Alcohol consumption, smoking and development of visible age-related signs: a prospective cohort study

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ABSTRACT

Background Visible age-related signs indicate biological age, as individuals that appear old for their age are more likely to be at poor health, compared with people that appear their actual age. The aim of this study was to investigate whether alcohol and smoking are associated with four visible age-related signs (arcus corneae, xanthelasmata, earlobe crease and male pattern baldness).

Methods We used information from 11 613 individuals in the Copenhagen City Heart Study (1976–2003). Alcohol intake, smoking habits and other lifestyle factors were assessed prospectively and visible age-related signs were inspected during subsequent examinations.

Results The risk of developing arcus corneae, earlobe crease and xanthelasmata increased stepwise with increased smoking as measured by pack-years. For alcohol consumption, a high intake was associated with the risk of developing arcus corneae and earlobe crease, but not xanthelasmata.

Conclusions High alcohol consumption and smoking predict development of visible age-related signs. This is the first prospective study to show that heavy alcohol use and smoking are associated with generally looking older than one's actual age.

INTRODUCTION

Smoking and heavy alcohol intake are well-known risk factors for several diseases including cancer and cardiovascular diseases, conditions whose incidence increases steeply by age. While for smoking there is no safe level of consumption, alcohol is more complex because a low-to-moderate intake is associated with a lower risk of coronary heart disease[1 2] and all-cause mortality,[3 4] indicating a J-shaped function.

Looking old for one's age is associated with poor health, cardiovascular disease and early death,[5 6] implying that biological age to some extent can be observed visually. As both heavy drinking and smoking accelerate the incidence of age-related diseases, the question remains whether the increased risk of disease and mortality when exposed to alcohol and smoking may be an expression for a general ageing of the body. This hypothesis is supported by a study investigating the association between alcohol consumption in men and telomere length, which is a marker of biological age.[7] The study showed that even minor alcohol consumption in midlife was significantly associated with shorter telomere length and the differences represented an up to 10-year gap in biological age between zero and highest consumption.

Some visible age-related signs have been found to predict cardiovascular disease and mortality. In particular, four signs have been examined. First, earlobe crease has in several studies been associated with an increased risk of cardiovascular disease and mortality.[8–11] Second, recent studies have demonstrated that xanthelasmata, which are yellow plaques that occur most commonly near the inner canthus of the eyelid, is associated with an increased risk of ischaemic heart disease, myocardial infarct, severe atherosclerosis and mortality.[5 6] Third, the evidence regarding male pattern baldness is somewhat conflicting, but some studies have found that vertex baldness may be a marker for increased risk of coronary heart disease.[12 13] Finally, for arcus corneae, which is a white or grey opaque ring in the corneal margin of the eye, no consensus regarding the quality of the signs as a predictive marker exists,[14] and a recent study indicates that arcus corneae may not be an important independent predictor of risk.[6] However, another study found that arcus corneae among men aged 30–49 years might be a prognostic factor of coronary heart disease.[15]

Given that visible age-related signs can be interpreted as markers of biological age, we hypothesise that alcohol and smoking are associated with ageing. The aim of this study was, therefore, to investigate how alcohol intake and smoking are associated with four visible age-related signs: arcus corneae, earlobe crease, xanthelasmata and male pattern baldness.

METHODS

Study population

The participants were enrolled in the Copenhagen City Heart Study (CCHS), which is a prospective cardiovascular study of the Danish general population. In 1976, a random sample of the Danish general population aged above 20 years living in the Copenhagen area was invited to participate in CCHS (number of participants 14 223; response rate 74%). This examination was followed by three more examinations: a second examination in 1981–1983, where all previously invited plus 500 new individuals aged 20–24 years were invited (number of participants 12 698; response rate 70%); a third examination in 1991–1994 where all previously invited plus 3000 new individuals aged 20–49 years were invited (number of participants 10 135; response rate 61%); and a fourth examination in 2001–2003 where all previously invited

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plus an additional sample of 1040 individuals aged 20–29 years were invited (number of participants 6238; response rate 50%). Eligibility criterion for participation was Danish citizenship. Participants born in Asia, Africa, the Middle East, South America or Greenland constituted less than 2% of participants; thus, more than 98% were of European descent. Enrolment and examination procedures have been described in more detail elsewhere.[16 17]

Before visiting the study clinic, participants completed a questionnaire about various issues related to health, including alcohol intake, smoking habits, physical activity and the presence of certain diseases. At the clinic visit, physical examinations were performed including measurement of height (without shoes) and weight (in light clothes). Questionnaire responses were checked for missing information and any uncertainties were clarified. All participants gave informed consent, and the ethics committee for Copenhagen and Frederiksberg approved the study (100.2039/91).

Alcohol consumption and smoking in pack-years

Participants were asked to state their usual amount of alcohol intake in a typical week, separately for beers (in bottles), wine (in glasses) and spirits (in units). On the basis of ethanol content in the different beverage types, this information was converted into a total number of standard drinks (12 g alcohol) per week.

Participants were asked whether they smoked or had smoked previously. Current smokers were additionally asked about duration of smoking in years and amount of tobacco in categories of daily cigarettes with and without filter, cheroots, cigars and pipes. We defined 1 cigarette as 1 g of tobacco, 1 cheroot or 1 pipe as 3 g of tobacco and 1 cigar as 5 g of tobacco. Smoking in pack-years was the accumulated exposure to smoking calculated as (years of smoking×daily grams of tobacco)/20.

Visible age-related signs

Trained nurses or medical laboratory technicians, unaware of the participants' risk and disease profile, determined the presence and extent of arcus corneae (a white or grey opaque ring in the corneal margin of the eye), xanthelasmata (yellow-orange plaques on the eyelids or medial canthus), earlobe crease (a diagonal fold or wrinkle in the skin of the earlobe) and male pattern baldness (includes fronto-parietal and crown top baldness in men). The physical manifestation of the visible age-related signs was visually illustrated in the study by Christoffersen *et al*.[5]

The visual inspection of the age-related signs was performed according to prespecified procedures and criteria. Earlobe crease was investigated on the right ear, with three possible outcomes (no earlobe crease, earlobe crease extending over less than half of the earlobe and earlobe crease extending over more than half of the earlobe). For the present study, we combined participants into two groups (no earlobe crease vs any earlobe crease present). The presence of arcus corneae was investigated on the right eye with three outcome possibilities, no arcus, half arcus or complete arcus. Participants were combined into two groups (no arcus corneae vs any arcus corneae present). The presence of xanthelasmata was determined on both eyes, with two possible outcomes (no xanthelasmata vs any xanthelasmata). The extent of baldness was inspected in men in the fronto-parietal region and the crown top region of the scalp.[18] In the fronto-parietal region, baldness was registered as no bald triangle, bald triangle but >3 cm in front of the ear or bald triangle <3 cm in front of the ear. For the present study, we combined participants into two groups (no bald triangle vs any bald triangle). In the crown top region, baldness was registered as thick hair, partly thin hair, bald spot or bald top and front. For the present study, we combined participants into two groups (thick hair vs thin hair or bald spot).

Arcus corneae, xanthelasmata and earlobe crease were inspected at the 1976, 1981–1983 and 1991–1994 examinations, and male pattern baldness was inspected at 1976 and 1991–1994 examinations only.

Final study population

Development of the age-related signs could occur during three time periods: between the 1976 and 1981–1983 examination, between the 1981–1983 and 1991–1994 examination and between the 1976 and 1991–1994 examination. Incident cases of the age-related signs from all three periods were included. The mean follow-up time was 11.5 years.

After exclusion of participants with missing information on alcohol intake, smoking, education, body mass index (BMI) and physical activity, (total missing n=102), 12 240 individuals (6828 women and 5412 men) remained that participated in at least two of the three examinations: 4591 participated in 1976 and 1981–1983 examinations, 500 participated in 1976 and 1991–1994 examinations, 734 participated in 1981–1983 and 1991–1994 examinations and 6415 participated in all three examinations and were included in both the first and second periods. We excluded participants who had already developed a specific age-related sign at baseline; thus, the number of participants in analysis differed for the four outcomes. Sample sizes were 9384 (2966 deleted) for arcus corneae, 9486 (3064 deleted) for earlobe crease and 11 613 (757 deleted) for xanthelasmata. For male pattern baldness, numbers were 639 (4367 deleted) for fronto-parietal and 3701 (2341 deleted) for crown top baldness (figure 1).

Statistical analysis

Analyses were performed using Stata v.14 using the *intcens* procedure developed to perform interval censored survival analysis, applying an exponential function for the distribution of case intensity. As some individuals were included in two time periods, we used a robust SE allowing for intragroup correlation, relaxing the usual requirement that observations are independent. Calendar time was used as the underlying axis in the analysis. Age was adjusted for by a linear and a squared term (p value for the squared term was <0.001).

The following covariates were considered potential confounders: age, education, BMI, physical activity in leisure time, diabetes mellitus, hypertension and cardiovascular disease. Analyses investigating alcohol intake were adjusted for smoking and vice versa. BMI, alcohol and smoking (in pack-years) were entered as linear variables for this purpose. Education was categorised according to years of completed school: <8, 8–10 and ≥11 years. Physical activity in leisure time, including transportation to and from work, was grouped into sedentary, light,

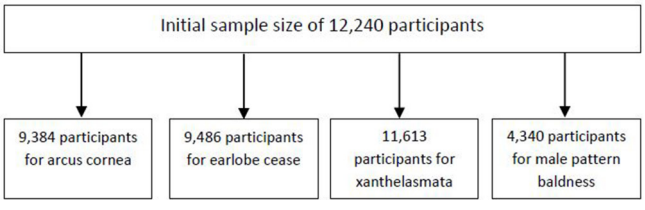

Figure 1 Flow diagram illustrating the samples sizes of analysis of specific age-related signs.

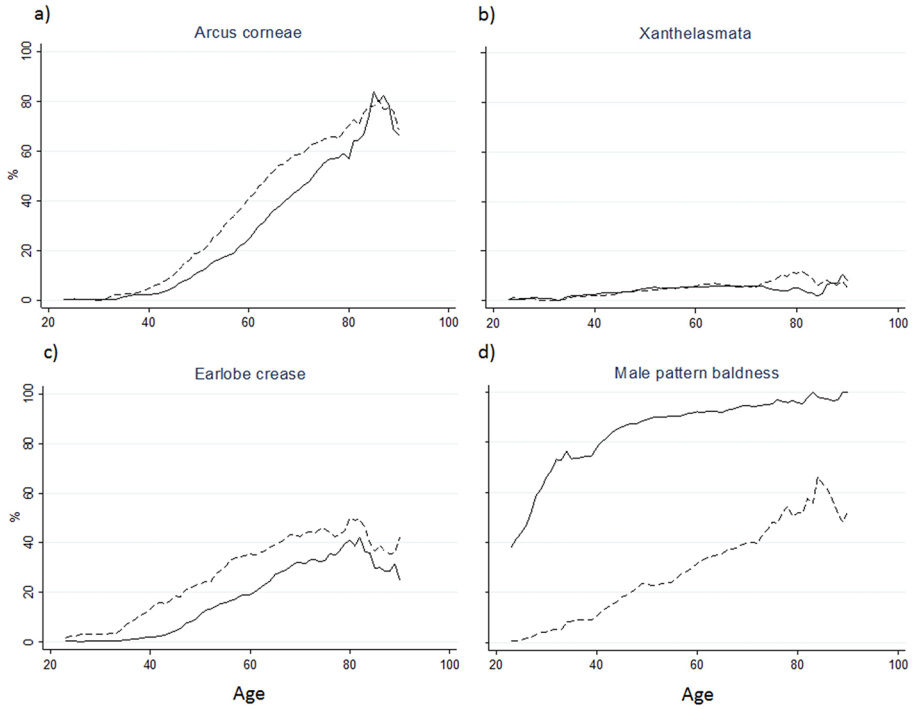

Figure 2 Prevalence (%) of visible age-related signs in the Copenhagen City Heart Study by age in women (solid line) and men (dashed line). For male pattern baldness, fronto-parietal baldness is marked as a solid line and crown top baldness as a dashed line.

moderate and strenuous levels. Diabetes mellitus and cardiovascular disease (stroke and myocardial infarct) was self-reported. We defined hypertension as systolic blood pressure >140 mm Hg or a diastolic blood pressure >90 mm Hg.

The prevalence of the four visible age-related signs by age (figure 2) was calculated using all available data from examinations in 1976, 1981–1983 and 1991–1994. A running average over a range of ±2 years was calculated to prevent the impact of random fluctuations in one particular year.

Sensitivity analyses were performed to assess competing risk from death, which was likely due to the relatively long time intervals between examinations (approximately 10 years). Therefore, Cox analysis taking into account competing risk was performed (stcox procedure). In such analysis, it was assumed that the time of development of the age-related sign in question occurred at the midpoint between baseline and follow-up. Using information from the Danish Civil Registration System, information on all deaths was obtained, and therefore the exact time of death was known.

To compare the relative impacts of alcohol and smoking, we calculated attributable fractions in heavy drinkers (>21 drinks/week) and in current smokers (ie, pack-years >0), respectively, as results indicated consistent increased risk at these levels (figures 3 and 4). The attributable fraction was calculated as (RR−1)/RR×100%. We derived 95% CIs by bootstrapping (10 000 replications), with the 2.5 and 97.5 percentiles of the distribution as lower and upper limits.

RESULTS

Baseline characteristics

Table 1 shows characteristics of the 11 631 participants. Of these, 44% were men and their mean age was 51 years (range: 21–93). The mean age for women was 51.5 years (range: 21–86). The median alcohol intake was 2.6 drinks/week among women and 11.4 drinks/week among men. Among women and men, 57% and 67% were current smokers.

Prevalence of visible age-related signs by age

Arcus corneae was the most prevalent age-related sign for both men and women, with a prevalence of 60% for men above 70 years and for women above 80 years (figure 2). The prevalence of earlobe crease was low but steadily increased with age until approximately 80 years. Xanthelasmata was the least prevalent visible age-related sign, with a prevalence of approximately 5% for men and women above 50 years of age. For male pattern baldness, the prevalence of fronto-parietal baldness was notably higher than crown top baldness. More than 80% of the men presented with fronto-parietal baldness above approximately 40 years of age.

Alcohol intake, smoking and arcus corneae

In total, 1344 and 1081 prospective cases of arcus corneae were observed among women and men. For women drinking ≥28 drinks/week, the HR was 1.33 (95% CI 0.93 to 1.90) of developing arcus corneae, compared with women drinking 1-<7 drinks/week (figure 3). For men, the HR was 1.35 (95% CI 1.14 to 1.61) for developing arcus corneae when drinking ≥35 drinks/week compared with drinking 1-<7 drinks/week. The HR of developing arcus corneae were 1.41 (95% CI 1.25 to 1.61) and 1.12 (95% CI 0.92 to 1.36) among women and men who smoked 15-<30 pack-years, compared with never-smokers (figure 4).

Alcohol intake, smoking and earlobe crease

Overall, 1341 and 985 prospective cases of earlobe crease were identified among women and men. The HR were 1.36 (95% CI 0.99 to 1.88) and 1.26 (95% CI 1.02 to 1.56) among women and men for developing earlobe crease when drinking

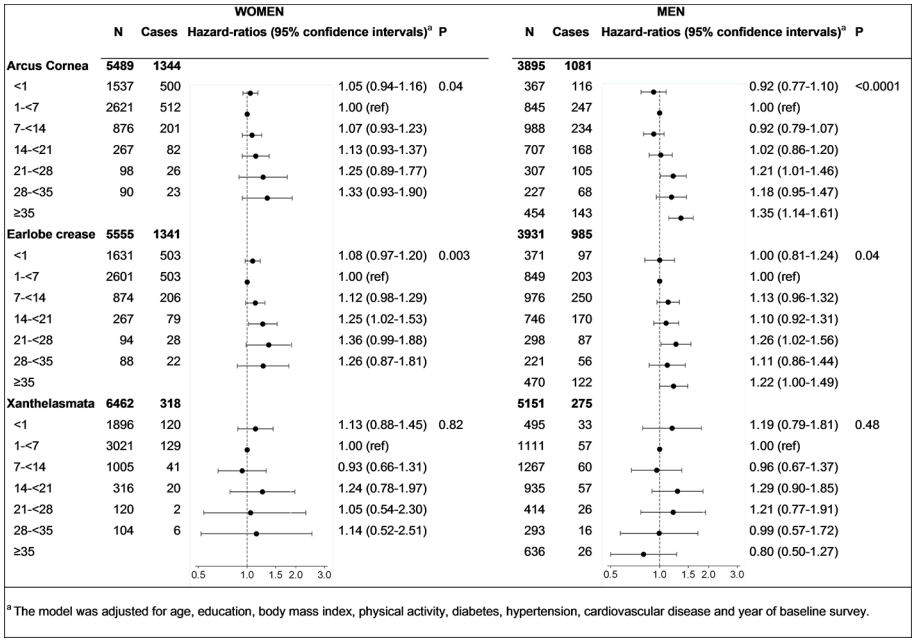

Figure 3 HRs and 95% CIs for developing arcus corneae, earlobe crease and xanthelasmata according to alcohol intake in the Copenhagen City Heart Study (1976–2003).

21-<28 drinks/week compared with those drinking 1-<7 drinks/week (figure 3). Smoking and developing earlobe was associated with earlobe crease for both women and men. In the fully adjusted model, we found an HR of developing earlobe crease at 1.26 (95% CI 1.07 to 1.48) and 1.30 (95% CI 1.05 to 1.61) among women and men smoking 30-<45 pack-years, compared with never-smokers (figure 4).

Alcohol intake, smoking and xanthelasmata

Overall, 318 and 275 prospective cases of xanthelasmata were identified among women and men. The association between alcohol intake and xanthelasmata was not significant for women or men (p_{trend}=0.82 for women and p_{trend}=0.48 for men) (figure 3). Smoking measured in pack-years was associated with an increased risk of developing xanthelasmata. The HR of developing xanthelasmata was 1.46 (95% CI 0.74 to 2.89) and 2.03 (95% CI 1.17 to 3.52) among women and men who smoked ≥45 pack-years, compared with never-smokers (figure 4).

Alcohol intake, smoking and male pattern baldness

Overall, 430 cases of fronto-parietal baldness and 508 cases of crown top baldness were identified among men. Alcohol intake was not associated with male pattern baldness (table 2). The HR for crown top baldness was 0.68 (95% CI 0.50 to 0.94) in those who had smoked for 45+ pack-years, implying that smoking is

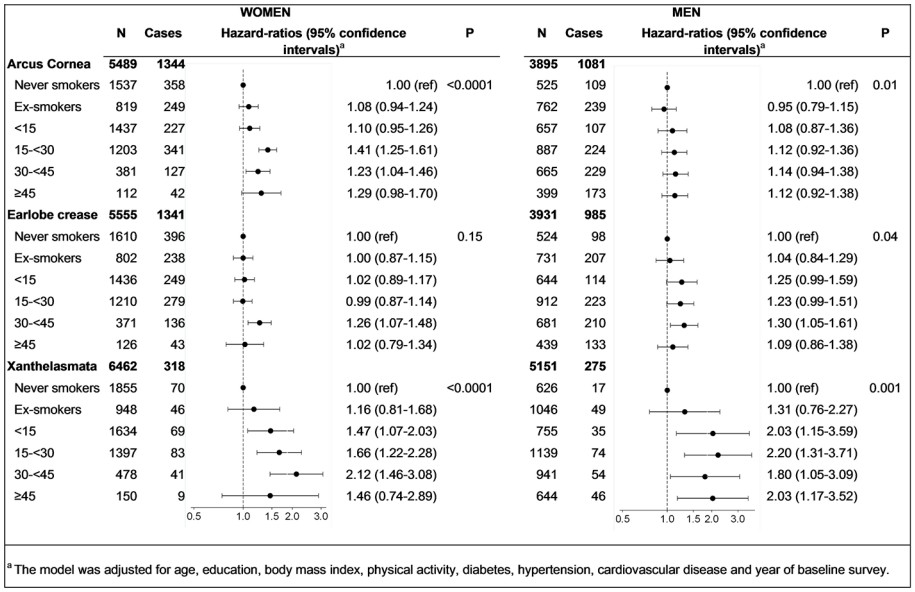

Figure 4 HRs and 95% CIs for developing arcus corneae, earlobe crease and xanthelasmata according to smoking in pack-years in the Copenhagen City Heart Study (1976–2003).

Table 1 Baseline characteristics of the study population in the Copenhagen City Heart Study (n=11 613)

	Women	Men
Total, n (%)	6462 (56)	5151 (44)
Age (years), mean (range)	51.5 (21–86)	51.0 (21–93)
Alcohol intake (drinks/week), median (10% and 90% percentiles)	2.6 (0, 13)	11.4 (2, 38)
Current smokers, n (%)	3659 (57)	3479 (67)
Smoking (pack-years), median (10% and 90% percentiles)*	15.0 (4, 34)	26.8 (8, 54)
Education (years), n (%)		
<8	2940 (46)	2259 (44)
8–10	2589 (40)	1899 (37)
≥11	933 (14)	993 (19)
Body mass index (kg/m^2), median (10% and 90% percentiles)	23.7 (20, 30)	25.4 (21, 30)
Physical activity in leisure time, n (%)		
Sedentary	1095 (17)	867 (17)
Light	3806 (59)	2499 (48)
Moderate	1500 (23)	1599 (31)
Strenuous	61 (1)	186 (4)
Diabetes, n (%)	56 (0.9)	97 (1.9)
Hypertension, n (%)	2359 (37)	2465 (48)
Cardiovascular disease, n (%)	88 (1)	148 (3)

*Among current smokers.

associated with decreased risk of balding. However, none of the other levels of smoking were associated with crown top baldness.

Sensitivity analysis

All analyses were repeated taking competing risk from death into account. For all of the visible age-related signs, results differed little from the main analyses (results not shown).

The results of the calculated attributable fractions were that, in heavy drinkers, 26% and 24% of the occurrence of arcus cornea and earlobe crease were attributable to this level of drinking (table 3). Likewise, 17% and 8% of the occurrence of arcus cornea and earlobe crease were attributable to smoking among the current smokers.

DISCUSSIONS

The principal finding of this study of 11 613 individuals representing the general population was that heavy drinking and smoking were associated with biological ageing of the body, measured by the development of arcus corneae, earlobe crease and xanthelasmata. Alcohol and smoking were not consistently associated with the development of male baldness.

Visible age-related signs have been found to predict cardiovascular disease and death, indicating that biological age to some extent can be observed visually.[5 6] In particular, earlobe crease, xanthelasmata and male pattern baldness have previously been found to predict cardiovascular disease and death.[5 6 8–13]

A systematic review investigating the predictive value of arcus corneae concluded that there is no consensus as to whether arcus corneae is an independent risk factor for cardiovascular disease and death.[14] In addition, two large prospective studies, based on the same study population as this study, found that arcus corneae was not associated with cardiovascular disease and death,[5 6] while another follow-up study has demonstrated that arcus cornea could be a prognostic factor for coronary heart disease in men.[15] Despite the lack of consensus regarding arcus corneae, the literature in general implies that appearing old for one's age is associated with cardiovascular disease and premature death independent of chronological age.[5 6 8–13] We found that a high alcohol intake and smoking were associated with increased occurrence of visible age-related signs and thus looking older than one's actual age. This may reflect that heavy drinking and smoking increases general ageing of the body.

Alcohol consumption and smoking did not predict the development of male pattern baldness, which otherwise is considered an age-related sign.[12 13] The statistical power for male pattern baldness was low, as men who already had male pattern baldness was not included in our analysis. This should be considered when interpreting the results. Research has been limited, but one study indicates that premature greying of hair and baldness are partly attributable to smoking.[19] A potential explanation for this is that the development of male pattern baldness is strongly influenced by genetic predisposition[20] and androgens.[21] Thus, alcohol intake and smoking habits and other lifestyle factors may play a minor role for developing fronto-parietal and crown top baldness.

Low-to-moderate alcohol intake has in several studies been associated with health benefits, including a lower risk of coronary heart disease[1 2] and all-cause mortality.[3 4] Although the finding that cardiovascular risk is lower in light-to-moderate drinkers is consistently observed in numerous studies, in various cultures and nationalities, the causal nature of alcohol's apparent beneficial effect is still discussed intensely,[22 23] a debate that is likely to continue until solid experiment evidence is produced. In our study, the occurrence of age-related signs in light to moderated drinkers was similar to that of non-drinkers, thus not indicating any beneficial effect of alcohol at this level.

Attributable fractions for the development of arcus cornea and earlobe crease, that is, the percentage of visible age-related signs that could be attributed to heavy drinking or smoking, respectively, in those who were drinking heavily or daily smokers were approximately similar of size. Thus, effects of heavy drinking and smoking seem to be comparable in this aspect.

Smoking measured as pack-years predicted the development of earlobe crease, consistent with previous studies.[10 24] Also, smoking was associated with the development of arcus corneae in men and women. Existing literature is cross-sectional in nature and results conflict.[25 26] We found a high alcohol intake to be a strong predictor of developing arcus corneae among both men and women. Scientific research on this subject is sparse but indicates a possible relation.[14 27] A high alcohol intake also predicted the development of earlobe crease among men, but not among women, which is in contrast to another study that demonstrated a lower frequency of earlobe crease among women who drank alcohol frequently.[28]

The strength of this study is the prospective population-based design including a large homogeneous sample of both men and women. We were able to adjust for important confounders such as physical activity, diabetes, hypertension and cardiovascular disease. Trained health professionals examined the participants in regard to visible age-related signs, which ensured an objective collection of outcome information. In addition, we used a method that took the interval censored nature of the data into account including a robust SE allowing for intragroup correlation.

This study has some limitations. First, information about alcohol intake and smoking habits was self-reported, which may have caused misclassification. Self-reported alcohol intake has nevertheless been found to be valid when

Table 2 HRs and 95% CIs for developing male pattern baldness according to alcohol intake and smoking among men in the Copenhagen City Heart Study (1976–2003)

			Adjusted*		Fully adjusted†	
	Total, n	Cases, n	HR	95% CI	HR	95% CI
Fronto-parietal baldness	639	430				
Alcohol intake (drinks/week)						
<1	56	39	0.92	0.77 to 1.10	0.92	0.77 to 1.10
1≤7	140	105	Ref.	–	Ref.	–
7≤14	158	101	0.87	0.76 to 1.00	0.88	0.77 to 1.01
14≤21	125	74	0.81	0.69 to 0.95	0.82	0.70 to 0.96
21≤28	46	30	0.87	0.70 to 1.07	0.85	0.69 to 1.05
28≤35	33	25	0.98	0.80 to 1.20	1.02	0.84 to 1.25
≥35	81	56	0.91	0.77 to 1.06	0.94	0.80 to 1.11
			p_{trend}=0.24		p_{trend}=0.38	
Smoking (pack-years)						
Never-smokers	101	60	Ref.	–	Ref.	–
Ex-smokers	105	75	1.17	0.98 to 1.41	1.08	0.89 to 1.31
<15	122	78	1.06	0.88 to 1.29	1.08	0.89 to 1.31
15≤30	166	111	1.10	0.92 to 1.32	1.03	0.85 to 1.24
30≤45	91	71	1.27	1.06 to 1.52	1.14	0.94 to 1.39
≥45	54	35	1.06	0.84 to 1.34	0.92	0.71 to 1.19
			p_{trend}=0.12		p_{trend}=0.89	
Crown top baldness	3701	508				
Alcohol intake (drinks/week)						
<1	347	54	1.01	0.76 to 1.35	0.95	0.71 to 1.26
1≤7	792	122	Ref.	–	Ref.	–
7≤14	911	121	0.87	0.69 to 1.09	0.90	0.72 to 1.13
14≤21	682	87	0.83	0.64 to 1.06	0.86	0.67 to 1.11
21≤28	296	36	0.80	0.57 to 1.13	0.81	0.57 to 1.13
28≤35	218	30	0.90	0.62 to 1.29	0.93	0.65 to 1.33
≥35	455	58	0.82	0.61 to 1.09	0.84	0.63 to 1.12
			p_{trend}=0.12		p_{trend}=0.16	
Smoking (pack-years)						
Never-smokers	425	64	Ref.	–	Ref.	–
Ex-smokers	715	109	1.03	0.78 to 1.36	0.81	0.61 to 1.07
<15	541	68	0.85	0.62 to 1.15	0.95	0.69 to 1.29
15 ≤30	860	95	0.75	0.56 to 1.00	0.67	0.50 to 0.89
30≤45	712	108	1.03	0.78 to 1.37	0.80	0.60 to 1.05
≥45	448	64	0.98	0.71 to 1.34	0.68	0.50 to 0.94
			p_{trend}=0.77		p_{trend}=0.03	

*Adjusted for age year of baseline survey.
†Alcohol intake and smoking were mutually adjusted for. The model was additionally adjusted for age, education, body mass index, physical activity, diabetes, hypertension, cardiovascular disease and year of baseline survey.

compared with formal dietary interview.[29] Although such comparison does not represent a true validation, dietary interview is considered to convey more accurate information than self-reported intake by questionnaire. Furthermore, increasing levels of biomarkers for alcohol intake such as alanine aminotransferase, aspartate aminotransferase and

Table 3 HR (95% CI) and attributable fraction (%) for arcus cornea and earlobe crease in participants with heavy alcohol intake and current smoking

	Alcohol intake (heavy drinking>21 drinks/week)		Smoking (current smoking)	
	HR (95% CI)	Attributable fraction (%)	HR (95% CI)	Attributable fraction (%)
Arcus corneae	1.35 (1.21 to 1.51)	26 (17–34)	1.21 (1.11 to 1.33)	17 (10–25)
Earlobe crease	1.31 (1.16 to 1.48)	24 (13–32)	1.09 (1.00 to 1.19)	8 (1–17)

γ-glutamyl transpeptidase with stepwise increasing level of self-reported alcohol intake were previously reported in CCHS.[30]

Similarly for smoking, lung function (measured by forced expiratory volume in 1 s) has been reported to decrease with increasing smoking, and the amount of carbon monoxide in expired air, which is a marker of recent smoking[31] was equally low in never-smokers and ex-smokers, indicating that there was not a substantial fraction of current smokers who classified themselves as ex-smokers.[32] Such observations speak in favour of the validity of the self-reported information on alcohol and smoking, and any misclassification was likely to be non-differential, as it would be independent from the participants' future development of visible age-related signs.

Second, another limitation is that the assessment of age-related signs, although performed by trained nurses and technicians by prespecified procedures and criteria, was based on visual inspection and that we did not have data to confirm the interobserver and intraobserver consistency of the assessment of age-related features over the period of assessment. Third, while we adjusted for a range of potential confounders such as age, education, BMI, physical activity, diabetes, hypertension and cardiovascular disease, psychosocial variables such as stress were not accounted for. Stress is known to be associated with increased risk of diseases such as cardiovascular disease,[33 34] and stress is associated with smoking and a high alcohol intake.[35] Stress may, therefore, have confounded results.

In summary, smoking and high levels of alcohol intake in the general population predicted biological ageing of the body, indicated by the development of arcus corneae and earlobe crease, but not xanthelasmata. A low-to-moderate alcohol intake was not associated with any of the visible age-related signs and neither smoking nor alcohol consumption was associated with male pattern baldness. Heavy alcohol use and smoking are associated with generally looking older than one's actual age.

What is already known on this subject

Heavy drinking and smoking accelerate the incidence of age-related diseases, such as cardiovascular disease and cancers.

What this study adds

The present study is the first prospective study to show that alcohol and smoking are associated with the development of visible age-related signs and thus generally looking older than one's actual age. A low-to-moderate alcohol intake was not associated with any of the age-related signs.

Contributors This manuscript was written by ALS, M-LM, PS, MG and JST. JST as the corresponding author planned and designed the work. JST approved the final version for publication. ALS and JST conducted the analysis and wrote the manuscript. M-LM contributed to writing of the manuscript. PS and MG revised the manuscript critically and persisted with knowledge to the included dataset.

Competing interests None declared.

Ethics approval The ethics committee for Copenhagen and Frederiksberg.

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