers). If one of these diseases had been diagnosed, participants were given a comorbidity index of 1, otherwise 0. Participants were also asked to specify their smoking habits and were classified as never, previous, or current smokers. For the regression analyses, previous and current smokers were combined under the term 'ever' smokers. Educational status was answered into five categories: basic school with no vocational education (elementary school only from 7 to 10 years of education depending on the age of the participants), vocational education up to 2 years (elementary school + e.g. store employees, carpenters,

or mason), 3–4 years of vocational education (elementary school + e.g. high school or business school), vocational education for more than 4 years (elementary school + high school + any university education), and under vocational education. Finally, hypothyroid patients were asked for how long a period they retrospectively had had symptoms compatible with their current hypothyroidism.

Blood specimen analyses

Thyroid function test results were continuously imported from the four laboratories covering the two study areas, as described in detail previously (16). Thus, serum TSH and thyroxine values for the patients were registered on the day they had hypothyroidism diagnosed. Serum samples collected at the time of investigation were used to analyze serum TSH in controls.

Thyroid autoantibodies (thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody (TgAb)) in patients and controls were measured in random order after the study had been completed (19, 20). Subjects with antibody concentration above the functional sensitivity given by the manufacturer (TPOAb, >30 kU/l; TgAb, >20 kU/l) were regarded as antibody positive (TPOAb+ and TgAb+).

Statistical analysis

We used Statistical Package for Social Sciences version 15.0 (SPSS, Chicago, IL, USA) for calculations and for statistical analyses. Data with no Gaussian distribution were expressed with median and interquartile range (25 and 75% percentiles). Groups of subjects were compared using Mann–Whitney U test, Pearson's χ^2 test, or Fischer's exact test depending on the data. Associations between having hypothyroidism diagnosed and alcohol consumption variables were analyzed in conditional univariate and multivariate logistic regression models and expressed as odds ratios (ORs) with 95% confidence intervals (95% CIs). A P value of <0.05 or an OR with 95% CI not including 1.0 was regarded as statistically significant. The conditional regression analyses required complete data. Therefore, the 2.5% of questions not answered by the participants were filled out by means of nearest neighbor imputation (21). We tested all explanatory variables and found no signs of multicollinearity. The following covariates were included in the regression models: family history of hypothyroidism (ever/never), smoking habits (ever/never), all-cause comorbidity (ever/never), and education (basic school + up to 2 years of vocational schooling vs more).

Ethical approval

This study was approved by Regional Ethics Committees in North Jutland and Copenhagen. Registry permission was obtained from the Danish Data Protection Agency. All participants gave their written informed consent. No conflicts of interest have occurred during implementation or completion of the study.

Results

We included 140 cases newly diagnosed with overt autoimmune hypothyroidism and 560 control subjects individually matched on sex, age, and region of inhabitancy. The baseline characteristics of cases and controls are depicted in Table 1. The hypothyroid cases had five times higher prevalence of thyroid autoantibodies. They also had 36% more prevalence of comorbidity, which was caused by a 64% higher prevalence of cardiovascular disorders.

Cases had a lower alcohol consumption during the last year compared with controls (3 vs 5 units of alcohol per week, $P=0.002$). Wine and beer were the predominant types of alcohol-containing beverages in both cases (24.5 and 64.1% respectively) and controls (25.2 and 61.9%). The stratified alcohol consumption of cases and controls is shown in Table 2, depicting both the average weekly consumption in the year preceding the participation program (recent consumption) and the weekly consumption in the calendar with the highest lifetime consumption (maximum consumption). ORs calculated in a univariate model revealed more abstainers among hypothyroid cases compared with controls, and fewer hypothyroid cases in the group with moderate recent alcohol consumption (11–20 units/week). Results were the same for maximum alcohol consumption. Baseline characteristics for the group of cases split according to alcohol consumption are shown in Table 3. No significant differences were found between groups.

The association between alcohol consumption and development of hypothyroidism was investigated in a conditional multivariate regression model taking various confounders into account (Fig. 2). Subjects with hypothyroidism were 1.98 times more likely to be abstainers compared with subjects with an alcohol consumption of 1–10 units weekly. This possible disease protection from alcohol was even more pronounced in subjects consuming 11–20 units/week. In this model, all-cause comorbidity was significantly associated with the development of overt autoimmune hypothyroidism (OR (95% CI): 1.66 (1.10–2.50)), whereas educational level was not.

In subgroup analyses (Fig. 3), we compared abstainers (0 units/week, reference group) to those who consumed at least 1 unit of alcohol/week and found an OR of 0.46 (0.28–0.75) meaning that the abstainers were 2.17 (1.35–3.57) times more likely to develop hypothyroidism compared with the combined group of non-abstainers. The group of non-abstainers who were predominantly drinking wine had the same reduced OR for disease as the group of preferential beer consumers (Fig. 3). However, the low OR in alcohol consumers was confined to the age below 60 years.

Table 1 Characteristics of hypothyroid cases and of matched population controls.

	Cases ($n=140$)	**Controls**[a] ($n=560$)	***P* value**
Sex (F/M (ratio))	117/23 (5.1)	468/92 (5.1)	1.00
Age (years)			
Median (25–75% range)	53.5 (45.7–61.3)	53.0 (45.3–61.7)	0.97
Inhabitancy			
Aalborg (moderate ID)	85 (60.7%)	340 (60.7%)	1.00
Copenhagen (mild ID)	55 (39.3%)	220 (39.3%)	
TPOAb (kU/l)			
Median (25–75% range)	4588 (1526–8502)	<30 (<30)	<0.001
TPOAb+	95.7%	18.8%	<0.001
TgAb (kU/l)			
Median (25–75% range)	130.4 (31–1103)	<20 (<20)	<0.001
TgAb+	80.7%	16.3%	<0.001
TSH (mU/l)			
Median (25–75% range)	54.5 (28.3–94.8)	1.24 (0.84–1.73)	<0.001
Education			
Basic school (only)	32 (22.9%)	126 (22.5%)	
≤2 years vocational	63 (45.0%)	232 (41.4%)	
3–4 years vocational	28 (20.0%)	148 (26.4%)	
>4 years vocational	14 (10.0%)	40 (7.1%)	
Under education	3 (2.1%)	14 (2.5%)	0.49
Smoking history			
Never smoker	51 (36.4%)	224 (40.0%)	
Previous smoker	47 (33.6%)	140 (25.0%)	
Current smoker	42 (30.0%)	196 (35.0%)	0.12
Comorbidity			
All-causes	81 (57.9%)	239 (42.7%)	0.001
Cardiovascular[b]	61 (43.6%)	149 (26.6%)	<0.001
Non-cardiovascular[c]	20 (14.3%)	90 (16.1%)	0.60

[a]Data were missing for TPOAb ($n=1$) and TgAb ($n=1$) of the 560 controls.
[b]Questionnaire obtained information on myocardial infarction, angina pectoris, cardiac arrhythmia, hypertension, or cerebral stroke.
[c]Questionnaire obtained information on epilepsy, diabetes mellitus, asthma, chronic obstructive pulmonary disease, or gastrointestinal ulcers.

Discussion

Principle findings

In this population-based study, we report the novel finding of a negative association between alcohol consumption and the incidence of overt autoimmune hypothyroidism. Our results suggest that a modest alcohol consumption of 1–10 units/week protects from developing autoimmune overt hypothyroidism and that a higher consumption of 11–20 units/week may be even more protective. On the other hand, the group with highest alcohol consumption (≥21 units/week) was not significantly different from the group of abstainers. We found no interaction with regard to sex or region of inhabitancy, which makes results applicable to other settings. However, we only observed the protective role of alcohol in subjects aged up to 60 years.

Beer vs wine consumption

In contrast to the beneficial effect of wine reported in cardiovascular disease (22), we found no difference between those who predominantly consumed wine vs

Table 2 Alcohol consumption in hypothyroid cases and controls. The reference group for univariate analysis was the group with alcohol intake of 1–10 units/week.

	Recent alcohol consumption[a]			**Maximum alcohol consumption**[b]		
	Cases ($n=140$)	Controls ($n=560$)	Univariate OR[c] (95% CI)	Cases ($n=140$)	Controls ($n=560$)	Univariate OR[c] (95% CI)
0 unit/week	35 (25.0%)	73 (13.0%)	2.12 (1.31–3.40)†	29 (20.7%)	65 (11.6%)	1.68 (1.02–2.77)*
1–10 units/week	85 (60.7%)	359 (64.1%)	1 (reference)	86 (61.4%)	316 (56.4%)	1 (reference)
11–20 units/week	11 (7.9%)	91 (16.3%)	0.47 (0.24–0.92)*	15 (10.7%)	115 (20.5%)	0.46 (0.25–0.83)*
≥ 21 units/week	9 (6.4%)	37 (6.6%)	0.97 (0.44–2.11)	10 (7.1%)	64 (11.4%)	0.52 (0.25–1.09)

[a]Average alcohol consumption (units/weekly) in the year preceding time of investigation.
[b]Average alcohol consumption (units/weekly) in the calendar year with the highest alcohol consumption during life.
[c]Statistically significant differences between the reference group (1–10 units/week) and other groups are depicted with *$P<0.05$; †$P<0.01$.

Table 3 Baseline characteristics in hypothyroid cases according to different recent alcohol habits.

	0 units/week[a] (*n*=35)	1–10 units/week (*n*=85)	11–20 units/week (*n*=11)	≥21 units/week (*n*=9)	*P* value
Sex (F/M (ratio))	31/4 (7.8)	72/13 (5.5)	8/3 (2.7)	6/3 (2.0)	0.26
Age (years)					
Median (25–75% range)	52.6 (48.1–59.1)	53.8 (42.2–62.5)	54.4 (47.2–58.0)	56.1 (50.0–64.1)	0.69
Inhabitancy					
Aalborg (moderate ID)	21 (60.0%)	51 (60.0%)	8 (72.7%)	5 (55.6%)	
Copenhagen (mild ID)	14 (40.0%)	34 (40.0%)	3 (27.3%)	4 (44.4%)	0.88
Duration of symptoms[b] (months)					
Median (25–75% range)	12 (4–18)	6 (4–12)	12 (2–21)	15 (9–27)	0.14
TPOAb (kU/l)					
Median (25–75% range)	5358 (663–21 817)	4119 (1230–7058)	4396 (1617–5355)	5792 (2669–26 053)	0.43
TPOAb+	97.1%	95.3%	90.9%	100%	0.75
TgAb (kU/l)					
Median (25–75% range)	357 (48–2750)	109 (26–959)	171 (10–591)	136 (46–5411)	0.28
TgAb+	85.7%	77.6%	72.7%	100%	0.32
TSH (mU/l)					
Median (25–75% range)	47.5 (32.5–94.9)	52.0 (26.5–91.8)	49.5 (19.8–88)	92.0 (34.6–127)	0.67
Total T_4 (nmol/l)					
Median (25–75% range)	40 (17–55)	40 (20–52)	39 (14–51)	21 (10–47)	0.70
Education[c]					
Up to 2 years vocational	25 (71.4%)	56 (65.9%)	7 (63.6%)	7 (77.8%)	
>2 years vocational	10 (28.6%)	29 (34.1%)	4 (36.4%)	2 (22.2%)	0.88
Smoking history					
Never smoker	13 (37.1%)	34 (40.0%)	2 (18.2%)	2 (22.2%)	
Previous smoker	9 (25.7%)	32 (37.6%)	4 (36.4%)	2 (22.2%)	
Current smoker	13 (37.1%)	19 (22.4%)	5 (45.5%)	5 (55.6%)	0.22
Comorbidity					
All-cause (present)	23 (65.7%)	42 (49.4%)	9 (81.8%)	7 (77.8%)	0.06
Cardiovascular[d]	16 (45.7%)	32 (37.6%)	6 (54.5%)	7 (77.8%)	0.11
Non-cardiovascular[e]	7 (20.0%)	10 (11.8%)	3 (27.3%)	0	0.20

[a]Recent alcohol abstainers had the following previous maximum alcohol consumption: 0 units/week (*n*=25), 1 units/week (*n*=1), 2 units/week (*n*=3), and 5–9 units/week (*n*=6).
[b]Missing data on duration of symptoms (*n*=17, 11 of these had no symptoms before diagnosis).
[c]Questionnaire obtained information on education according to vocational education more than basic school: for analyses, subjects under education were included in the group with highest education.
[d]Questionnaire obtained information on known cardiovascular disease: myocardial infarction, angina pectoris, cardiac arrhythmia, hypertension, or cerebral stroke.
[e]Questionnaire obtained information on known non-cardiovascular disease: epilepsy, diabetes mellitus, asthma, and other types of chronic obstructive pulmonary disease and gastrointestinal ulcers.

beer. This may have two implications. First, the protective substance may be ethanol *per se* or a substance present in both liquids. Secondly, it argues against the hypothesis that the protective role against various diseases of alcohol consumption may be caused in general by antioxidants in wine products.

Alcohol and thyroid

The direct effect of alcohol on the incidence of hypothyroidism has never been investigated, but a number of other studies have addressed other effects of alcohol on the thyroid gland. Hegedüs *et al.* (23, 24) reported a direct detrimental effect of alcohol on the thyroid gland with fibrosis and gland shrinkage in alcoholics who had consumed more than 8 units of alcohol per day for at least 5 years. In a previous DanThyr study, we found reduced thyroid volume and fewer solitary nodules in those consuming more than 8 units of alcohol per week compared with the abstainers (25), whereas the group of light alcohol consumers (1–7 units/week) did not differ from the abstainers group. No association was found between alcohol consumption and multinodularity (25). It has also been shown that alcohol consumption may reduce the risk for papillary thyroid cancer (26). Some studies reported lower serum tri-iodothyronine and higher serum TSH among people who had a moderate-to-high (25) or an excessive (24) alcohol consumption. Finally, it has been shown that the TSH response to TRH is diminished in alcoholics (27).

Alcohol and autoimmunity

Our study gives no hint to the mechanism behind a possible protective effect of alcohol on the development of overt hypothyroidism. Several studies have shown a protective role for alcohol on the development of other autoimmune disorders such as rheumatoid arthritis (10, 11) and systemic lupus erythematosus (12, 13). We searched for any study revealing not only a possible role of alcohol in the development of other autoimmune

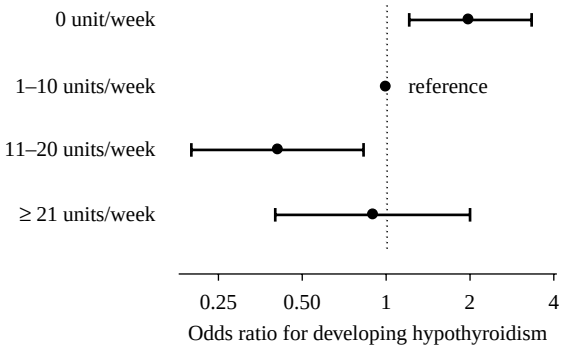

Figure 2 The dose effect of alcohol consumption on the occurrence of overt autoimmune hypothyroidism analyzed in a conditional multivariate regression model. Odds ratios (95% confidence intervals) for the four groups of alcohol intake, 0/1–10/11–20/≥21 units per week were as follows: 1.98 (1.21–3.33)/1 (reference group, 1–10 units/week)/0.41 (0.20–0.83)/0.90 (0.41–2.00). Adjustment was made for confounders: ever vs never smoking, family history of hypothyroidism, all-cause comorbidity, and education (basic school + up to 2 years of vocational schooling vs more).

endocrine disorders ('alcohol' + 'Addison', 88 hits; 'alcohol' + 'diabetes type I'/'autoimmune diabetes', 18 hits) but also the association between alcohol and various autoantibodies ('alcohol' + 'parietal cell antibody', 21 hits; 'alcohol' + 'antigliadin antibody', 15 hits; 'alcohol' + 'adrenal antibody', 1 hit; 'alcohol' + 'pancreas antibody', 200 hits). All abstracts were scrutinized, and only one very recent study did reveal any association. Rasouli *et al.* (28) reported a lower risk of developing autoimmune diabetes (multivariate hazard ratio was 0.38 (0.15–0.98)) in subjects of low alcohol consumption (2–7 vs 0.01–2 g/day).

How alcohol modulates the autoimmunogenic response to various epitopes is an open question. The interaction between alcohol and the immune system is very complex (29, 30). Modification of a diversity of immune responses may be involved, such as loss of natural killer cell activity (31), changes in immunoglobulins (32, 33, 34), and altered cytokine production (32). Moreover, human studies of high alcohol intake individuals as well as animal studies have revealed alterations in both Th1- and Th2-mediated immunity (35).

Association or causation

Association does not imply causation. However, a number of criteria for causal association such as temporality are met in this study (36). Also, the strength of the association between alcohol consumption and the development of hypothyroidism as well as the similar findings in beer and wine consumers support a causal association more than just presence of confounders not taken into account in our analyses. Even if the mechanisms behind our findings are unclear, the biological plausibility is supported by the findings in several studies of a negative association between alcohol consumption and other autoimmune diseases (10, 11, 12, 13).

Strengths and limitations

Persons who consume alcohol, especially if preferring beer, are often smokers (18) and *vice versa*. In addition, beer and liquor consumers more often suffer from other diseases (18). To adjust for this, smoking and comorbidity were introduced as possible confounders in our models and this did not alter the results.

Subjects having no alcohol consumption comprise a heterogeneous group. They may have dropped alcohol because of comorbidity, after previously being heavy drinkers, or they have been lifelong abstainers. As outlined in Table 3, the group of hypothyroid patients with no alcohol consumption in the last year (recent abstainers, $n=35$) was mostly lifelong abstainers, followed by patients with a previous moderate maximum alcohol consumption, whereas no previous heavy drinkers were identified in this group. Comorbidity was included in all final models. All-cause comorbidity was associated with a small increase in the risk for hypothyroidism in all models.

A number of questions from the questionnaire were left unanswered (2.5%). *Post hoc* analysis excluding these persons was performed, and the association between alcohol consumption and development of hypothyroidism was unaltered (results not shown).

We have no external control for the answers given by the participants in the questionnaire. However, other

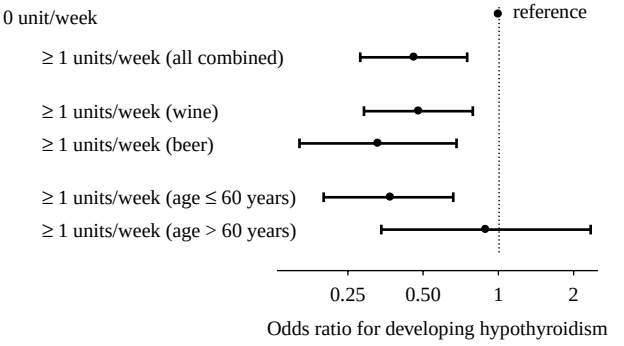

Figure 3 The protective effect of alcohol stratified according to type of alcohol (wine vs beer) and age analyzed in conditional multivariate regression models. Compared with abstainers (reference group), odds ratios (95% confidence interval) were as follows: ≥1 units/week, all types, 0.46 (0.28–0.75); ≥1 units/week, predominantly wine (called 'wine'), 0.48 (0.29–0.79); ≥1 units/week, predominantly beer ('beer'), 0.33 (0.16–0.68); ≥1 units/week, age ≤60 years, 0.36 (0.20–0.65), ≥1 units/week, age >60 years, 1.01 (0.37–2.73). Adjustment was made for confounders: ever vs never smoking, family history of hypothyroidism, all-cause comorbidity, and education (basic school + up to 2 years of vocational schooling vs more).

studies have concluded that the reliability of self-reported alcohol consumption is rather good (37, 38). If the results of our study had been influenced by recall bias, the studies by Giovannucci *et al.* (39, 40) suggest that an even stronger effect may have been found if the design of our study had been prospective.

Finally, case–control studies as this have the inherent possibility of selection bias among both cases and controls (41). Our study was population based. Still, not all people invited became participants (15, 17), and we cannot exclude that some self-selection took place.

Conclusion

We have shown that alcohol, in doses up to 3 units/day, may have a protective role in the development of overt autoimmune hypothyroidism in both men and women aged 60 years or below.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement

Dr P Laurberg and A Carlé had full access to all data in the study and take full responsibility for the integrity of the data and the accuracy of all analyses. Study concept and design: P Laurberg, H Perrild, T Jørgensen, N Knudsen, L Ovesen, L B Rasmussen, I B Pedersen, and A Carlé. Acquisition of data: A Carlé, I B Pedersen, and N Knudsen. Analysis and interpretation of data: A Carlé, P Laurberg, T Jørgensen, N Knudsen, I B Pedersen, L Ovesen, H Perrild, and L B Rasmussen. Drafting of the manuscript: A Carlé. Critical revision of the manuscript for important intellectual content and final approval: P Laurberg, H Perrild, T Jørgensen, N Knudsen, L Ovesen, L B Rasmussen, and I B Pedersen. Statistical analyses: A Carlé and P Laurberg. Obtained funding: A Carlé, P Laurberg, H Perrild, T Jørgensen, N Knudsen, L Ovesen, L B Rasmussen, and I B Pedersen. Study supervision: P Laurberg and T Jørgensen.

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