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Visible Age-Related Signs and Risk of Ischemic Heart Disease in the General Population: A Prospective Cohort Study

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Abstract

***Background*—**Cardiovascular disease is one of the most common age-related diseases, and also one of the most common causes of death in the general population. We tested the hypothesis that visible age-related signs associate with risk of ischemic heart disease (IHD), myocardial infarction (MI), and death in the general population, independent of chronological age.

***Methods and Results*—**10,885 individuals aged 20-93 years free of IHD were followed from 1976-8 until June 2011 with 100% complete follow-up. During these 35 years of follow-up, 3,401 participants developed IHD and 1,708 developed MI. Presence of frontoparietal baldness, crown top baldness, earlobe crease, and xanthelasmata was associated with increased risk of IHD and/or MI after multifactorial adjustment for chronological age and well-known cardiovascular risk factors. The risk of IHD and MI increased stepwise with increasing number of age-related signs with multifactorially adjusted hazard ratios up to 1.40 (95% confidence interval 1.20 to 1.62) for IHD and 1.57 (1.28 to 1.93) for MI, in individuals with 3-4 versus no age-related signs at baseline (P for trend <0.001). In all age-groups in both women and men, absolute 10-year risk of IHD and MI increased with increasing number of visible age-related signs.

***Conclusions*—**Male pattern baldness, earlobe crease, and xanthelasmata – alone or in combination – associate with increased risk of ischemic heart disease and myocardial infarction independent of chronological age and other well-known cardiovascular risk factors. This is the first prospective study to show that looking old for your age is a marker of poor cardiovascular health.

Key words: epidemiology, risk factor, acute myocardial infarction, ischemic heart disease

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The physical examination of a patient often includes an assessment of whether a patient looks younger or older than his or her actual age.[1;2] This practice assumes that the perceived age of a patient correlates with age-related disease and mortality, and thus that patients appearing older than their chronological age are more likely to be in poor health, compared with patients appearing their actual age. Previous studies have found that male pattern baldness,[3] grey hair,[3;4] and facial wrinkles[4;5] as well as presence of arcus corneae[3] are all associated with looking old for one's age.

Male pattern baldness, grey hair, and facial wrinkles are all common signs of aging. Presence of one or more of these visible age-related signs have been associated with increased risk of ischemic cardiovascular disease in most,[6-11] but not all studies.[12;13] In contrast, male pattern baldness, grey hair, and facial wrinkles did not associate with death.[14-16] Earlobe crease, xanthelasmata, and arcus corneae are appearance factors, which like the common age-related signs occur more frequently with increasing age. Earlobe crease is a diagonal fold or wrinkle in the skin of the earlobe, while xanthelasmata and arcus corneae are cholesterol deposits on the eyelids and in the cornea respectively.[17-19] Most studies confirm an association between earlobe crease and risk of cardiovascular disease[20-24] or death,[25] although some studies argue that this association is mainly due to an association between earlobe crease and increasing age.[26] We have recently shown that xanthelasmata and arcus corneae are associated with an increased risk of ischemic heart disease (IHD) and death independent of age and sex – and for xanthelasmata also independent of plasma lipid levels.[27]

Cardiovascular disease is one of the most common age-related diseases, and also one of the most common causes of death in the general population. Assuming that presence of visible age-related signs are a marker of the actual biological age of an individual, we tested the

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hypothesis that age-related signs – individually and combined – associate with risk of IHD, myocardial infarction (MI), and death in the general population, independent of chronological age. We studied 10,885 participants from the Copenhagen City Heart Study cohort and followed them from 1976-1978 until June 2011.

Methods

Participants

The Copenhagen City Heart Study is a prospective cardiovascular study of the Danish general population initiated in 1976-1978 with follow-up examinations in 1981-1983, 1991-1994, and 2001-2003. We invited 19,329 white women and men of Danish descent stratified into 5-year age groups from 20 years to 80 years or older, and drawn randomly from the Copenhagen Central Person Registry. Data were obtained from a self-administered questionnaire, a physical examination, and from blood samples. All questionnaires were checked during the examination by the staff in collaboration with the participant.[28]

Of those participants invited, 14,223 (74%) attended and 10,885 individuals (56%) in whom complete information on all relevant variables including age-related signs were available at baseline, were included in this study. Participants were followed up using their unique Central Person Register number from baseline at the 1976-1978 examination through June 2011. Follow-up for all endpoints, including IHD, MI, and death, was 100% complete, i.e. none were lost to follow-up. The study was approved by institutional review boards and by Danish ethical committees (the Copenhagen and Frederiksberg committee and the Copenhagen County committee; KF-100.2039/91, KF-01-144/01, H-KF-01-144/01), and conducted according to the Declaration of Helsinki. Participants gave written informed consent.

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Age-related signs

Trained nurses or medical laboratory technicians, who were unaware of the participants' risk and disease profile, determined the presence and extent of male pattern baldness, grey hair, facial wrinkles, earlobe crease, xanthelasmata, and arcus corneae by careful visual inspection during the physical examination, according to prespecified criteria (**Figure 1** for representative examples). For a detailed description of the criteria used to diagnose the age-related signs, see the Supplementary Methods section.

Ischemic heart disease, myocardial infarction, and death

Diagnosis of MI and IHD (World Health Organization: International Classification of Diseases, Eighth Revision codes 410 and 410-414; International Classification of Diseases Tenth Revision codes I21-I22 and I20-I25) were collected and verified by reviewing all hospital admissions and diagnoses entered in the National Danish Patient Registry, all causes of death entered in the National Danish Causes of Death Registry, and medical records from hospitals and general practitioners. IHD was fatal or non-fatal MI or characteristic symptoms of angina pectoris, including revascularization procedures;[29] death from other causes lead to censoring. A diagnosis of MI followed the changing definitions over time. After 2000 the diagnosis was based on either one of: 1. Typical rise and fall of biochemical markers of myocardial necrosis (troponin or CK-MB) with at least one of the following: Ischemic symptoms; development of pathological Q waves on the ECG; ECG changes indicative of ischemia, or coronary artery intervention; or 2. Pathological findings of an acute, healed or healing MI,[30] with later changes as indicated.[31] Information on date of death was obtained from the National Danish Central Person Registry, which is 100% complete.

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Covariates

Enzymatic methods (Boehringer Mannheim, Mannheim, Germany) were used on fresh plasma samples to measure plasma levels of total cholesterol and triglycerides. Body mass index was measured weight in kilograms divided by height in meters squared. Hypertension was use of antihypertensive medication, a systolic blood pressure of more than 140 mm Hg, and/or a diastolic blood pressure of more than 90 mm Hg. Diabetes mellitus was self-reported disease, use of insulin or oral hypoglycaemic agents, and/or nonfasting plasma glucose levels of more than 11 mmol/L (>198 mg/dL). Smoking in packyears was the accumulated smoking exposure calculated from the questionnaires and categorized as 0 packyears (non-smokers and smokers having smoked less than 1 pack of cigarettes per day for 1 month), <10 packyears (smokers having smoked corresponding to 1 pack of cigarettes per day for a period between 1 month and 10 years), 10 to 20 packyears (smokers having smoked corresponding to 1 pack of cigarettes per day for a period between 10 and 20 years), and ≥20 packyears (smokers having smoked corresponding to 1 pack of cigarettes per day for 20 years or more). Regular alcohol consumers drank alcohol at least twice weekly, while light drinkers consumed alcohol less often. Physical inactivity was leisure time activity less than four hours weekly. Women reported menopausal status and use of hormonal replacement therapy. Family history of ischemic vascular disease was at least one parent with a previous MI or ischemic stroke. Education and income were included as markers of socioeconomic status of the participants. Education was <8 years of education versus ≥8 years of education. Income was a 1976-1978 income <10,000 Danish kroner per month versus ≥10,000 Danish kroner per month (app. 1,730 US dollars).

Statistical analyses

STATA software, version 12.0 (Stata Corp, College Station, Texas, USA) was used for all

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analyses. Two-sided probability values less than 0.05 were considered significant. The Mann-Whitney U test or Pearson χ^2 test were used in two-group comparisons. Cumulative incidences of IHD and MI were plotted with the use of Kaplan-Meier curves, and differences between individuals with increasing number of visible age-related signs were examined by log-rank tests. Cox proportional hazards regression models were used to estimate hazard ratios with 95% confidence intervals for IHD, MI, and death as a function of age-related signs, individually and combined. Participants with multiple episodes of IHD were censored after the first event. We used time (in years) from study entry as the time scale to calculate crude hazard ratios and hazard ratios adjusted for age at study entry. We further used age as the time scale and left truncation (or delayed entry) to calculate adjusted hazard ratios. Using age as the time scale is the gold standard for prospective studies on risk of disease and mortality, since this is the scale over which the most dramatic change in risk occurs.[32] This further implies that age is automatically adjusted for in the best possible way, since at every time point each individual is compared with individuals of the exact same age. Because participants were not followed from birth, the choice of age as time scale requires data to be analyzed using delayed entry.[32] This takes into account that a period of ignorance exists before an individual enters into the study, a period in which the individual may have been subjected to the effects on risk associated with visible age-related signs. Additional adjustments were for sex, or multifactorially for sex, total cholesterol, triglycerides, body mass index, hypertension, diabetes mellitus, smoking in packyears, alcohol consumption, physical inactivity, postmenopausal status and use of hormonal replacement therapy, family history of ischemic vascular disease, education and income. The assumption of linearity on the log risk scale was examined for continuous covariates (age at study entry, total cholesterol, triglycerides, and body mass index) by including each covariate squared, one at a

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time, in the fully adjusted regression models. We used piecewise linear splines with four knots placed at percentiles of the data, when adjusting for these factors in the Cox regression model. Proportionality of hazards over time was assessed by plotting –ln[-ln(survival)] versus ln(analysis time), and tested using Schoenfeld residuals. No major violations of the proportional hazards assumption were observed. Competing risk of any death was accounted for by censoring at the date of death.

Interaction between presence or absence of visible age-related signs and sex on risk of IHD, MI, and death were evaluated by the inclusion of two-factor interaction terms in the Cox regression model, using a likelihood ratio test between models excluding and including the interaction term.

Absolute 10-year risks of IHD and MI in women and men as a function of age (<40 years, 40-49 years, 50-59 years, 60-69 years, 70-79 years) and number of visible age-related signs were estimated by calculation of subhazard ratios using the method of Fine and Gray,[33] thus accounting for the competing risk of death. Data were presented as estimated incidence rates (number of events per 10 years) in percent.

For a description of the various sensitivity analyses performed, see the Supplementary Methods section.

Results

Baseline characteristics of individuals from the general population by incident IHD, MI, and death are shown in **Table 1**. During a follow-up of up to 35 years (mean follow-up 23 years), 3,401 participants developed IHD, 1,708 developed MI, and 7,722 died. Baseline characteristics of individuals excluded from the study are shown in **Supplementary Table 1.**

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Individual age-related signs and risk of ischemic heart disease and death

The associations between presence of age-related signs and risk of IHD, MI, and death are presented in **Figure 2** (unadjusted, or adjusted for age at study entry) and **Figure 3** (adjusted for age and sex, or multifactorially, see below). There was no interaction between visible age-related signs and sex on risk of either endpoint (**Supplementary Figure 1**). However, results for frontoparietal and crown top baldness are stratified by sex to account for the fact that male pattern baldness is more common in men compared to women.

All visible age-related signs associated with increased risk of IHD, MI, and total death before adjustment for potential confounders (**Figure 2**). After adjustment for age at study entry, or age and sex combined, presence of frontoparietal baldness, crown top baldness, greying of hair, earlobe crease, xanthelasmata, and arcus corneae remained associated with increased risk of IHD and/or MI, and xanthelasmata and arcus corneae in addition with total death (**Figure 2**, right columns and **Figure 3**, left columns for the individual endpoints). After multifactorial adjustment for well-known cardiovascular risk factors and markers of socioeconomic status (age, sex, total cholesterol, triglycerides, body mass index, hypertension, diabetes, smoking in packyears, alcohol consumption, physical activity, postmenopausal status, hormonal replacement therapy, education, income, and family history of ischemic vascular disease) only frontoparietal baldness, crown top baldness, earlobe crease, and xanthelasmata remained independently associated with IHD and/or MI. Frontoparietal baldness associated with multifactorially adjusted hazard ratios of 1.14 (0.98 to 1.33) for IHD and 1.40 (1.12 to 1.76) for MI in men, with similar though less significant results in women. Corresponding values for crown top baldness were 1.09 (1.00 to 1.19) and 1.13 (1.01 to 1.28) in men – again with similar findings in women. Hazard ratios for IHD and MI in individuals with earlobe crease were respectively, 1.09 (1.01 to 1.18) and 1.09

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(0.98 to 1.22). In individuals with xanthelasmata, multifactorially adjusted hazard ratios were 1.30 (1.12 to 1.50) for IHD and 1.37 (1.12 to 1.67) for MI (**Figure 3**). After multifactorial adjustment, only xanthelasmata remained associated with increased risk of total death with a hazard ratio of 1.13 (1.02 to 1.24) (**Figure 3**). Results on the association between visible age-related signs and risk of death from myocardial infarction were essentially similar to results for risk of myocardial infarction (compare **Supplementary Figure 2** with **Figure 3**, middle right column).

Multiple age-related signs and risk of ischemic heart disease and death

To account for the likelihood of having more than one visible age-related sign at the same time, we further scrutinized frontoparietal baldness, crown top baldness, earlobe crease, and xanthelasmata, all of which individually associated with an increased risk of IHD and/or MI after multifactorial adjustment. For each individual we counted the number of these age-related signs, resulting in a range from zero to a maximum of four age-related signs.

The cumulative incidences of IHD and MI increased stepwise with increasing number of age-related signs, and were similar for the crude analysis and for the analysis adjusted for age at study entry (log-rank trend, P<0.0001) (**Supplementary Figure 3** and **Figure 4**). Multifactorially adjusted hazard ratios were 1.40 (1.20 to 1.62) for IHD and 1.57 (1.28 to 1.93) for MI in individuals with 3-4 age-related signs compared to individuals with no age-related signs at baseline (P for trend <0.001) (**Figure 5**). To account for the fact that male pattern baldness is much more common in men compared to women, we also performed analyses stratified by sex; results were similar for women and men (**Supplementary Figure 3** and **Figures 4 and 5**). After multifactorial adjustment, increasing number of age-related signs did not associate with total death (**Figure 5**).

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The significant associations between increasing number of age-related signs and risk of IHD and MI were examined further by calculating absolute 10-year risks. In all age groups in both women and men, absolute 10-year risks of IHD and MI increased with increasing number of age-related signs (**Figure 6**). The highest absolute 10-year risk of IHD of 21% was in men 70-79 years of age presenting with 3-4 age-related signs. In men 70-79 years of age without age-related signs the corresponding 10-year risk of IHD was 13%. Equivalent values in women were 18% and 12%. The highest absolute 10-year risk of MI of 10% was in men aged 60-69 years presenting with 3-4 age-related signs. In men 60-69 years of age without age-related signs the corresponding 10-year risk of MI was 6%. Equivalent values in women were 7% and 4%.

Sensitivity analyses

To account for the strong association between age-related signs and chronological age we performed further adjustment for age at study entry (**Supplementary Figures 4 and 5**). The results on risk of IHD, MI, and total death were similar to those shown in **Figures 3 and 5**.

Analyses treating age-related signs, individually and combined, as time-varying covariates, were similar to the model using only the baseline assessment of age-related signs (**Supplementary Tables 2-9**).

Discussion

This is the first prospective study to find that looking old for your age is a marker of poor cardiovascular health. The principal findings are that the visible age-related signs: male pattern baldness, earlobe crease, and xanthelasmata, individually and combined, associate with increased risk of IHD and MI in the general population, independent of chronological age and other well-known cardiovascular risk factors. In contrast, greying of hair and arcus corneae associate with

increased risk of IHD and MI after adjustment for age and sex, but not after multifactorial adjustment; and facial wrinkles did not associate with risk.

Comparison with other studies

The present prospective study is substantially larger than most previous studies on the association between age-related signs and risk of cardiovascular disease. With one exception,[10] all previous studies have investigated the association between a single age-related sign and risk of cardiovascular disease, although individuals may develop several age-related signs at the same time. Therefore, we investigated both the association between individual age-related signs and combinations of several age-related signs and risk of IHD.

Most previous case-control studies on the individual age-related signs, male pattern baldness, earlobe crease or xanthelasmata, and risk of cardiovascular disease have confirmed an association, although no consensus exists on the importance of these age-related signs in clinical practice. There is a strong genetic predisposition to male pattern baldness, and several studies have suggested involvement of the androgen pathway.[34] The hair follicles are a target for androgens, and the expression of androgen receptors was significantly higher in dermal papilla cells from balding scalp compared with non-balding scalp follicles.[35] This and other observations[36;37] lead to the hypothesis that free testosterone acts on both the hair follicle and the vessel wall, leading to both male pattern baldness and proliferation of smooth muscle cells – a key event in the formation of the atherosclerotic plaque. In addition, recent genomewide association studies have revealed loci on chromosome 7 and 20 associated with male pattern baldness, suggesting a possible role for androgen-independent pathways as a common cause of male pattern baldness and cardiovascular disease.[38-40] Possible explanations for the increased risk of IHD associated with presence of earlobe crease and xanthelasmata may be altered

characteristics of the connective tissue in these individuals reflected both in the dermis and in the arterial intima. This might lead to an increased propensity to retain cholesterol in the connective tissue, which in turn could explain the association to cardiovascular disease.[18;41]

Physiological hair greying is caused by defective renewal of melanocyte stem cells, which has been suggested to be caused by accumulation of DNA damage associated with aging.[42] Since DNA damage may also be a causal factor in atherosclerosis,[43] greying of hair may be a marker of susceptibility to atherosclerosis and possibly other age-related diseases. In the present study, greying of hair did not associate with risk of IHD or MI after multifactorial adjustment, although in the 12 year follow-up of the same study, an association with myocardial infarction was found in men.[6] Facial wrinkles are strongly correlated with environmental factors such as sun exposure and smoking.[44] In agreement with this, facial wrinkles did not associate with risk of cardiovascular disease in the present study with up to 35 years follow-up, or in the same study after 12 years follow-up.[6] To our knowledge, no other studies have determined the association between greying of hair or facial wrinkles and risk of cardiovascular disease.

As previously shown,[27] arcus corneae was associated with an increased risk of IHD after adjustment for age and sex only, but did not remain associated with risk after multifactorial adjustment. In support of these findings, a recent prospective study with eight years follow-up reported similar results.[45] Thus, it seems that presence of arcus corneae reflects an adverse cardiovascular risk profile – probably in particular an adverse lipid profile.

To further study the association between age-related signs and risk of cardiovascular disease, we combined presence of frontoparietal baldness, crown top baldness, earlobe crease, and xanthelasmata, which by themselves were independently associated with risk of IHD or MI. Presence of increasing number of age-related signs from 0-4 associated with stepwise increases

in risk of both IHD and MI. The only other study that has examined the combined effects of several visible age-related signs supports our findings that coexistence of several of these associated with increases in risk of coronary artery disease above that associated with the individual signs.[10]

We calculated the absolute 10-year risk of IHD and MI and found that it increased with increasing number of visible age-related signs in all age-groups in both women and men. This may allow clinicians to use presence of visible age-related signs together with chronological age and sex in the risk assessment of individual patients, thus making sure that individuals considered at high risk are managed accordingly with respect to both lifestyle changes and LDL cholesterol-lowering therapy.[46]

Strengths and limitations of study

Our study has several strengths. We studied a homogeneous white general population of 100% Danes; we had a 74% participation rate and up to 35 years of complete follow-up. Complete information on all variables was available at baseline on 56% of all participants. Moreover, no participants used lipid-lowering therapy at baseline in 1976-78, and thus none of the lipid profiles of the participants were biased from treatment effects. This makes this study unique in its ability to evaluate the association between age-related signs and risk of cardiovascular disease.

A limitation to the generalizability of our study is that we only examined whites. The prevalence of different age-related signs, as well as the association with risk of IHD may differ among different ethnicities. Therefore, our findings may not necessarily translate to populations of other ethnicities. Another limitation is that the diagnosis of all age-related signs, though performed by trained nurses and technicians according to prespecified criteria, was based on

visual inspection, and that we did not have data to confirm the inter- and intra-observer consistency of the assessment of age-related features over the period of assessment. However, the prevalence of the age-related signs in our study corresponds well with previous reports in the literature.[12;18;19;22] Finally, although we have adjusted for a large number of covariates, an ever-present influence of unmeasured confounders may still influence our results. In particular, LDL cholesterol, HDL cholesterol, lipoprotein(a), and apolipoproteins were not measured at baseline in 1976-78, and thus were not adjusted for. However, we adjusted for total cholesterol (i.e. cholesterol in LDL, HDL, remnants, and lipoprotein(a)) and for nonfasting triglycerides. The use of cardioprotective medication over time, was not registered and accordingly not adjusted for. This however would probably have led to bias towards the null. In addition, some covariates were partly self-reported, specifically hypertension and diabetes, but could be verified for the majority by relevant ICD diagnosis, or by treatment with relevant drugs.

Conclusion

We show that male pattern baldness, earlobe crease, and xanthelasmata – alone or in combination – associate with increased risk of IHD and MI in the general population, independent of chronological age and other well-known cardiovascular risk factors. In contrast, greying of hair and arcus corneae was not associated with increased risk of IHD and MI after adjustment for these risk factors.

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Conflict of Interest Disclosures: None.

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Table 1. Baseline characteristics of individuals from the Copenhagen City Heart Study stratified by incident ischemic heart disease, myocardial infarction, and total death during follow-up.

	Ischemic heart disease		Myocardial infarction		Total death	
	No event	IHD	No event	MI	No event	Death
No. of individuals – No. (%)	7,484 (69)	3,401 (31)	9,177 (84)	1,708 (16)	3,163 (29)	7,722 (71)
Age – years	52 (42-59)	56 (49-64)*	53 (43-60)	56 (49-63)*	41 (36-48)	57 (50-64)*
Sex (F/M)	3,704/3,780	1,353/2,048*	4,483/4,694	574/1,134*	1,780/1,383	3,277/4,445*
Total cholesterol - mmol/L	5.9 (5.1-6.7)	6.2 (5.5-7.0)*	5.9 (5.2-6.7)	6.3 (5.6-7.2)*	5.6 (4.9-6.3)	6.1 (5.4-7.0)*
Triglycerides - mmol/L	1.4 (1.0-2.0)	1.6 (1.2-2.4)*	1.4 (1.0-2.1)	1.8 (1.2-2.5)*	1.2 (0.9-1.8)	1.6 (1.1-2.3)*
Body mass index - kg/m^2	24 (22-27)	26 (23-28)*	25 (22-27)	26 (23-28)*	24 (22-26)	25 (23-28)*
Hypertension – No. (%)	3,291 (44)	2,044 (60)*	4,275 (47)	1,060 (62)*	853 (27)	4,482 (58)*
Diabetes mellitus – No. (%)	162 (2)	156 (5)*	227 (2)	91 (5)*	15 (0.5)	303 (4)*
Smoking – packyears	10 (0-25)	15 (0-30)*	10 (0-26)	17 (0-30)*	3 (0-15)	16 (0-30)*
Regular alcohol consumer – No. (%)	4,110 (55)	1,807 (53)	5,006 (55)	911 (53)	1,635 (52)	4,282 (55)*
Physically inactive – No. (%)	5,414 (72)	2,528 (74)†	6,672 (73)	1,270 (74)	2,131 (67)	5,811 (75)*
Postmenopausal – No. (%)	2,256 (61)	1,076 (80)*	2,865 (64)	467 (81)*	572 (32)	2,760 (84)*
Hormonal replacement therapy – No. (%)	489 (22)	207 (19)	613 (21)	83 (18)	179 (31)	517 (19)*
Lipid-lowering therapy – No. (%)	0	0	0	0	0	0
Family history of IVD – No. (%)	2,228 (30)	1,231 (36)*	2,802 (31)	657 (38)*	901 (28)	2,558 (33)*
Education < 8 years – No. (%)	3,382 (45)	1,769 (52)*	4,232 (46)	919 (54)*	1,047 (33)	4,104 (53)*
Income < 10,000 DKK/month – No. (%)	5,905 (79)	2,789 (82)*	7,296 (80)	1,398 (82)†	2,368 (75)	6,326 (82)*
Frontoparietal baldness (F/M) – No. (%)	295(8)/ 3,220(85)	140(10)†/ 1,871(91)*	366(8)/ 4,039(86)	69(12)†/ 1,052(93)*	118(7)/ 1,055(76)	317(10)*/ 4,036(91)***
Crown top baldness (F/M) – No. (%)	29(1)/ 1,659(44)	26(2)†/ 1,099(54)*	45(1)/ 2,150(46)	10(2)/ 608(54)*	3(0.2)/ 393(28)	52(2)*/ 2,365(47)*
Greying of hair – No. (%)	2,545 (34)	1,547 (46)*	3,307 (36)	785 (46)*	487 (15)	3,605 (47)*
Facial wrinkles – No. (%)	4,006 (54)	2,197 (65)*	5,100 (56)	1,103 (65)*	1,068 (34)	5,135 (67)*
Earlobe crease – No. (%)	1,465 (20)	970 (29)*	1,934 (21)	501 (29)*	331 (10)	2,104 (27)*
Xanthelasmata – No. (%)	298 (4)	190 (6)*	382 (4)	106 (6)*	83 (3)	405 (5)*
Arcus corneae – No. (%)	1,710 (23)	1,079 (32)*	2,262 (25)	527 (31)*	244 (8)	2,545 (33)*

Data are median (interquartile range) or percent. Hypertension was use of anti-hypertensive medication, a systolic blood pressure of 140 mm Hg or greater, and/or a diastolic blood pressure of 90 mm Hg or greater. Diabetes mellitus was self-reported disease, use of insulin or oral hypoglycaemic agents, and/or non-fasting plasma glucose levels of more than 11 mmol/L (>198 mg/dL). Packyears was the accumulated smoking exposure calculated from the questionnaires. Regular alcohol consumer was consumption of alcohol at least twice weekly. Physically inactive was leisure time activity less than 4 hours weekly. Women reported menopausal status and use of hormonal replacement therapy. Family history of ischemic vascular disease (IVD) was at least one parent with a previous myocardial infarction or ischemic stroke. Education was less than 8 years of education. Income in 1976-1978 was less than 10,000 Danish kroner (DKK) per month (app. 1,730 US dollars). Frontoparietal baldness, crown top baldness, earlobe crease, xanthelasmata, and arcus corneae were all presence of the trait. Facial wrinkles were prominent facial wrinkles. Greying of hair was moderate to complete greying of hair. Individuals who dyed their hair or used a wig were excluded from the study. To convert triglycerides to mg/dL, divide by 0.0113; to convert cholesterol to mg/dL, divide by 0.0259. *P<0.001, †P<0.05 by Mann-Whitney U test or Pearson χ^2 test.

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Figure Legends:

Figure 1. Photographs of visible age-related signs. a) Frontoparietal baldness. b) Crown top baldness. c) Earlobe crease. d) Arcus corneae. e) Xanthelasmata. Photographs: Børge G. Nordestgaard and Mette Christoffersen.

Figure 2. Crude estimates and estimates adjusted for age at study entry for risk of ischemic heart disease, myocardial infarction, and total death in the Copenhagen City Heart Study in individuals with versus without moderate to complete greying of hair, prominent facial wrinkles, earlobe crease, xanthelasmata, arcus corneae, frontoparietal baldness, or crown top baldness. Hazard ratios and 95% confidence intervals for ischemic heart disease, myocardial infarction, and total death are from the Copenhagen City Heart Study 1976-1978 examination (n=10,885; follow-up up to 35 years; mean follow-up 23 years). Data are analyzed from study entry using time (in years) as the time scale. The left columns for each endpoint are crude estimates without any corrections; right columns for each endpoint are adjusted for age at study entry using piecewise linear splines. *The number indicates the upper 95% confidence interval limit, when this exceeds the width of the graph/scale of the hazard ratio.

Figure 3. Adjusted risk estimates for ischemic heart disease, myocardial infarction, and total death in the Copenhagen City Heart Study in individuals with versus without moderate to complete greying of hair, prominent facial wrinkles, earlobe crease, xanthelasmata, arcus corneae, frontoparietal baldness, or crown top baldness. Hazard ratios and 95% confidence intervals for ischemic heart disease, myocardial infarction, and total death are from the

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Copenhagen City Heart Study 1976-1978 examination (n=10,885; follow-up up to 35 years; mean follow-up 23 years). Data are analyzed using age as the time scale and left truncation. The left columns for each endpoint are adjusted for age and sex. The right columns for each endpoint are multifactorially adjusted for age, sex, total cholesterol, triglycerides, body mass index, hypertension, diabetes, smoking in packyears, alcohol consumption, physical inactivity, education, income, family history of ischemic vascular disease, and in women also for postmenopausal status and hormonal replacement therapy using piecewise linear splines for continuous covariates. *The number indicates the upper/lower 95% confidence interval limit, when this exceeds the width of the graph/scale of the hazard ratio.

Figure 4. Cumulative incidences of ischemic heart disease and myocardial infarction as a function of age in the Copenhagen City Heart Study in individuals with no (green line), one (yellow line), two (blue line) or three to four (red line) visible age-related signs. Age-related signs included are frontoparietal baldness, crown top baldness, earlobe crease, and xanthelasmata. Cumulative incidences were by the Kaplan-Meier method with age as the x-axis. IHD, ischemic heart disease; MI, myocardial infarction.

Figure 5. Risk of ischemic heart disease, myocardial infarction, and total death in the Copenhagen City Heart Study as a function of increasing numbers of visible age-related signs. Age-related signs included are frontoparietal baldness, crown top baldness, earlobe crease, and xanthelasmata. Hazard ratios and 95% confidence intervals for ischemic heart disease, myocardial infarction, and total death are from the Copenhagen City Heart Study 1976-1978 examination (n=10,885; follow-up up to 35 years; mean follow-up 23 years). Data are analyzed

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using age as the time scale and left truncation, and presented overall and stratified by sex. The left columns for each endpoint are adjusted for age and sex. The right columns for each endpoint are multifactorially adjusted for age, sex, total cholesterol, triglycerides, body mass index, hypertension, diabetes, smoking in packyears, alcohol consumption, physical inactivity, education, income, family history of ischemic vascular disease, and in women also for postmenopausal status and hormonal replacement therapy using piecewise linear splines for continuous covariates. *The number indicates the upper/lower 95% confidence interval limit, when this exceeds the width of the graph/scale of the hazard ratio.

Figure 6. Absolute 10-year risk of ischemic heart disease and myocardial infarction in the Copenhagen City Heart Study in individuals with no (green), one (yellow), two (blue) or three to four (red) visible age-related signs stratified by sex and 10-year age-groups. Age-related signs included are frontoparietal baldness, crown top baldness, earlobe crease, and xanthelasmata. Competing risk of death was accounted for using the method of Fine and Gray.[33] IHD, ischemic heart disease; MI, myocardial infarction.

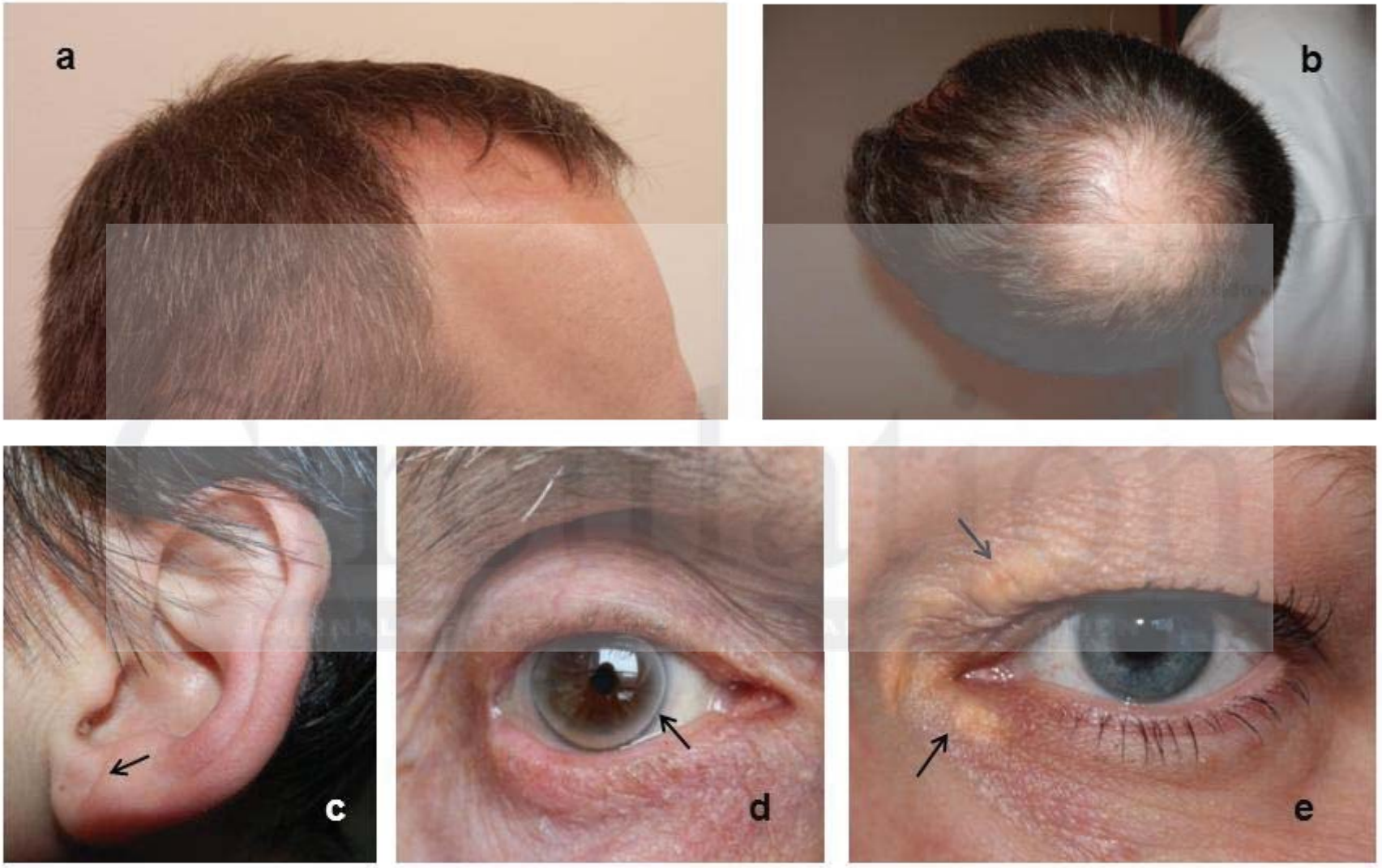

Figure 1

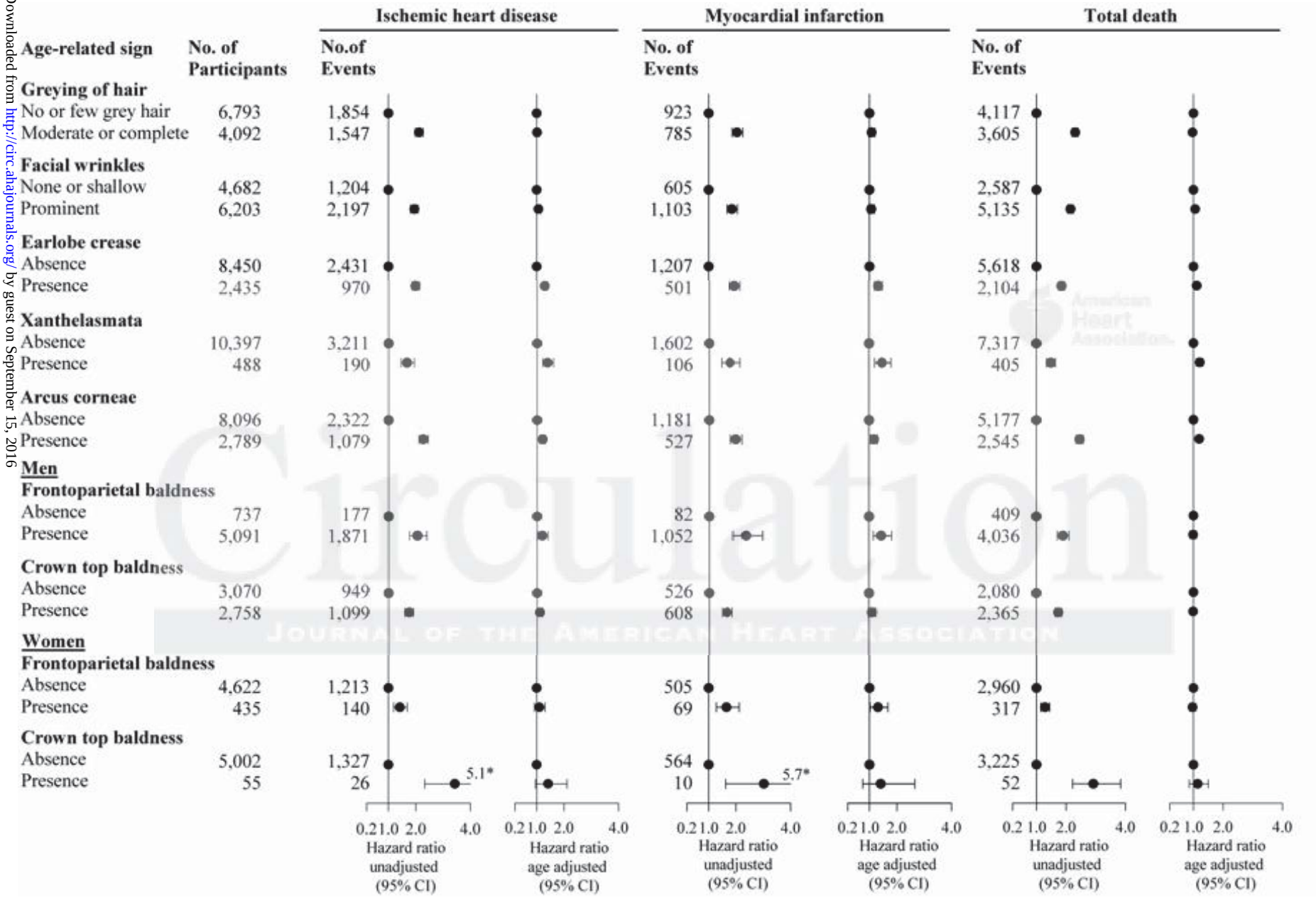

Figure 2

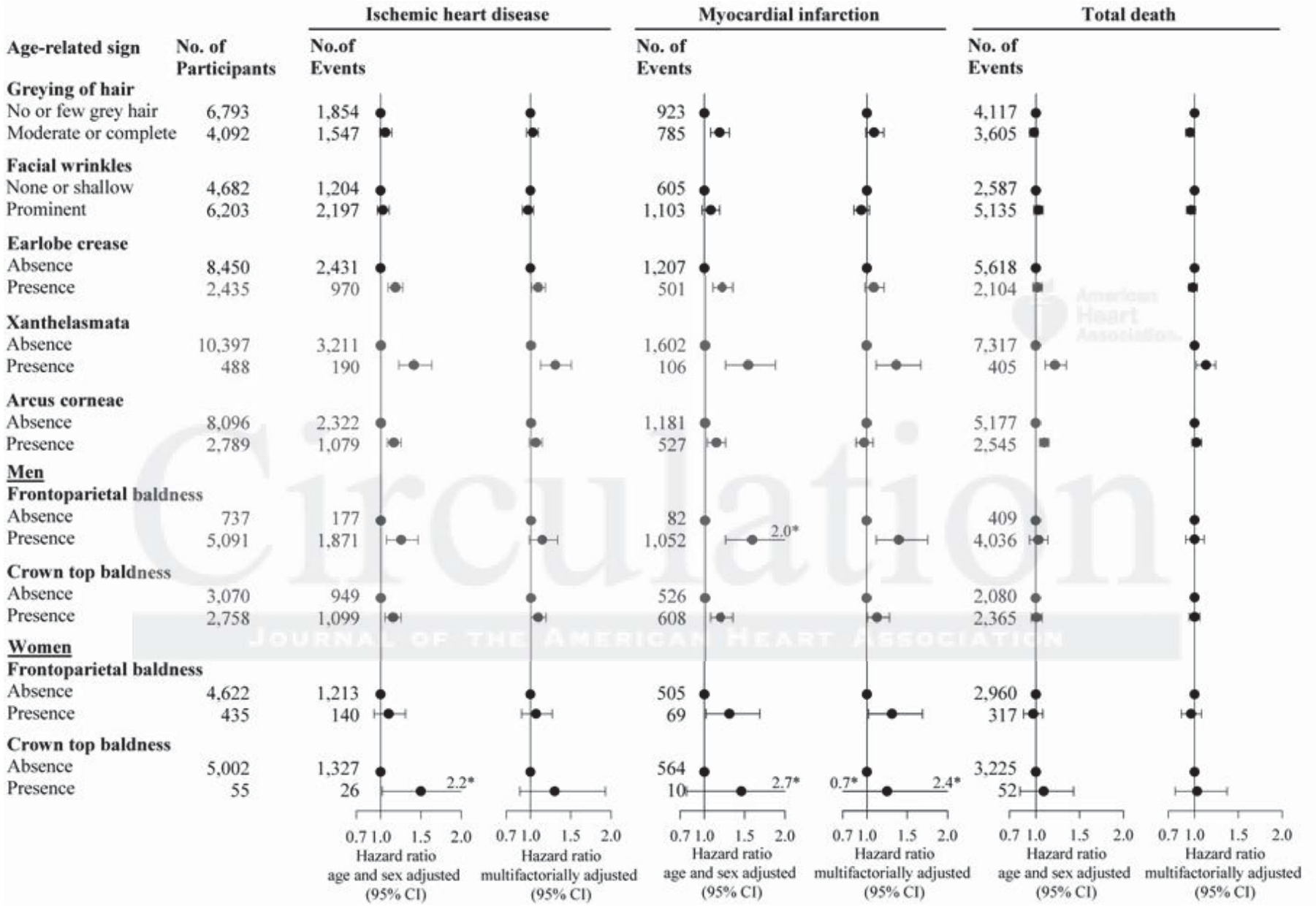

Figure 3

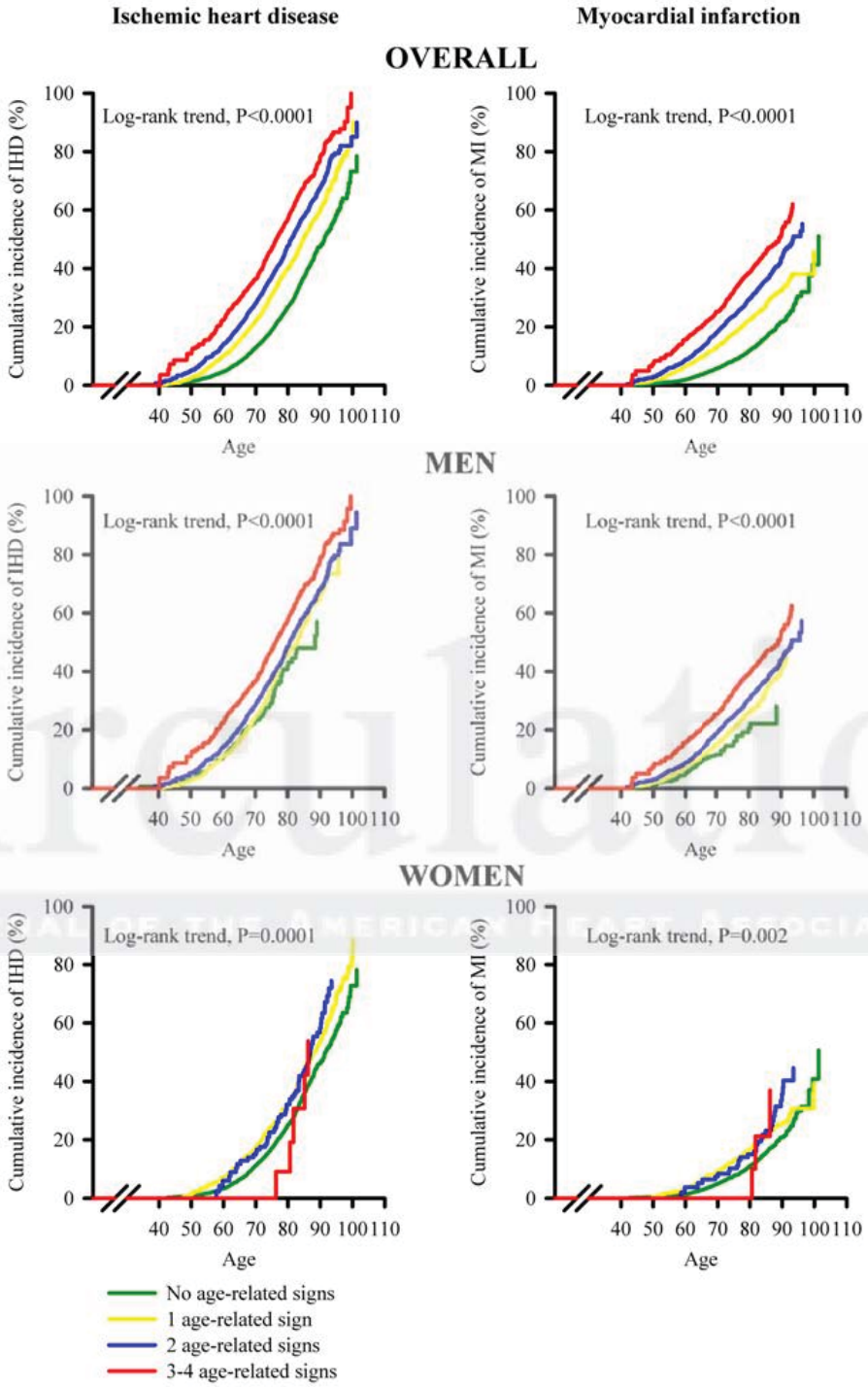

Figure 4

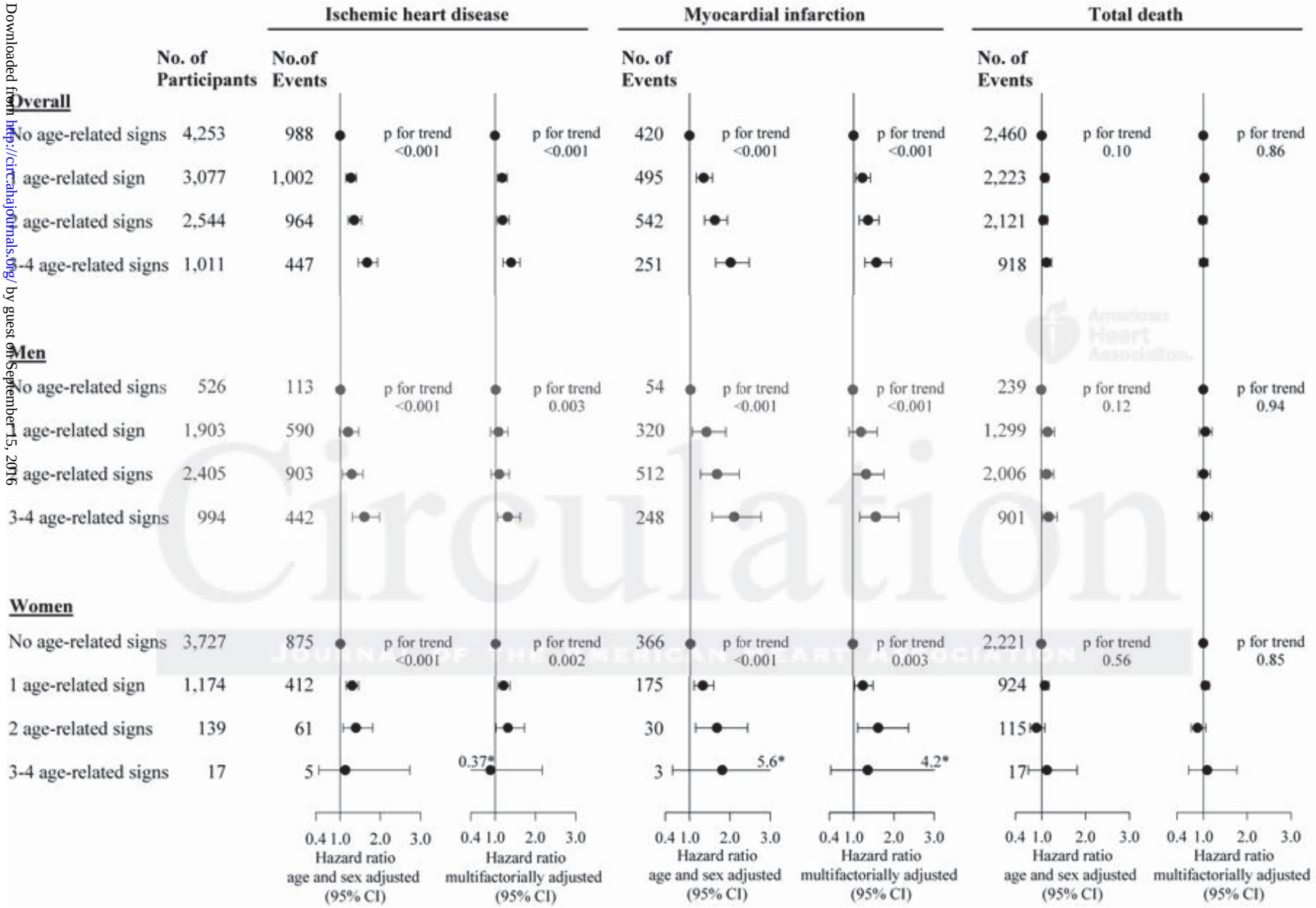

Figure 5

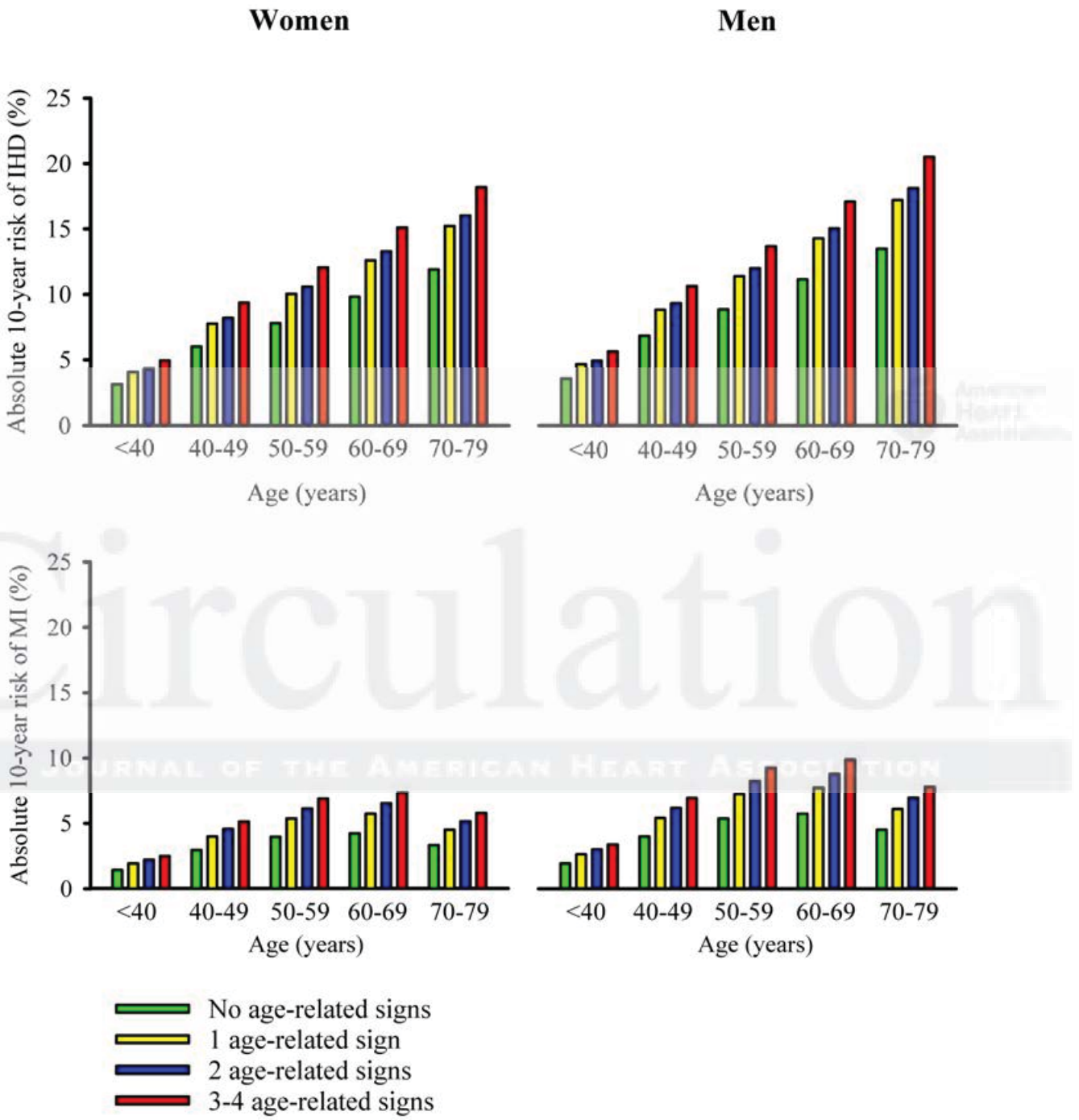

Figure 6

Visible Age-Related Signs and Risk of Ischemic Heart Disease in the General Population: A Prospective Cohort Study

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SUPPLEMENTAL MATERIAL

METHODS

Age-related signs

Presence of age-related signs was registered at the baseline 1976-1978 examination and at the first follow-up examination in 1981-1983.

The extent of male pattern baldness was described in two regions of the scalp – the frontoparietal region and the crown top region - according to Hamilton,[1] with minor modifications (for photographs of baldness in the frontoparietal and crown top region see Figure 1). In the frontoparietal region, baldness was registered as (1) no bald triangle; (2) bald triangle but >3 cm in front of the ear; or (3) bald triangle <3 cm in front of the ear. For the present study, we combined individuals into two groups: (1) no bald triangle; or (2) bald triangle. In the crown top region, baldness was registered as (1) thick hair; (2) partly thin hair; (3) bald spot; or (4) bald top and front. For the present study, we combined individuals into two groups: (1) thick hair; or (2) thin hair or bald spot (corresponding to groups 2-4).

The extent of grey hair was described as (0) dyed hair; (1) no grey hairs; (2) few grey hairs; (3) moderate grey hairs, (4) completely grey/white hair, or (5) wig. For the present study, we combined individuals into two groups: (1) no or few grey hairs; or (2) moderate to complete greying of hair. Individuals who dyed their hair or used a wig were excluded from the study.

The extent of facial wrinkles was determined in the crow's-foot area lateral to the canthus of the right eye according to Daniell,[2] with minor modifications. Participants were classified as having (1) no wrinkles; (2) one to three shallow wrinkles less than 1.5 cm in length; (3) one to six shallow wrinkles less than 3 cm in length; (4) several prominent wrinkles not more than 4 cm in length plus shallow wrinkles; or (5) several prominent

wrinkles more than 4 cm in length plus shallow wrinkles. For the present study, we combined individuals into two groups: (1) no or shallow wrinkles (corresponding to groups 1-3 above); or (2) prominent wrinkles (groups 4-5).

Earlobe crease was determined on the right ear, and was (1) no earlobe crease; (2) earlobe crease extending over less than half of the earlobe; or (3) earlobe crease extending over more than half of the earlobe (for a photograph of earlobe crease see Figure 1). For the present study, we combined individuals into two groups: (1) no earlobe crease; or (2) earlobe crease present (corresponding to groups 2 and 3 above).

Arcus corneae was determined on the right eye, and was (1) no arcus; (2) half arcus; or (3) complete arcus (for a photograph of arcus corneae see Figure 1). For the present study, we combined individuals into two groups: (1) no arcus corneae; or (2) arcus corneae present (corresponding to groups 2 and 3 above).

Xanthelasmata was determined on both eyes, and was: (1) no xanthelasmata; or (2) xanthelasmata present (for a photograph of xanthelasmata see Figure 1).

Sensitivity analyses

To account for the robust association between age-related signs and age, we included an additional adjustment for age by including age at study entry as a covariate in a separate adjusted Cox regression analysis with age as the time scale.

We further included the assessment of age-related signs at the 1981-1983 follow-up examination, thus treating age-related signs as time-varying covariates. We analyzed four different models: Model 1 and 2 included 10,885 individuals from the 1976-1978 examination of the Copenhagen City Heart Study of whom 8,579 (79%) further attended the 1981-1983 follow-up examination. For all participants, complete information on all relevant variables including age-related signs was available at baseline. In model 2 we

assumed that individuals do not acquire fewer age-related signs over time. Accordingly individuals with fewer age-related signs at the 1981-1983 examination compared to the 1976-1978 examination were reclassified using the registration from the 1976-1978 examination throughout the study period. Model 3 and 4 included 12,122 individuals from the Copenhagen City Heart Study of whom 8,601 (71%) attended both the baseline 1976-1978 examination and the 1981-1983 follow-up examination, 2,320 (19%) individuals who attended only the 1976-1978 baseline examination, and 1,201 (10%) individuals who attended only the 1981-1983 follow-up examination. Participants entered the study at the time for the first examination they attended. For all participants, complete information on all relevant variables including age-related signs was available at study entry. In model 4 we assumed that individuals do not acquire fewer age-related signs over time, accordingly individuals with fewer age-related signs at the 1981-1983 examination compared to the 1976-1978 examination were reclassified, thus using the registration from the 1976-1978 examination throughout the study period.

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FIGURE LEGENDS

Supplementary Figure 1. Risk of ischemic heart disease, myocardial infarction, and total death in the Copenhagen City Heart Study in individuals with versus without age-related signs stratified by sex.

Hazard ratios and 95% confidence intervals for ischemic heart disease, myocardial infarction, and total death are from the Copenhagen City Heart Study 1976-1978 examination (n=10,885; follow-up up to 35 years; mean follow-up 23 years). Multifactorial adjustment was for age, sex, total cholesterol, triglycerides, body mass index, hypertension, diabetes, smoking in packyears, alcohol consumption, physical inactivity, education, income, family history of ischemic vascular disease, and in women also for postmenopausal status and hormonal replacement therapy using splines for continuous covariates.

*P-value for interaction between presence or absence of age-related signs and sex on risk of ischemic heart disease, myocardial infarction, and total death. Within strata of sex, individuals without age-related signs (reference group) have a hazard ratio of one, and are not shown.

Supplementary Figure 2. Adjusted risk estimates for death from myocardial infarction in the Copenhagen City Heart Study in individuals with versus without moderate to complete greying of hair, prominent facial wrinkles, earlobe crease, xanthelasmata, arcus corneae, frontoparietal baldness, or crown top baldness.

Hazard ratios and 95% confidence intervals for ischemic heart disease, myocardial infarction, and total death are from the Copenhagen City Heart Study 1976-1978 examination (n=10,885; follow-up up to 35 years; mean follow-up 23 years). Multifactorial adjustment was for age, sex, total cholesterol, triglycerides, body mass index, hypertension, diabetes, smoking in

packyears, alcohol consumption, physical inactivity, education, income, family history of ischemic vascular disease, and in women also for postmenopausal status and hormonal replacement therapy using splines for continuous covariates. *The number indicates the upper 95% confidence interval limit, when this exceeds the width of the graph/scale of the hazard ratio.

Supplementary Figure 3. Cumulative incidence of ischemic heart disease and myocardial infarction as a function of time since study entry in the Copenhagen City Heart Study in individuals with no (green line), one (yellow line), two (blue line) or three to four (red line) visible age-related signs.

Age-related signs included are frontoparietal baldness, crown top baldness, earlobe crease, and xanthelasmata. Cumulative incidences were by the Kaplan-Meier method with time since study entry as the x-axis. IHD, ischemic heart disease; MI, myocardial infarction.

Supplementary Figure 4. Adjusted risk estimates for ischemic heart disease, myocardial infarction, and total death in the Copenhagen City Heart Study in individuals with versus without moderate to complete greying of hair, prominent facial wrinkles, earlobe crease, xanthelasmata, arcus corneae, frontoparietal baldness, or crown top baldness with additional adjustment for age at study entry.

Hazard ratios and 95% confidence intervals for ischemic heart disease, myocardial infarction, and total death are from the Copenhagen City Heart Study 1976-1978 examination (n=10,885; follow-up up to 35 years; mean follow-up 23 years). We adjusted for age using age as the time scale and left truncation and by including age at study entry as a covariate in the Cox regression. Left columns for each endpoint are adjusted for age, sex, and age at study entry. Right columns for each endpoint are multifactorially adjusted for age, sex, age at study entry,

total cholesterol, triglycerides, body mass index, hypertension, diabetes, smoking in packyears, alcohol consumption, physical inactivity, education, income, family history of ischemic vascular disease, and in women also for postmenopausal status and hormonal replacement therapy using splines for continuous covariates. *The number indicates the upper 95% confidence interval limit, when this exceeds the width of the graph/scale of the hazard ratio.

Supplementary Figure 5. Risk estimates for ischemic heart disease, myocardial infarction, and total death in the Copenhagen City Heart Study as a function of increasing number of age-related signs with additional adjustment for age at study entry.

Age-related signs included are frontoparietal baldness, crown top baldness, earlobe crease, and xanthelasmata. Hazard ratios and 95% confidence intervals for ischemic heart disease, myocardial infarction, and total death are from the Copenhagen City Heart Study 1976-1978 examination (n=10,885; follow-up up to 35 years; mean follow-up 23 years). Data are presented overall and stratified by sex. We adjusted for age using age as the time scale and left truncation and by including age at study entry as a covariate in the Cox regression. Left columns for each endpoint are adjusted for age, sex, and age at study entry. Right columns for each endpoint are multifactorially adjusted for age, sex, age at study entry, total cholesterol, triglycerides, body mass index, hypertension, diabetes, smoking in packyears, alcohol consumption, physical inactivity, education, income, family history of ischemic vascular disease, and in women also for postmenopausal status and hormonal replacement therapy using splines for continuous covariates. *The number indicates the upper 95% confidence interval limit, when this exceeds the width of the graph/scale of the hazard ratio.

TABLES

Supplementary Table 1. Baseline characteristics of individuals from the Copenhagen City Heart Study who were excluded from the analysis due to incomplete information on relevant variables stratified by incident ischemic heart disease, myocardial infarction, and total death during follow-up.

	Ischemic heart disease		Myocardial infarction		Total death	
	No event	**IHD**	**No event**	**MI**	**No event**	**Death**
No. of individuals – No. (%)	2,147 (73)	805 (27)	2,556 (87)	396 (13)	838 (28)	2,114 (72)
Age - years	53 (44-59)	57 (51-63)*	53 (45-60)	57 (51-63)*	44 (38-51)	57 (51-63)*
Sex (F/M)	1,885/262	633/172*	2,225/331	293/103*	758/80	1,760/354*
Total cholesterol - mmol/L	6.1 (5.3-6.9)	6.5 (5.7-7.2)*	6.1 (5.4-6.9)	6.7 (5.7-7.5)*	5.7 (5.0-6.4)	6.4 (5.6-7.2)*
Triglycerides - mmol/L	1.3 (1.0-1.7)	1.5 (1.1-2.1)*	1.3 (1.0-1.8)	1.6 (1.2-2.2)*	1.1 (0.9-1.5)	1.4 (1.1-2.0)*
Body mass index - kg/m^2	24 (22-27)	25 (23-28)*	24 (22-27)	25 (23-28)*	23 (21-26)	24 (22-28)*
Hypertension – No. (%)	926 (43)	473 (59)*	1,162 (45)	237 (60)*	228 (27)	1,171 (55)*
Diabetes mellitus – No. (%)	45 (2)	36 (5)*	64 (3)	17 (4)†	5 (0.6)	76 (4)*
Smoking – packyears	7 (0-19)	10 (0-23)*	7 (0-19)	11 (0-24)*	2 (0-12)	10 (0-23)*
Regular alcohol consumer – No. (%)	860 (41)	317 (40)	1,023 (41)	154 (40)	327 (40)	850 (41)
Physically inactive – No. (%)	1,674 (77)	650 (81)†	1,996 (78)	308 (78)	637 (76)	1,667 (79)
Postmenopausal – No. (%)	1,222 (65)	529 (84)*	1,494 (67)	257 (88)*	286 (38)	1,465 (83)*
Hormonal replacement therapy – No. (%)	325 (27)	112 (21)†	385 (26)	52 (20)	103 (36)	334 (23)*
Lipid-lowering therapy – No. (%)	0	0	0	0	0	0
Family history of IVD – No. (%)	722 (34)	286 (36)	873 (34)	135 (34)	272 (32)	736 (35)
Education < 8 years – No. (%)	1,045 (49)	449 (56)†	1,267 (50)	227 (58)†	330 (40)	1,164 (56)*

Income < 10,000 DKK/month – No. (%)	1,454 (80)	552 (84)†	1,732 (80)	274 (85)	505 (72)	1,501 (85)*
Frontoparietal baldness (F/M) – No. (%)	134(7)/218(86)	69(11)†/143(90)	172(8)/281(88)	31(11)/80(87)	43(6)/58(74)	160(9)†/303(91)*
Crown top baldness (F/M) – No. (%)	13(1)/107(47)	10(2)†/86(55)	18(1)/145(49)	5(2)/48(51)	2(0.3)/25(34)	21(1)†/168(54)†
Greying of hair – No. (%)	307 (40)	173 (49)†	389 (42)	91 (47)	46 (19)	434 (50)*
Facial wrinkles – No. (%)	1,042 (50)	493 (63)*	1,282 (52)	253 (66)*	270 (33)	1,265 (62)*
Earlobe crease – No. (%)	292 (15)	154 (22)*	366 (16)	80 (23)†	69 (9)	377 (20)*
Xanthelasmata – No. (%)	71 (3)	47 (6)†	89 (4)	29 (8)*	21 (3)	97 (5)†
Arcus corneae – No. (%)	394 (19)	218 (28)*	501 (21)	111 (29)*	55 (7)	557 (28)*

Data are median (interquartile range) or percent. Hypertension was use of anti-hypertensive medication, a systolic blood pressure of 140 mm Hg or greater, and/or a diastolic blood pressure of 90 mm Hg or greater. Diabetes mellitus was self-reported disease, use of insulin or oral hypoglycaemic agents, and/or non-fasting plasma glucose levels of more than 11 mmol/L (>198 mg/dL). Packyears was the accumulated smoking exposure calculated from the questionnaires. Regular alcohol consumer was consumption of alcohol at least twice weekly. Physically inactive was leisure time activity less than 4 hours weekly. Women reported menopausal status and use of hormonal replacement therapy. Family history of ischemic vascular disease (IVD) was at least one parent with a previous myocardial infarction or ischemic stroke. Education was less than 8 years of education. Income in 1976-1978 was less than 10,000 Danish kroner (DKK) per month (app. 1,340 EUROs). Frontoparietal baldness, crown top baldness, earlobe crease, xanthelasmata, and arcus corneae were all presence of the trait. Facial wrinkles were prominent facial wrinkles. Greying of hair was moderate to complete greying of hair. Individuals who dyed their hair or used a wig were excluded from the study. To convert triglycerides to mg/dL, divide by 0.0113; to convert cholesterol to mg/dL, divide by 0.0259. *P<0.001, †P<0.05 by Mann-Whitney U test or Pearson $\chi 2$ test.

Supplementary Table 2. Risk estimates for ischemic heart disease, myocardial infarction, and total death by presence or absence of greying of hair in the Copenhagen City Heart Study in models treating greying of hair as a time-varying covariate.

		Hazard ratio (95% confidence interval) Age and sex adjusted				Hazard ratio (95% confidence interval) Multifactorially adjusted			
		Model 1 (n=10,885)	**Model 2 (n=10,885)**	**Model 3 (n=12,122)**	**Model 4 (n=12,122)**	**Model 1 (n=10,885)**	**Model 2 (n=10,885)**	**Model 3 (n=12,122)**	**Model 4 (n=12,122)**
IHD	No or few grey hair	1	1	1	1	1	1	1	1
	Moderate or complete	1.03 (0.96-1.11)	1.02 (0.95-1.10)	1.03 (0.96-1.10)	1.01 (0.94-1.09)	1.00 (0.93-1.08)	0.99 (0.92-1.07)	0.98 (0.91-1.05)	0.97 (0.90-1.04)
MI	No or few grey hair	1	1	1	1	1	1	1	1
	Moderate or complete	1.17 (1.06-1.30)	1.16 (1.05-1.29)	1.18 (1.07-1.30)	1.16 (1.05-1.29)	1.09 (0.98-1.21)	1.08 (0.98-1.20)	1.09 (0.99-1.21)	1.09 (0.98-1.20)
Death	No or few grey hair	1	1	1	1	1	1	1	1
	Moderate or complete	0.94 (0.90-0.99)	0.95 (0.90-1.00)	0.94 (0.90-0.99)	0.94 (0.90-0.99)	0.92 (0.88-0.97)	0.93 (0.88-0.98)	0.92 (0.87-0.96)	0.92 (0.88-0.97)

Hazard ratios and 95% confidence intervals for ischemic heart disease, myocardial infarction, and total death are from the Copenhagen City Heart Study 1976-1978 examination and 1981-1983 examination with greying of hair treated as a time-varying covariate.

Model 1: 10,885 individuals from the 1976-1978 examination of the Copenhagen City Heart Study of whom 8,579 (79%) further attended the 1981-1983 follow-up examination. During follow-up 3,401 participants developed IHD, 1,708 developed MI, and 7,722 died.

Model 2: 10,885 individuals from the 1976-1978 examination of the Copenhagen City Heart Study of whom 8,579 (79%) further attended the 1981-1983 follow-up examination. During follow-up 3,401 participants developed IHD, 1,708 developed MI, and 7,722 died. Individuals with less greying of hair at the 1981-1983 examination compared to the 1976-1978 examination were reclassified, thus using the status for greying of hair from the 1976-1978 examination throughout the study period.

Model 3: 12,122 individuals from the Copenhagen City Heart Study of whom 8,601 (71%) attended both the baseline 1976-1978 examination and the 1981-1983 follow-up examination, 2,320 (19%) individuals who attended only the 1976-1978 baseline examination, and 1,201 (10%) individuals who attended only the 1981-1983 follow-up examination. During follow-up 3,687 participants developed IHD, 1,856 developed MI, and 8,449 died.

Model 4: 12,122 individuals from the Copenhagen City Heart Study of whom 8,601 (71%) attended both the baseline 1976-1978 examination and the 1981-1983 follow-up examination, 2,320 (19%) individuals who attended only the 1976-1978 baseline examination, and 1,201 (10%) individuals who attended only the 1981-1983 follow-up examination. During follow-up 3,687 participants developed IHD, 1,856 developed MI, and 8,449 died. Individuals with less greying of hair at the 1981-1983 examination

compared to the 1976-1978 examination were reclassified, thus using the status for greying of hair from the 1976-1978 examination throughout the study period.

Supplementary Table 3. Risk estimates for ischemic heart disease, myocardial infarction, and total death by presence or absence of facial wrinkles in the Copenhagen City Heart Study in models treating facial wrinkles as a time-varying covariate.

		Hazard ratio (95% confidence interval) Age and sex adjusted				Hazard ratio (95% confidence interval) Multifactorially adjusted			
		Model 1 (n=10,885)	**Model 2 (n=10,885)**	**Model 3 (n=12,122)**	**Model 4 (n=12,122)**	**Model 1 (n=10,885)**	**Model 2 (n=10,885)**	**Model 3 (n=12,122)**	**Model 4 (n=12,122)**
IHD	None or shallow	1	1	1	1	1	1	1	1
	Prominent	1.07 (0.99-1.15)	1.01 (0.93-1.10)	1.07 (1.00-1.15)	1.02 (0.94-1.10)	1.04 (0.97-1.12)	0.96 (0.88-1.05)	1.03 (0.96-1.10)	0.96 (0.89-1.04)
MI	None or shallow	1	1	1	1	1	1	1	1
	Prominent	1.15 (1.04-1.28)	1.10 (0.97-1.24)	1.16 (1.05-1.28)	1.11 (0.99-1.24)	1.05 (0.95-1.17)	0.97 (0.86-1.09)	1.05 (0.95-1.16)	0.98 (0.87-1.10)
Death	None or shallow	1	1	1	1	1	1	1	1
	Prominent	1.03 (0.98-1.08)	0.98 (0.92-1.03)	1.03 (0.99-1.08)	0.97 (0.92-1.03)	0.99 (0.94-1.04)	0.93 (0.88-0.99)	1.00 (0.95-1.05)	0.94 (0.89-1.00)

Hazard ratios and 95% confidence intervals for ischemic heart disease, myocardial infarction, and total death are from the Copenhagen City Heart Study 1976-1978 examination and 1981-1983 examination with facial wrinkles treated as a time-varying covariate.

Model 1: 10,885 individuals from the 1976-1978 examination of the Copenhagen City Heart Study of whom 8,579 (79%) further attended the 1981-1983 follow-up examination. During follow-up 3,401 participants developed IHD, 1,708 developed MI, and 7,722 died.

Model 2: 10,885 individuals from the 1976-1978 examination of the Copenhagen City Heart Study of whom 8,579 (79%) further attended the 1981-1983 follow-up examination. During follow-up 3,401 participants developed IHD, 1,708 developed MI, and 7,722 died. Individuals with fewer facial wrinkles at the 1981-1983 examination compared to the 1976-1978 examination were reclassified, thus using the status for facial wrinkles from the 1976-1978 examination throughout the study period.

Model 3: 12,122 individuals from the Copenhagen City Heart Study of whom 8,601 (71%) attended both the baseline 1976-1978 examination and the 1981-1983 follow-up examination, 2,320 (19%) individuals who attended only the 1976-1978 baseline examination, and 1,201 (10%) individuals who attended only the 1981-1983 follow-up examination. During follow-up 3,687 participants developed IHD, 1,856 developed MI, and 8,449 died.

Model 4: 12,122 individuals from the Copenhagen City Heart Study of whom 8,601 (71%) attended both the baseline 1976-1978 examination and the 1981-1983 follow-up examination, 2,320 (19%) individuals who attended only the 1976-1978 baseline examination, and 1,201 (10%) individuals who attended only the 1981-1983 follow-up examination. During follow-up 3,687 participants developed IHD, 1,856 developed MI, and 8,449 died. Individuals with fewer facial wrinkles at the 1981-1983 examination

compared to the 1976-1978 examination were reclassified, thus using the status for facial wrinkles from the 1976-1978 examination throughout the study period.

Supplementary Table 4. Risk estimates for ischemic heart disease, myocardial infarction, and total death by presence or absence of earlobe crease in the Copenhagen City Heart Study in models treating earlobe crease as a time-varying covariate.

		Hazard ratio (95% confidence interval) Age and sex adjusted				Hazard ratio (95% confidence interval) Multifactorially adjusted			
		Model 1 (n=10,885)	**Model 2 (n=10,885)**	**Model 3 (n=12,122)**	**Model 4 (n=12,122)**	**Model 1 (n=10,885)**	**Model 2 (n=10,885)**	**Model 3 (n=12,122)**	**Model 4 (n=12,122)**
IHD	Absence	1	1	1	1	1	1	1	1
	Presence	1.12 (1.04-1.21)	1.13 (1.05-1.21)	1.12 (1.04-1.21)	1.13 (1.05-1.21)	1.03 (0.96-1.12)	1.05 (0.97-1.12)	1.03 (0.96-1.11)	1.04 (0.97-1.12)
MI	Absence	1	1	1	1	1	1	1	1
	Presence	1.24 (1.11-1.37)	1.24 (1.12-1.37)	1.24 (1.12-1.37)	1.24 (1.13-1.37)	1.10 (0.99-1.22)	1.11 (1.00-1.23)	1.10 (1.00-1.22)	1.11 (1.01-1.22)
Death	Absence	1	1	1	1	1	1	1	1
	Presence	0.99 (0.95-1.05)	1.00 (0.95-1.05)	1.00 (0.95-1.05)	1.00 (0.95-1.04)	0.95 (0.91-1.00)	0.96 (0.91-1.00)	0.96 (0.92-1.01)	0.96 (0.92-1.01)

Hazard ratios and 95% confidence intervals for ischemic heart disease, myocardial infarction, and total death are from the Copenhagen City Heart Study 1976-1978 examination and 1981-1983 examination with earlobe crease treated as a time-varying covariate.

Model 1: 10,885 individuals from the 1976-1978 examination of the Copenhagen City Heart Study of whom 8,579 (79%) further attended the 1981-1983 follow-up examination. During follow-up 3,401 participants developed IHD, 1,708 developed MI, and 7,722 died.

Model 2: 10,885 individuals from the 1976-1978 examination of the Copenhagen City Heart Study of whom 8,579 (79%) further attended the 1981-1983 follow-up examination. During follow-up 3,401 participants developed IHD, 1,708 developed MI, and 7,722 died. Individuals with absence of an earlobe crease at the 1981-1983 examination in contrast to presence of an earlobe crease at the 1976-1978 examination were reclassified, thus using the status for earlobe crease from the 1976-1978 examination throughout the study period.

Model 3: 12,122 individuals from the Copenhagen City Heart Study of whom 8,601 (71%) attended both the baseline 1976-1978 examination and the 1981-1983 follow-up examination, 2,320 (19%) individuals who attended only the 1976-1978 baseline examination, and 1,201 (10%) individuals who attended only the 1981-1983 follow-up examination. During follow-up 3,687 participants developed IHD, 1,856 developed MI, and 8,449 died.

Model 4: 12,122 individuals from the Copenhagen City Heart Study of whom 8,601 (71%) attended both the baseline 1976-1978 examination and the 1981-1983 follow-up examination, 2,320 (19%) individuals who attended only the 1976-1978 baseline examination, and 1,201 (10%) individuals who attended only the 1981-1983 follow-up examination. During follow-up 3,687 participants developed IHD, 1,856 developed MI, and 8,449 died. Individuals with absence of an earlobe crease at the 1981-1983

examination in contrast to presence of an earlobe crease at the 1976-1978 examination were reclassified, thus using the status for earlobe crease from the 1976-1978 examination throughout the study period.

Supplementary Table 5. Risk estimates for ischemic heart disease, myocardial infarction, and total death by presence or absence of xanthelasmata in the Copenhagen City Heart Study in models treating xanthelasmata as a time-varying covariate.

		Hazard ratio (95% confidence interval) Age and sex adjusted				Hazard ratio (95% confidence interval) Multifactorially adjusted			
		Model 1 (n=10,885)	**Model 2 (n=10,885)**	**Model 3 (n=12,122)**	**Model 4 (n=12,122)**	**Model 1 (n=10,885)**	**Model 2 (n=10,885)**	**Model 3 (n=12,122)**	**Model 4 (n=12,122)**
IHD	Presence	1	1	1	1	1	1	1	1
	Absence	1.39 (1.22-1.59)	1.32 (1.18-1.49)	1.37 (1.21-1.56)	1.31 (1.17-1.47)	1.27 (1.11-1.45)	1.22 (1.08-1.37)	1.22 (1.07-1.39)	1.19 (1.06-1.33)
MI	Presence	1	1	1	1	1	1	1	1
	Absence	1.63 (1.37-1.94)	1.57 (1.34-1.83)	1.57 (1.32-1.86)	1.52 (1.31-1.77)	1.41 (1.19-1.69)	1.39 (1.18-1.62)	1.36 (1.14-1.61)	1.34 (1.15-1.56)
Death	Presence	1	1	1	1	1	1	1	1
	Absence	1.21 (1.10-1.32)	1.17 (1.08-1.26)	1.20 (1.10-1.31)	1.16 (1.07-1.25)	1.11 (1.01-1.22)	1.08 (1.00-1.17)	1.11 (1.02-1.21)	1.08 (1.00-1.17)

Hazard ratios and 95% confidence intervals for ischemic heart disease, myocardial infarction, and total death are from the Copenhagen City Heart Study 1976-1978 examination and 1981-1983 examination with xanthelasmata treated as a time-varying covariate.

Model 1: 10,885 individuals from the 1976-1978 examination of the Copenhagen City Heart Study of whom 8,579 (79%) further attended the 1981-1983 follow-up examination. During follow-up 3,401 participants developed IHD, 1,708 developed MI, and 7,722 died.

Model 2: 10,885 individuals from the 1976-1978 examination of the Copenhagen City Heart Study of whom 8,579 (79%) further attended the 1981-1983 follow-up examination. During follow-up 3,401 participants developed IHD, 1,708 developed MI, and 7,722 died. Individuals with absence of xanthelasmata at the 1981-1983 examination in contrast to presence of xanthelasmata at the 1976-1978 examination were reclassified, thus using the status for xanthelasmata from the 1976-1978 examination throughout the study period.

Model 3: 12,122 individuals from the Copenhagen City Heart Study of whom 8,601 (71%) attended both the baseline 1976-1978 examination and the 1981-1983 follow-up examination, 2,320 (19%) individuals who attended only the 1976-1978 baseline examination, and 1,201 (10%) individuals who attended only the 1981-1983 follow-up examination. During follow-up 3,687 participants developed IHD, 1,856 developed MI, and 8,449 died.

Model 4: 12,122 individuals from the Copenhagen City Heart Study of whom 8,601 (71%) attended both the baseline 1976-1978 examination and the 1981-1983 follow-up examination, 2,320 (19%) individuals who attended only the 1976-1978 baseline examination, and 1,201 (10%) individuals who attended only the 1981-1983 follow-up examination. During follow-up 3,687 participants developed IHD, 1,856 developed MI, and 8,449 died. Individuals with absence of xanthelasmata at the 1981-1983

examination in contrast to presence of xanthelasmata at the 1976-1978 examination were reclassified, thus using the status for xanthelasmata from the 1976-1978 examination throughout the study period.

Supplementary Table 6. Risk estimates for ischemic heart disease, myocardial infarction, and total death by presence or absence of arcus corneae in the Copenhagen City Heart Study in models treating arcus corneae as a time-varying covariate.

		Hazard ratio (95% confidence interval) Age and sex adjusted				Hazard ratio (95% confidence interval) Multifactorially adjusted			
		Model 1 (n=10,885)	**Model 2 (n=10,885)**	**Model 3 (n=12,122)**	**Model 4 (n=12,122)**	**Model 1 (n=10,885)**	**Model 2 (n=10,885)**	**Model 3 (n=12,122)**	**Model 4 (n=12,122)**
IHD	Absence	1	1	1	1	1	1	1	1
	Presence	1.13 (1.05-1.22)	1.12 (1.05-1.21)	1.12 (1.04-1.20)	1.11 (1.04-1.19)	1.03 (0.96-1.12)	1.02 (0.95-1.10)	1.02 (0.95-1.10)	1.01 (0.94-1.08)
MI	Absence	1	1	1	1	1	1	1	1
	Presence	1.09 (0.99-1.21)	1.10 (0.99-1.22)	1.10 (0.99-1.21)	1.09 (0.99-1.21)	0.93 (0.84-1.04)	0.93 (0.84-1.03)	0.94 (0.85-1.04)	0.94 (0.85-1.04)
Death	Absence	1	1	1	1	1	1	1	1
	Presence	1.10 (1.05-1.15)	1.09 (1.04-1.15)	1.09 (1.05-1.15)	1.08 (1.04-1.13)	1.02 (0.98-1.08)	1.01 (0.96-1.06)	1.02 (0.97-1.07)	1.01 (0.96-1.05)

Hazard ratios and 95% confidence intervals for ischemic heart disease, myocardial infarction, and total death are from the Copenhagen City Heart Study 1976-1978 examination and 1981-1983 examination with arcus corneae treated as a time-varying covariate.

Model 1: 10,885 individuals from the 1976-1978 examination of the Copenhagen City Heart Study of whom 8,579 (79%) further attended the 1981-1983 follow-up examination. During follow-up 3,401 participants developed IHD, 1,708 developed MI, and 7,722 died.

Model 2: 10,885 individuals from the 1976-1978 examination of the Copenhagen City Heart Study of whom 8,579 (79%) further attended the 1981-1983 follow-up examination. During follow-up 3,401 participants developed IHD, 1,708 developed MI, and 7,722 died. Individuals with absence of arcus corneae at the 1981-1983 examination in contrast to presence of arcus corneae at the 1976-1978 examination were reclassified, thus using the status for arcus corneae from the 1976-1978 examination throughout the study period.

Model 3: 12,122 individuals from the Copenhagen City Heart Study of whom 8,601 (71%) attended both the baseline 1976-1978 examination and the 1981-1983 follow-up examination, 2,320 (19%) individuals who attended only the 1976-1978 baseline examination, and 1,201 (10%) individuals who attended only the 1981-1983 follow-up examination. During follow-up 3,687 participants developed IHD, 1,856 developed MI, and 8,449 died.

Model 4: 12,122 individuals from the Copenhagen City Heart Study of whom 8,601 (71%) attended both the baseline 1976-1978 examination and the 1981-1983 follow-up examination, 2,320 (19%) individuals who attended only the 1976-1978 baseline examination, and 1,201 (10%) individuals who attended only the 1981-1983 follow-up examination. During follow-up 3,687 participants developed IHD, 1,856 developed MI, and 8,449 died. Individuals with absence of arcus corneae at the 1981-1983 examination in contrast to presence of arcus corneae at the 1976-1978 examination were reclassified, thus using the status for arcus corneae from the 1976-1978 examination throughout the study period.

Supplementary Table 7. Risk estimates for ischemic heart disease, myocardial infarction, and total death by presence or absence of frontoparietal baldness in the Copenhagen City Heart Study in models treating frontoparietal baldness as a time-varying covariate.

		Hazard ratio (95% confidence interval) Age and sex adjusted				Hazard ratio (95% confidence interval) Multifactorially adjusted			
		Model 1 (n=10,885)	**Model 2 (n=10,885)**	**Model 3 (n=12,122)**	**Model 4 (n=12,122)**	**Model 1 (n=10,885)**	**Model 2 (n=10,885)**	**Model 3 (n=12,122)**	**Model 4 (n=12,122)**
Men									
IHD	Absence	1	1	1	1	1	1	1	1
	Presence	1.17 (1.00-1.37)	1.26 (1.01-1.58)	1.13 (0.97-1.31)	1.17 (0.96-1.42)	1.12 (0.95-1.31)	1.21 (0.96-1.51)	1.07 (0.93-1.24)	1.11 (0.91-1.35)
MI	Absence	1	1	1	1	1	1	1	1
	Presence	1.31 (1.06-1.63)	1.63 (1.18-1.27)	1.26 (0.81-1.55)	1.44 (1.09-1.91)	1.20 (0.97-1.49)	1.49 (1.07-2.07)	1.16 (0.94-1.42)	1.31 (0.99-1.74)
Death	Absence	1	1	1	1	1	1	1	1
	Presence	0.98 (0.88-1.08)	0.99 (0.85-1.15)	0.97 (0.88-1.07)	0.95 (0.83-1.08)	0.96 (0.86-1.06)	0.98 (0.84-1.13)	0.97 (0.88-1.07)	0.95 (0.83-1.08)
Women									
IHD	Absence	1	1	1	1	1	1	1	1
	Presence	1.12 (0.97-1.29)	1.12 (0.99-1.28)	1.11 (0.97-1.28)	1.11 (0.98-1.26)	1.12 (0.97-1.29)	1.11 (0.97-1.26)	1.11 (0.96-1.27)	1.10 (0.97-1.25)
MI	Absence	1	1	1	1	1	1	1	1
	Presence	1.01 (0.80-1.26)	1.11 (0.91-1.35)	1.01 (0.81-1.26)	1.10 (0.91-1.33)	1.04 (0.82-1.30)	1.13 (0.92-1.38)	1.02 (0.82-1.27)	1.10 (0.90-1.33)
Death	Absence	1	1	1	1	1	1	1	1
	Presence	1.00 (0.91-1.09)	0.97 (0.89-1.05)	0.99 (0.91-1.09)	0.96 (0.89-1.04)	1.01 (0.91-1.11)	0.97 (0.89-1.06)	0.99 (0.90-1.08)	0.95 (0.88-1.04)

Hazard ratios and 95% confidence intervals for ischemic heart disease, myocardial infarction, and total death are from the Copenhagen City Heart Study 1976-1978 examination and 1981-1983 examination with frontoparietal baldness treated as a time-varying covariate.

Model 1: 10,885 individuals from the 1976-1978 examination of the Copenhagen City Heart Study of whom 8,579 (79%) further attended the 1981-1983 follow-up examination. During follow-up 3,401 participants developed IHD, 1,708 developed MI, and 7,722 died.

Model 2: 10,885 individuals from the 1976-1978 examination of the Copenhagen City Heart Study of whom 8,579 (79%) further attended the 1981-1983 follow-up examination. During follow-up 3,401 participants developed IHD, 1,708 developed MI, and 7,722 died. Individuals with absence of frontoparietal baldness at the 1981-1983 examination in contrast to presence of frontoparietal baldness at the 1976-1978 examination were reclassified, thus using the status for frontoparietal baldness from the 1976-1978 examination throughout the study period.

Model 3: 12,122 individuals from the Copenhagen City Heart Study of whom 8,601 (71%) attended both the baseline 1976-1978 examination and the 1981-1983 follow-up examination, 2,320 (19%) individuals who attended only the 1976-1978 baseline examination, and 1,201 (10%) individuals who attended only the 1981-1983 follow-up examination. During follow-up 3,687 participants developed IHD, 1,856 developed MI, and 8,449 died.

Model 4: 12,122 individuals from the Copenhagen City Heart Study of whom 8,601 (71%) attended both the baseline 1976-1978 examination and the 1981-1983 follow-up examination, 2,320 (19%) individuals who attended only the 1976-1978 baseline

examination, and 1,201 (10%) individuals who attended only the 1981-1983 follow-up examination. During follow-up 3,687 participants developed IHD, 1,856 developed MI, and 8,449 died. Individuals with absence of frontoparietal baldness at the 1981-1983 examination in contrast to presence of frontoparietal baldness at the 1976-1978 examination were reclassified, thus using the status for frontoparietal baldness from the 1976-1978 examination throughout the study period.

Supplementary Table 8. Risk estimates for ischemic heart disease, myocardial infarction, and total death by presence or absence of crown top baldness in the Copenhagen City Heart Study in models treating crown top baldness as a time-varying covariate.

		Hazard ratio (95% confidence interval) Age and sex adjusted				Hazard ratio (95% confidence interval) Multifactorially adjusted			
		Model 1 (n=10,885)	**Model 2 (n=10,885)**	**Model 3 (n=12,122)**	**Model 4 (n=12,122)**	**Model 1 (n=10,885)**	**Model 2 (n=10,885)**	**Model 3 (n=12,122)**	**Model 4 (n=12,122)**
Men									
IHD	Absence	1	1	1	1	1	1	1	1
	Presence	1.15 (1.05-1.26)	1.18 (1.07-1.29)	1.15 (1.06-1.25)	1.17 (1.07-1.28)	1.10 (1.01-1.21)	1.12 (1.03-1.23)	1.10 (1.01-1.20)	1.12 (1.03-1.23)
MI	Absence	1	1	1	1	1	1	1	1
	Presence	1.20 (1.07-1.36)	1.26 (1.11-1.43)	1.21 (1.08-1.36)	1.26 (1.12-1.42)	1.14 (1.01-1.29)	1.19 (1.05-1.35)	1.14 (1.02-1.29)	1.19 (1.06-1.34)
Death	Absence	1	1	1	1	1	1	1	1
	Presence	0.99 (0.93-1.05)	0.99 (0.93-1.05)	1.00 (0.94-1.06)	0.99 (0.93-1.05)	0.99 (0.93-1.06)	0.99 (0.93-1.05)	1.00 (0.94-1.06)	0.99 (0.93-1.05)
Women									
IHD	Absence	1	1	1	1	1	1	1	1
	Presence	1.25 (0.93-1.69)	1.26 (0.96-1.66)	1.27 (0.95-1.70)	1.27 (0.97-1.66)	1.08 (0.79-1.47)	1.08 (0.82-1.44)	1.14 (0.85-1.53)	1.14 (0.87-1.49)
MI	Absence	1	1	1	1	1	1	1	1
	Presence	1.03 (0.61-1.72)	1.15 (0.74-1.81)	1.09 (0.67-1.77)	1.19 (0.78-1.83)	0.91 (0.54-1.53)	1.02 (0.65-1.61)	0.96 (0.59-1.57)	1.05 (0.68-1.62)
Death	Absence	1	1	1	1	1	1	1	1
	Presence	1.00 (0.82-1.22)	0.98 (0.82-1.18)	1.01 (0.83-1.22)	0.98 (0.82-1.18)	0.98 (0.80-1.20)	0.95 (0.79-1.14)	0.96 (0.79-1.16)	0.93 (0.78-1.11)

Hazard ratios and 95% confidence intervals for ischemic heart disease, myocardial infarction, and total death are from the Copenhagen City Heart Study 1976-1978 examination and 1981-1983 examination with crown top baldness treated as a time-varying covariate.

Model 1: 10,885 individuals from the 1976-1978 examination of the Copenhagen City Heart Study of whom 8,579 (79%) further attended the 1981-1983 follow-up examination. During follow-up 3,401 participants developed IHD, 1,708 developed MI, and 7,722 died.

Model 2: 10,885 individuals from the 1976-1978 examination of the Copenhagen City Heart Study of whom 8,579 (79%) further attended the 1981-1983 follow-up examination. During follow-up 3,401 participants developed IHD, 1,708 developed MI, and 7,722 died. Individuals with absence of crown top baldness at the 1981-1983 examination in contrast to presence of crown top baldness at the 1976-1978 examination were reclassified, thus using the status for crown top baldness from the 1976-1978 examination throughout the study period.

Model 3: 12,122 individuals from the Copenhagen City Heart Study of whom 8,601 (71%) attended both the baseline 1976-1978 examination and the 1981-1983 follow-up examination, 2,320 (19%) individuals who attended only the 1976-1978 baseline examination, and 1,201 (10%) individuals who attended only the 1981-1983 follow-up examination. During follow-up 3,687 participants developed IHD, 1,856 developed MI, and 8,449 died.

Model 4: 12,122 individuals from the Copenhagen City Heart Study of whom 8,601 (71%) attended both the baseline 1976-1978 examination and the 1981-1983 follow-up examination, 2,320 (19%) individuals who attended only the 1976-1978 baseline

examination, and 1,201 (10%) individuals who attended only the 1981-1983 follow-up examination. During follow-up 3,687 participants developed IHD, 1,856 developed MI, and 8,449 died. Individuals with absence of crown top baldness at the 1981-1983 examination in contrast to presence of crown top baldness at the 1976-1978 examination were reclassified, thus using the status for crown top baldness from the 1976-1978 examination throughout the study period.

Supplementary Table 9. Risk estimates for ischemic heart disease, myocardial infarction, and total death as a function of increasing numbers of visible age-related signs in the Copenhagen City Heart Study in models treating number of age-related signs as a time-varying covariate.

		Hazard ratio (95% confidence interval) Age and sex adjusted				Hazard ratio (95% confidence interval) Multifactorially adjusted			
		Model 1 (n=10,885)	**Model 2 (n=10,885)**	**Model 3 (n=12,122)**	**Model 4 (n=12,122)**	**Model 1 (n=10,885)**	**Model 2 (n=10,885)**	**Model 3 (n=12,122)**	**Model 4 (n=12,122)**
Overall									
IHD	No age-related signs	1	1	1	1	1	1	1	1
	1 age-related sign	1.12 (1.01-1.24)	1.17 (1.05-1.30)	1.14 (1.04-1.26)	1.19 (1.08-1.32)	1.06 (0.95-1.17)	1.10 (0.99-1.22)	1.05 (0.96-1.16)	1.10 (1.00-1.22)
	2 age-related signs	1.36 (1.12-1.42)	1.32 (1.17-1.50)	1.25 (1.12-1.40)	1.31 (1.16-1.48)	1.14 (1.01-1.29)	1.19 (1.05-1.35)	1.11 (0.99-1.25)	1.17 (1.03-1.32)
	3-4 age-related signs	1.53 (1.33-1.76)	1.61 (1.40-1.86)	1.49 (1.30-1.71)	1.56 (1.36-1.79)	1.29 (1.12-1.49)	1.35 (1.17-1.56)	1.26 (1.10-1.44)	1.31 (1.14-1.51)
MI	No age-related signs	1	1	1	1	1	1	1	1
	1 age-related sign	1.13 (0.97-1.31)	1.22 (1.04-1.43)	1.15 (1.00-1.33)	1.25 (1.08-1.45)	1.03 (0.89-1.21)	1.15 (0.98-1.35)	1.00 (0.87-1.16)	1.09 (0.94-1.27)
	2 age-related signs	1.42 (1.20-1.69)	1.58 (1.32-1.90)	1.44 (1.22-1.69)	1.60 (1.34-1.90)	1.23 (1.03-1.47)	1.40 (1.16-1.69)	1.21 (1.03-1.43)	1.34 (1.12-1.60)
	3-4 age-related signs	1.78 (1.46-2.16)	2.06 (1.68-2.53)	1.72 (1.42-2.08)	1.98 (1.63-2.41)	1.40 (1.15-1.71)	1.65 (1.34-2.03)	1.35 (1.12-1.64)	1.55 (1.27-1.89)
Death	No age-related signs	1	1	1	1	1	1	1	1
	1 age-related sign	1.02 (0.95-1.09)	1.03 (0.97-1.11)	1.02 (0.96-1.08)	1.02 (0.96-1.09)	0.99 (0.93-1.06)	1.00 (0.94-1.08)	0.99 (0.93-1.05)	0.99 (0.93-1.06)
	2 age-related signs	1.01 (0.94-1.09)	0.99 (0.92-1.08)	1.02 (0.94-1.10)	0.99 (0.92-1.07)	0.97 (0.89-1.05)	0.95 (0.87-1.03)	0.97 (0.90-1.05)	0.94 (0.87-1.02)
	3-4 age-related signs	1.04 (0.95-1.15)	1.02 (0.93-1.12)	1.04 (0.95-1.14)	1.01 (0.92-1.10)	0.98 (0.89-1.07)	0.94 (0.86-1.04)	0.98 (0.89-1.07)	0.94 (0.85-1.03)

		Hazard ratio (95% confidence interval) Age and sex adjusted				Hazard ratio (95% confidence interval) Multifactorially adjusted			
		Model 1 (n=10,885)	**Model 2 (n=10,885)**	**Model 3 (n=12,122)**	**Model 4 (n=12,122)**	**Model 1 (n=10,885)**	**Model 2 (n=10,885)**	**Model 3 (n=12,122)**	**Model 4 (n=12,122)**
Men									
IHD	No age-related signs	1	1	1	1	1	1	1	1
	1 age-related sign	1.13 (0.91-1.41)	1.25 (0.92-1.71)	1.02 (0.84-1.25)	1.02 (0.79-1.32)	1.06 (0.85-1.32)	1.18 (0.87-1.61)	0.96 (0.78-1.17)	0.95 (0.74-1.23)
	2 age-related signs	1.29 (1.04-1.59)	1.44 (1.06-1.95)	1.18 (0.97-1.42)	1.19 (0.92-1.52)	1.14 (0.92-1.41)	1.28 (0.94-1.73)	1.04 (0.86-1.26)	1.05 (0.81-1.34)
	3-4 age-related signs	1.58 (1.26-1.97)	1.76 (1.29-2.40)	1.44 (1.18-1.77)	1.45 (1.12-1.88)	1.33 (1.06-1.66)	1.48 (1.08-2.02)	1.21 (0.99-1.49)	1.22 (0.94-1.57)
MI	No age-related signs	1	1	1	1	1	1	1	1
	1 age-related sign	1.19 (0.88-1.61)	1.35 (0.87-2.09)	1.06 (0.81-1.39)	1.06 (0.74-1.61)	1.06 (0.79-1.43)	1.20 (0.77-1.86)	0.94 (0.71-1.23)	0.93 (0.65-1.33)
	2 age-related signs	1.47 (1.10-1.96)	1.73 (1.12-2.66)	1.36 (1.04-1.76)	1.42 (1.00-2.01)	1.23 (0.92-1.64)	1.42 (0.92-2.19)	1.13 (0.87-1.47)	1.16 (0.82-1.64)
	3-4 age-related signs	1.88 (1.39-2.55)	2.28 (1.47-3.53)	1.69 (1.29-2.23)	1.82 (1.28-2.60)	1.47 (1.08-1.99)	1.75 (1.13-2.71)	1.36 (0.99-1.73)	1.39 (0.98-1.98)
Death	No age-related signs	1	1	1	1	1	1	1	1
	1 age-related sign	1.03 (0.89-1.18)	1.07 (0.87-1.31)	0.99 (0.87-1.13)	0.98 (0.82-1.17)	0.99 (0.86-1.15)	1.03 (0.84-1.27)	0.98 (0.85-1.12)	0.96 (0.81-1.15)
	2 age-related signs	1.02 (0.89-1.18)	1.05 (0.86-1.28)	1.00 (0.88-1.13)	0.97 (0.81-1.15)	0.96 (0.84-1.11)	0.98 (0.80-1.20)	0.96 (0.85-1.10)	0.93 (0.78-1.10)
	3-4 age-related signs	1.06 (0.91-1.22)	1.07 (0.87-1.31)	1.03 (0.89-1.18)	0.98 (0.83-1.17)	0.99 (0.86-1.15)	0.98 (0.80-1.21)	0.98 (0.85-1.12)	0.92 (0.77-1.10)

		Hazard ratio (95% confidence interval) Age and sex adjusted				Hazard ratio (95% confidence interval) Multifactorially adjusted			
		Model 1 (n=10,885)	**Model 2 (n=10,885)**	**Model 3 (n=12,122)**	**Model 4 (n=12,122)**	**Model 1 (n=10,885)**	**Model 2 (n=10,885)**	**Model 3 (n=12,122)**	**Model 4 (n=12,122)**
Women									
IHD	No age-related signs	1	1	1	1	1	1	1	1
	1 age-related sign	1.13 (1.00-1.27)	1.17 (1.04-1.31)	1.14 (1.01-1.27)	1.17 (1.05-1.31)	1.05 (0.93-1.19)	1.09 (0.97-1.22)	1.06 (0.94-1.18)	1.09 (0.98-1.22)
	2 age-related signs	1.27 (1.03-1.57)	1.28 (1.06-1.55)	1.27 (1.03-1.56)	1.27 (1.05-1.53)	1.18 (0.96-1.46)	1.20 (0.99-1.45)	1.19 (0.97-1.46)	1.19 (0.99-1.44)
	3-4 age-related signs	0.88 (0.44-1.77)	1.13 (0.62-2.06)	0.87 (0.43-1.75)	1.12 (0.61-2.03)	0.77 (0.38-1.55)	0.94 (0.51-1.72)	0.79 (0.39-1.59)	0.96 (0.52-1.74)
MI	No age-related signs	1	1	1	1	1	1	1	1
	1 age-related sign	1.10 (0.91-1.32)	1.20 (1.01-1.44)	1.12 (0.94-1.33)	1.20 (1.01-1.42)	0.97 (0.80-1.16)	1.08 (0.90-1.29)	0.98 (0.82-1.17)	1.07 (0.90-1.27)
	2 age-related signs	1.60 (1.19-2.15)	1.62 (1.23-2.13)	1.54 (1.15-2.06)	1.55 (1.19-2.03)	1.53 (1.14-2.07)	1.54 (1.17-2.03)	1.46 (1.09-1.96)	1.46 (1.11-1.91)
	3-4 age-related signs	0.55 (0.14-2.23)	1.34 (0.55-3.24)	0.54 (0.13-2.18)	1.29 (0.53-3.13)	0.50 (0.13-2.04)	1.13 (0.46-2.75)	0.48 (0.12-1.95)	1.06 (0.44-2.59)
Death	No age-related signs	1	1	1	1	1	1	1	1
	1 age-related sign	1.02 (0.95-1.10)	1.04 (0.96-1.12)	1.01 (0.94-1.09)	1.02 (0.95-1.10)	1.00 (0.93-1.08)	1.02 (0.95-1.10)	0.98 (0.91-1.06)	0.99 (0.92-1.07)
	2 age-related signs	1.00 (0.87-1.15)	0.95 (0.83-1.07)	1.02 (0.89-1.17)	0.96 (0.85-1.09)	0.96 (0.84-1.11)	0.91 (0.80-1.04)	0.98 (0.85-1.12)	0.92 (0.81-1.05)
	3-4 age-related signs	0.94 (0.63-1.39)	1.02 (0.72-1.44)	0.92 (0.62-1.37)	1.01 (0.71-1.42)	0.86 (0.58-1.29)	1.04 (0.66-1.33)	0.84 (0.56-1.25)	0.88 (0.62-1.25)

Hazard ratios and 95% confidence intervals for ischemic heart disease, myocardial infarction, and total death are from the Copenhagen City Heart Study 1976-1978 examination and 1981-1983 examination with number of age-related signs treated as a time-varying covariate.

Model 1: 10,885 individuals from the 1976-1978 examination of the Copenhagen City Heart Study of whom 8,579 (79%) further attended the 1981-1983 follow-up examination. During follow-up 3,401 participants developed IHD, 1,708 developed MI, and 7,722 died.

Model 2: 10,885 individuals from the 1976-1978 examination of the Copenhagen City Heart Study of whom 8,579 (79%) further attended the 1981-1983 follow-up examination. During follow-up 3,401 participants developed IHD, 1,708 developed MI, and 7,722 died. Individuals with fewer age-related signs at the 1981-1983 examination compared to the 1976-1978 examination were reclassified, thus using the number of age-related signs from the 1976-1978 examination throughout the study period.

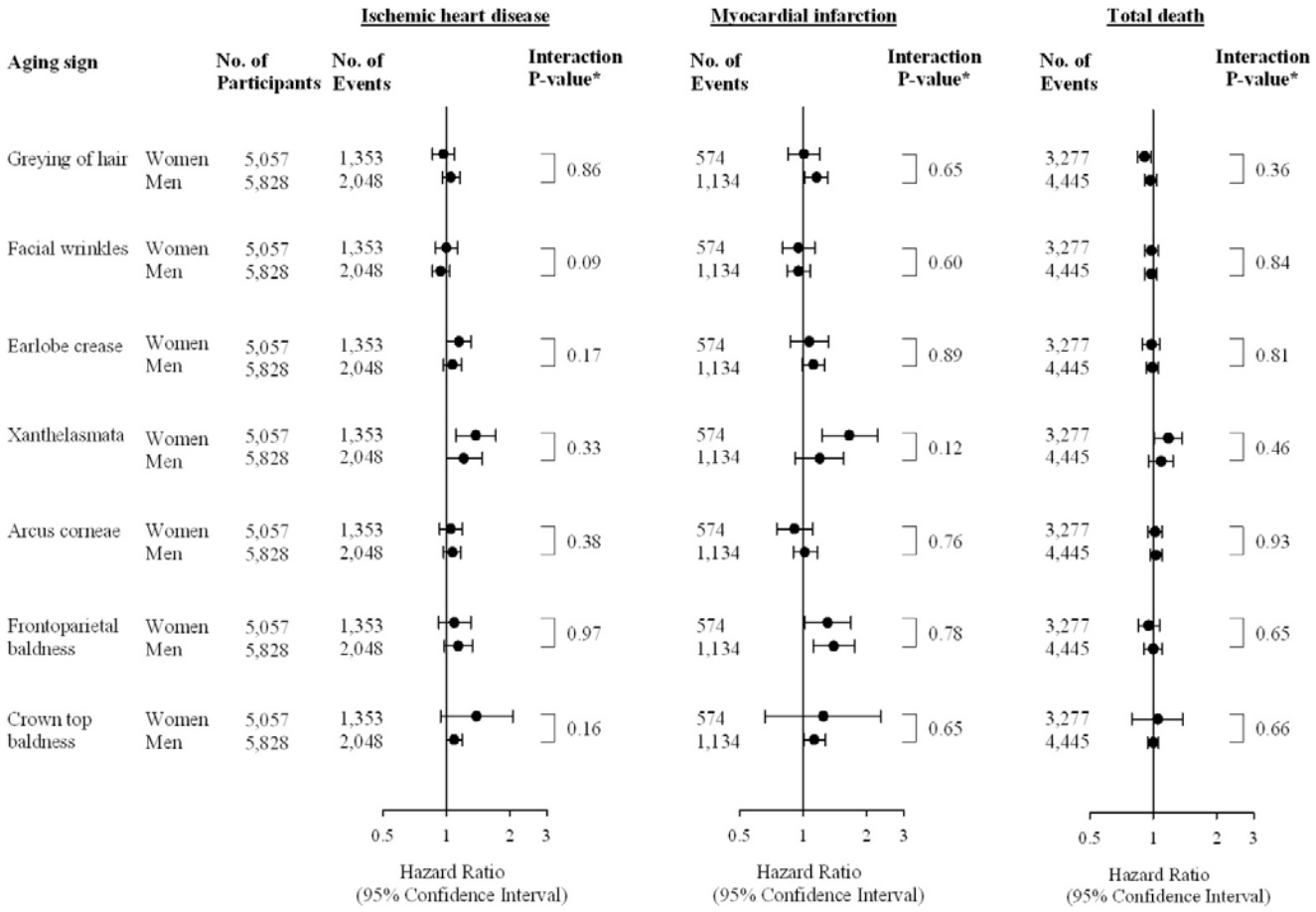
Model 3: 12,122 individuals from the Copenhagen City Heart Study of whom 8,601 (71%) attended both the baseline 1976-1978 examination and the 1981-1983 follow-up examination, 2,320 (19%) individuals who attended only the 1976-1978 baseline examination, and 1,201 (10%) individuals who attended only the 1981-1983 follow-up examination. During follow-up 3,687 participants developed IHD, 1,856 developed MI, and 8,449 died.

Model 4: 12,122 individuals from the Copenhagen City Heart Study of whom 8,601 (71%) attended both the baseline 1976-1978 examination and the 1981-1983 follow-up examination, 2,320 (19%) individuals who attended only the 1976-1978 baseline examination, and 1,201 (10%) individuals who attended only the 1981-1983 follow-up examination. During follow-up 3,687 participants developed IHD, 1,856 developed MI, and 8,449 died. Individuals with fewer age-related signs at the 1981-1983

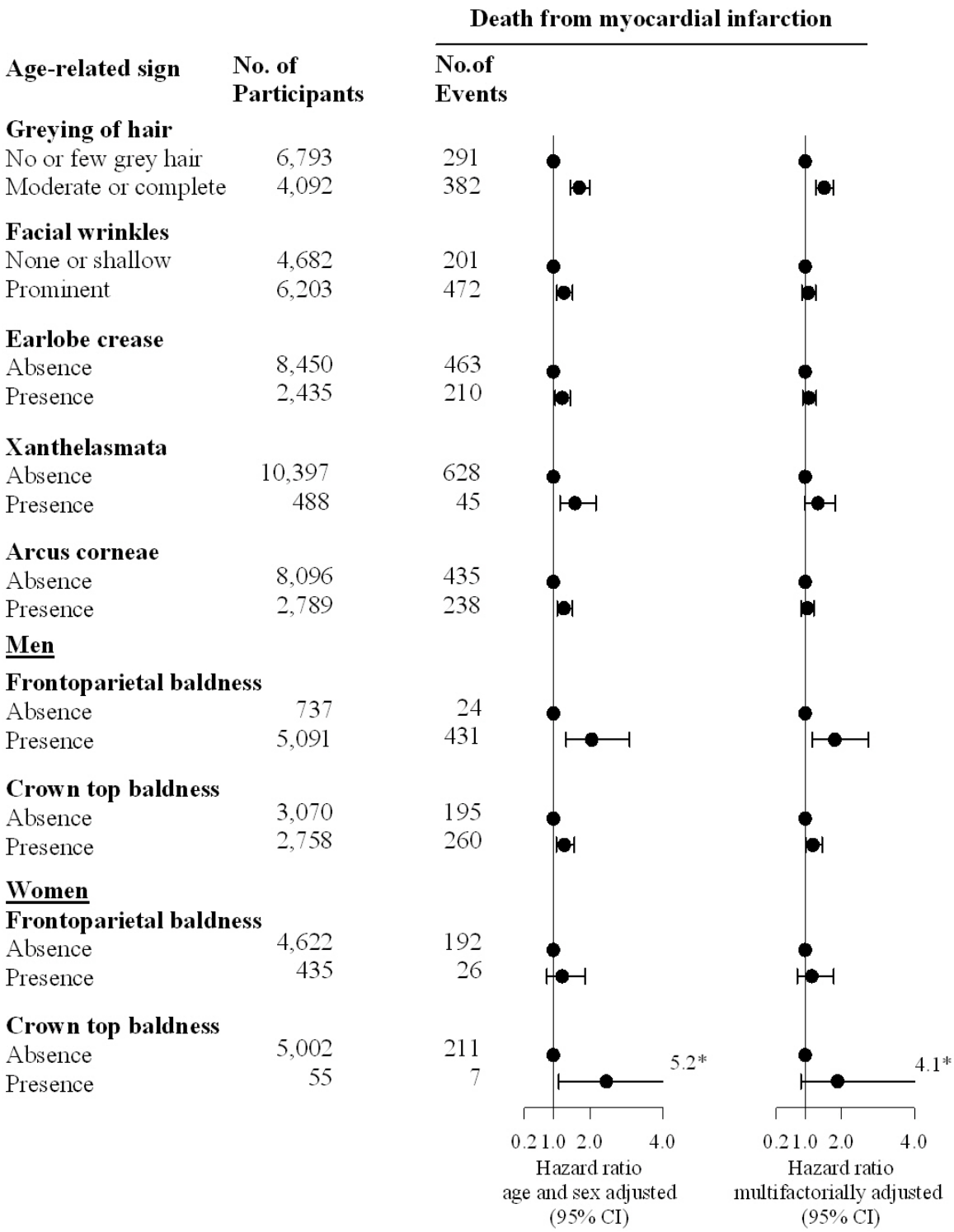
examination compared to the 1976-1978 examination were reclassified, thus using the number of age-related signs from the 1976-1978 examination throughout the study period.

FIGURES

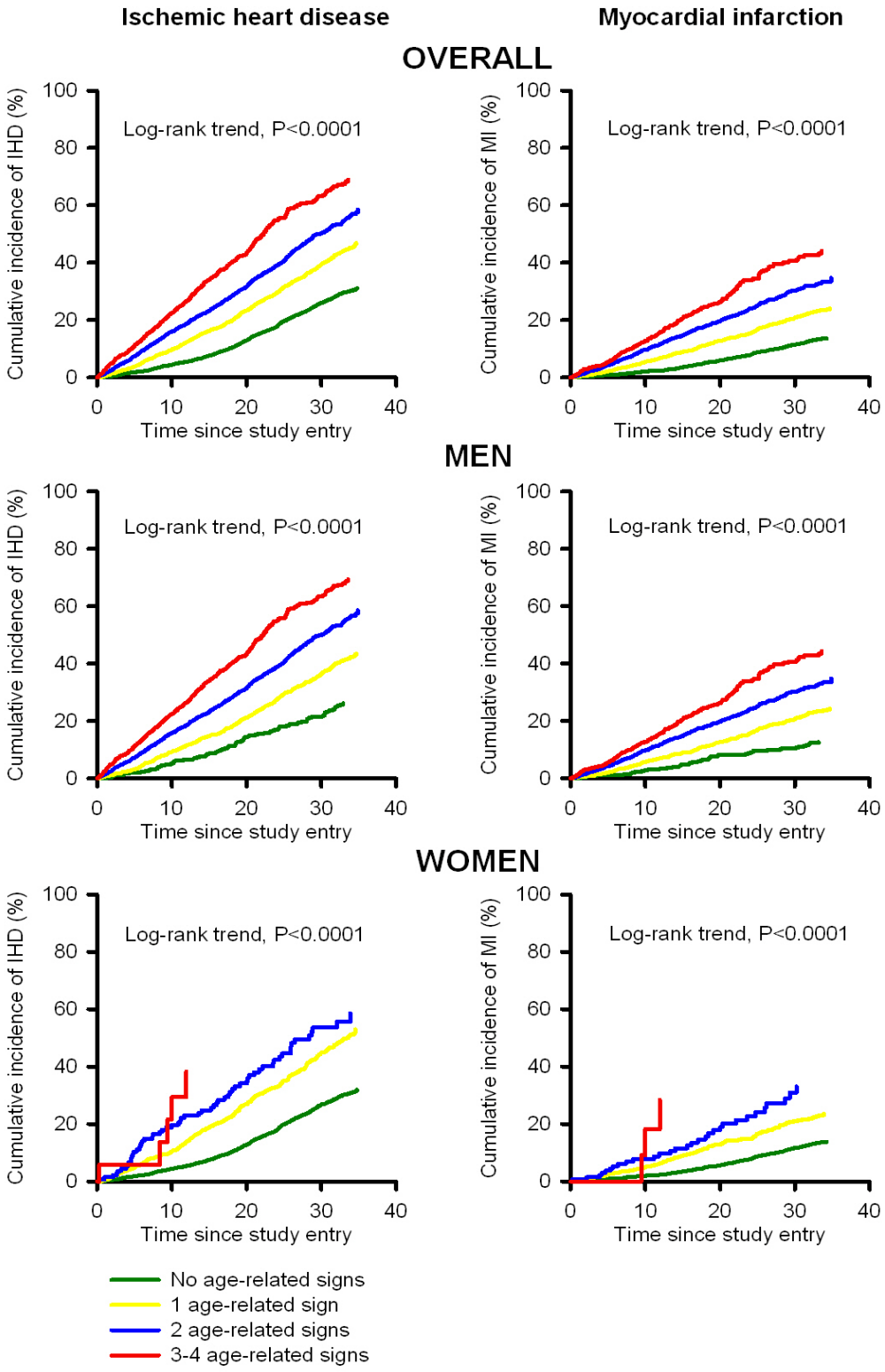
Supplementary Figure 1



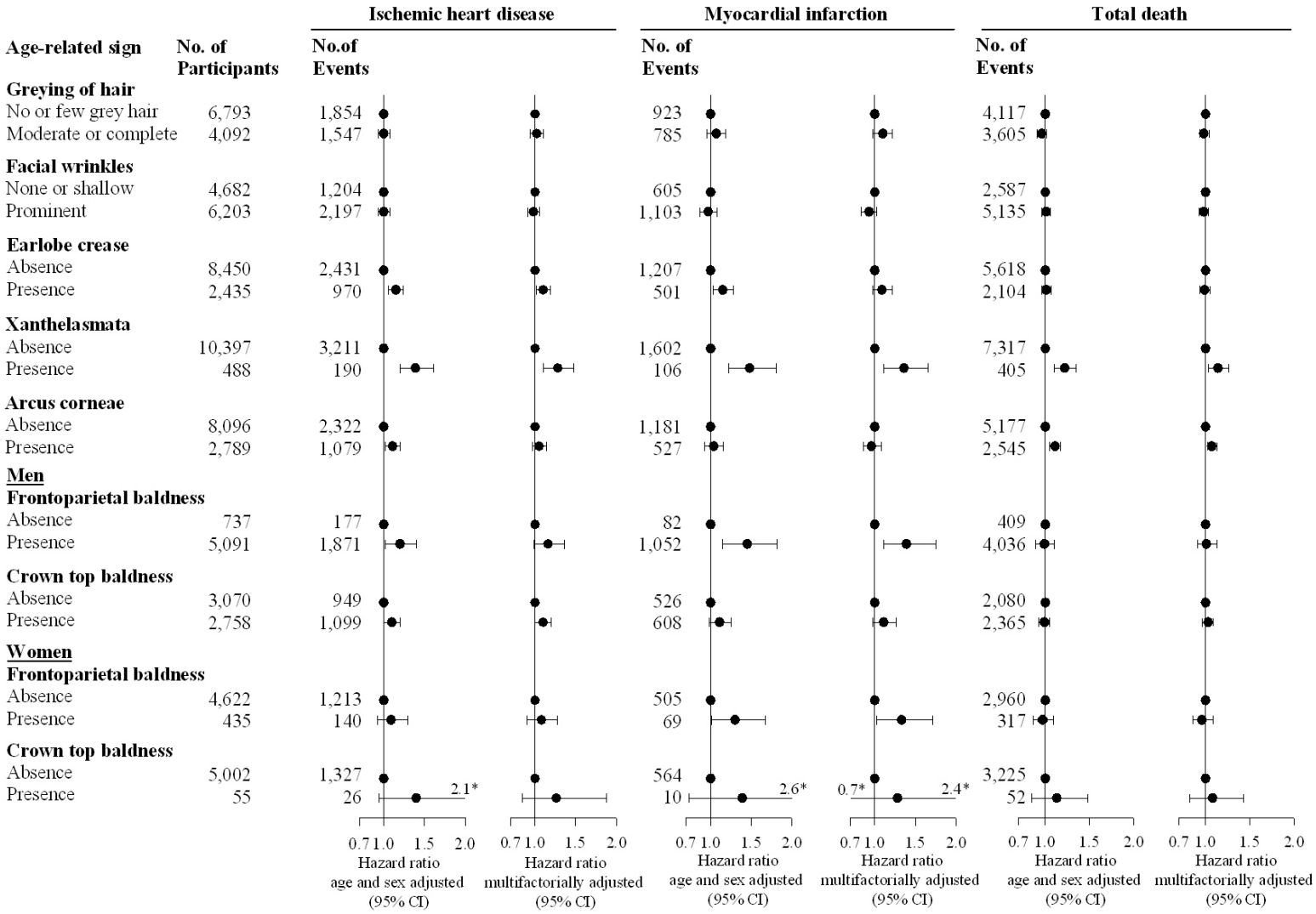
Supplementary Figure 2



Supplementary Figure 3



Supplementary Figure 4



Supplementary Figure 5