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Original Article

HEALTHY AGING RESEARCH

Physical activity and the development of visible age-related signs in the general population: a prospective cohort study

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Background: Physical inactivity is a well-known risk factor for multiple diseases and may be associated with increased aging of the body. Visible age-related signs indicate biological age, as individuals appearing old for their age are more likely to be at poor health, compared with people appearing their actual age. The aim of this study was to test the hypothesis that physical activity is associated with biological aging, indicated by 5 visible age-related signs (arcus corneae, xanthelasmata, earlobe crease, facial wrinkles, and pattern baldness).

Materials and Method: We used information from 11,613 individuals in the Copenhagen City Heart Study. Physical activity and other lifestyle factors were assessed prospectively and visible age-related signs were inspected at subsequent examinations. We performed interval censored survival analyses, using a SE allowing for intragroup correlation, as some individuals were included twice.

Results: Physical activity was not related to the risk of developing earlobe crease, facial wrinkles or pattern baldness. Among men, but not women, moderate physical activity was associated to a lower risk of developing xanthelasmata compared with inactivity (hazard ratio, 0.68; 95% confidence interval, 0.49–0.95) while among women, vigorous physical activity was associated to a higher risk of arcus cornea (hazard ratio, 1.51; 95% confidence interval, 1.05–2.15).

Conclusion: Independent of chronological age, physical activity was not related to visible signs of aging. Aging is a part of a complex multifactorial process. This is the first prospective study to investigate the relation between physical activity level and looking old for your age.

Keywords: Aging, Visible age-related signs, Physical activity

Aging is inevitable, but some show slower declines than others. Looking old for one's age is associated with poor health, cardiovascular disease and early death[1–3] implying that biological age to some extent can be observed visually. Regular physical activity is associated with longer life expectancy[4] and lower risk of several diseases including cardiovascular diseases, diabetes and some types of cancers[5,6], conditions whose incidence increases steeply by age. Physical activity tends to decline with age[7] but possibly maintaining a physically active lifestyle can slow down the aging process. How physical activity is related to the process of aging is not completely clear, but possibly related to changes in myokines and telemore length. There is increasing evidence that regular physical activity is associated to longer leukocyte telomere length which, in turn, is associated with lower cardiovascular and all-cause mortality[8]. A study involving mice have shown that exercise could delay or even undo the signs of early aging in these animals[9]. However, this remains to be confirmed in human observational studies. Previous observational studies on the association between physical activity and skin aging have found no correlations[10,11]. However, skin aging is largely influenced by exposure to sunlight[12] and therefore, we also need to look at other visual signs of aging.

The normal aging process is characterized by progressive stiffening in collagen-rich connective tissues such as skin, cornea, cartilage, lung, and arteries[13]. Some visible age-related signs have been found to predict cardiovascular disease and mortality: earlobe crease (a diagonal fold or wrinkle in the skin of the earlobe)[14–17] and xanthelasmata (yellow-orange plaques on the eyelids or median canthus)[1,2]. Also, some studies have found that vertex baldness may be a marker for increased risk of coronary heart disease[18,19], while the evidence regarding arcus corneae (white or gray opaque ring in the corneal margin of eye) as a predictive marker of coronary heart disease and early death is unclear[2,20,21].

Given that visible age-related signs can be interpreted as markers of biological age, we hypothesize that regular moderate-to-vigorous physical activity delays the aging process. Therefore, the aim of this study was to investigate the association between

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physical activity and biological aging, indicated by 5 visible age-related signs: arcus corneae, xanthelasmata, earlobe crease, facial wrinkles, and pattern baldness.

Materials and methods

Study design and population

The Copenhagen City Heart Study is a prospective study of the Danish general population above 20 years living in the Copenhagen area initiated in 1976–1978 (number of participants 14,223; response rate 74%) with follow-up examinations in 1981–1983, 1991–1994, and 2001–2003. Enrollment and examination procedures have been described in more detail elsewhere[22,23]. Before the clinical health examination, participants completed a questionnaire (including questions on physical activity). All participants gave informed consent and the ethics committee for Copenhagen and Frederiksberg approved the study (100.2039/91). Presences of visible age-related signs were inspected at the 1976–1978, 1981–1983, and 1991–1994 examination. Therefore, development of the age-related signs could occur in 3 time periods: between the 1976–1978 and the 1981–1983 examination, between the 1981–1983 and 1991–1994 examination and between the 1976 and 1991–94 examination. Incident cases of the age-related signs from all 3 periods were included. The mean follow-up time was 11.5 years.

After exclusion of participants with missing information on physical activity, education, body mass index (BMI), alcohol intake and smoking status, 12,240 individuals remained that participated in both a baseline and at least 2 of the 3 examination: 4591 participated in 1976 and 1981–1983 examinations, 500 participated in 1976 and 1991–1994 examinations, 734 participated in 1981–1983 examinations and 6415 participated in all 3 examinations, and were included in both the first and the second period. In total, we used information from 11,613 participants. We excluded participants who had already developed a specific age-related sign at baseline; thus, the number of participants in the analysis differed for the 4 outcomes.

Assessments

Visible age-related signs

Arcus corneae was determined on the right eye and coded as (1) no arcus corneae or (2) arcus corneae present (half arcus; or complete arcus). Xanthelasmata was determined on both eyes as: (1) no xanthelasmata or (2) xanthelasmata present. Earlobe crease was determined on the right ear as (1) no earlobe crease or (2) earlobe crease present. The extent of facial wrinkles in the crow's-foot area (lateral to the canthus of the right eye) was determined according to Daniell[24], with minor modifications. Participants were classified as having (1) no wrinkles or 1–6 shallow wrinkles <3 cm in length or (2) several prominent wrinkles. Pattern baldness was described in 2 regions of the scalp —frontoparietal and crown top—according to Hamilton[25], with minor modifications. In the frontoparietal region, baldness was registered as (1) no bald triangle or (2) bald triangle bald triangle. In the crown top region, baldness was registered as (1) thick hair or partly thin hair or (3) bald spot or bold top and front. The physical manifestation of the visible age-related signs was described in detail and visually illustrated in Christoffersen et al[1]. Facial wrinkles and pattern baldness were not examined in the 1991–1993 examination.

Physical activity

Leisure time physical activity was assessed at each examination by questionnaire as the average physical activity level during the last year, graded in 4 levels based on a modified version of a self-administrated questionnaire constructed by Saltin and Grimby[26,27]: (1) being almost entirely inactive (eg, reading, watching television) or engaging in light physical activity for <2 hours per week; (2) engaging in light physical activity for 2–4 hours per week (eg, walking, cycling, light gardening, light physical exercise); (3) engaging in light physical activity for > 4 hours per week or more vigorous activity for 2–4 hours per week (eg, brisk walking, fast cycling, heavy gardening, sports that cause perspiration or exhaustion; (4) engaging in highly vigorous physical activity for more than 4 hours per week, regular heavy exercise, or competitive sports several times per week. This physical activity questionnaire has been shown to discriminate between inactive persons and their more active counterparts with respect to maximal oxygen uptake[26] and has shown the ability to predict mortality[28].

Covariates

The following covariates were considered potential confounders: age at the baseline, education (younger than 8, 8–10, and 11 y and older), BMI (measured weight in kilograms divided by height in meters squared), alcohol intake (drinks per week), smoking dose (pack-years), self-reported diabetes mellitus (yes, no), self-reported cardiovascular disease (stroke and myocardial infarct) (yes, no), and hypertension defined as a systolic blood pressure > 140 mm Hg or a diastolic blood pressure > 90 mm Hg (yes, no).

Statistical analysis

Analyses on the 5 visible age-related signs were performed separately 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 2 time periods, we used a robust SE allowing for intragroup correlation, relaxing the usual requirement that the observations be independent. Calendar time was used as the underlying axis in the analysis. Age was adjusted for by a linear and a squared term as the *P*-value for the squared term was low ($P < 0.001$). BMI, alcohol, and smoking was entered as linear variables. Analyses were stratified by sex.

The prevalence of the 5 visible age-related signs by age (**Fig. 1**) 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. Crown top baldness is only showed for men, as very few women develop these age-related signs (n = 1).

The association between life time smoking exposure (pack-years) and the risk of developing visible signs of ageing as well as between physical activity and all-cause mortality were analyzed in parallel as positive controls. Also, sensitivity analyses were performed using an alternative analysis strategy, in order to test if competing risk from death would have affected results, which

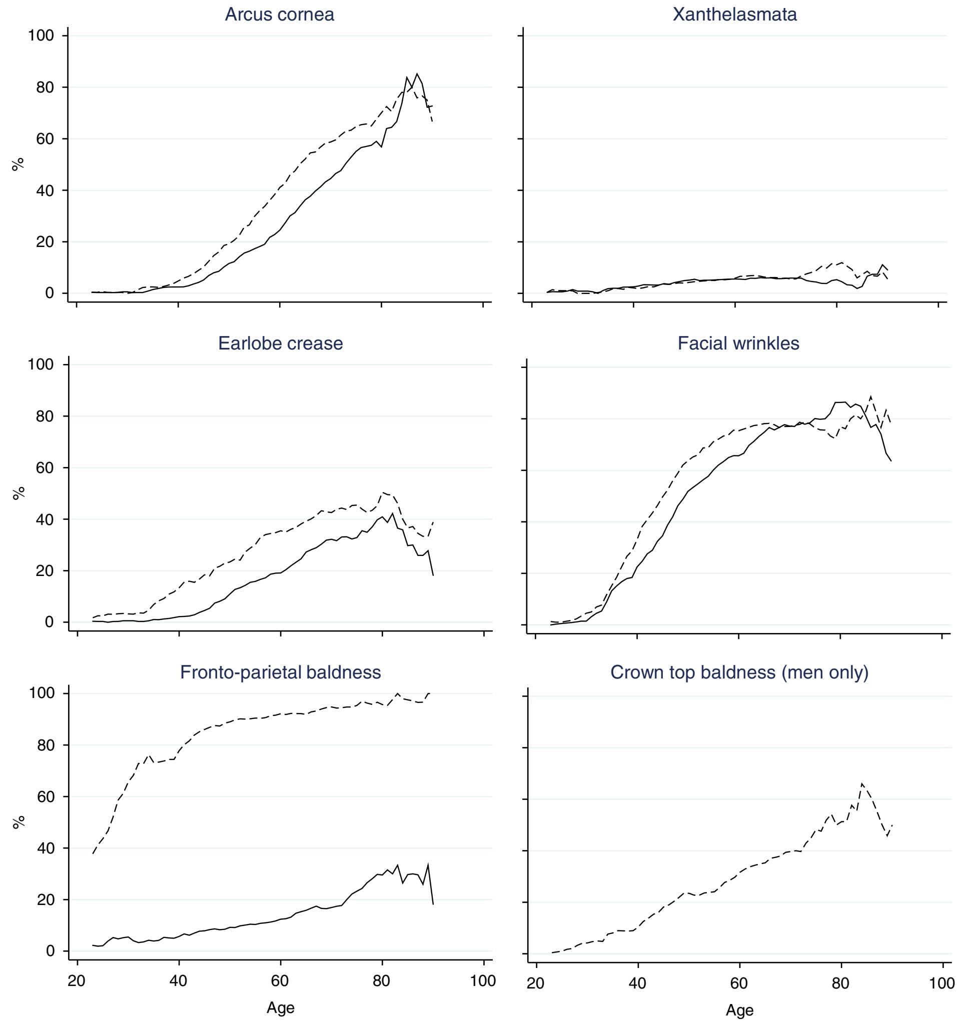

Figure 1. Prevalence (%) of visible age-related signs in the Copenhagen City Heart Study by age in women (full line) and men (dashed line).

was likely due to the relatively long time intervals between examinations (~10 y). Therefore, Cox analysis taking into account competing risk from death was performed (stcox procedure). In such analysis, it was assumed that the time of the development of the age-related sign in question was occurring at the midpoint between the baseline measurement and follow-up. Using information from the Danish Civil Registration System, information on all deaths was obtained, and therefore the exact time of end of follow-up was known for participants who died.

Results

Table 1 shows baseline characteristics of the 11,613 participants. Of these 44% were men and the mean age was 51 years (range: 21–93 y) (**Table 1**). In total, 17% were physically inactive in their leisure time whereas 54% were lightly, 26% were moderately, and 2% were vigorously physically active in leisure time.

During follow-up, 2425 individuals (26%) developed arcus corneae, 593 (5%) developed xanthelasmata, 2326 (25%) developed earlobe crease, and 2076 (43%) developed severe facial wrinkles. For pattern baldness, 430 men (67%) and 457 women (14%) developed frontoparietal baldness and 508 men (14%) developed crown top baldness.

Figure 1 shows the prevalence of the visible age-related signs by age. After age 40, the prevalence of all visible age-related signs increased. At age 80, ~80% had severe facial wrinkles, 60% had arcus cornea (more men than women), and 50% men had crown top baldness. For pattern baldness, among men the prevalence of frontoparietal baldness was notably higher than crown top baldness. More than 80% of the men above 40 years of age had frontoparietal baldness. The prevalence of earlobe crease was lower, but steadily increasing with age up until ~80 years. Xanthelasmata was the least prevalent visible age-related sign, with a prevalence of ~5% for both men and women above 50 years of age.

The associations between physical activity level in leisure time and risk of developing visible age-related signs are shown in **Figure 2**. After adjustment for the explanatory variables included as possible confounders, physical activity in leisure time was not associated to the risk of developing earlobe crease, facial wrinkles, and pattern baldness among either men or women. There was no interaction between physical activity and sex on the risk of developing visible age-related signs but when stratified by sex,

Table 1

Baseline characteristics of the study population (the copenhagen city heart study) (N = 11,613).

	Women (n = 6462)				Men (n = 5151)			
	Inactive	**Light**	**Moderate**	**Vigorous**	**Inactive**	**Light**	**Moderate**	**Vigorous**
Total [n (%)]	1095 (17)	3806 (59)	1500 (23)	61 (1)	867 (17)	2499 (48)	1599 (31)	186 (4)
Age [mean (range)] (y)	53 (22, 84)	52 (21, 84)	50 (21, 86)	44 (22, 70)	52 (22, 87)	52 (21, 93)	50 (21, 90)	43 (21, 71)
Education [n (%)] (y)								
< 8	649 (60)	1676 (44)	593 (40)	22 (36)	469 (54)	1074 (43)	651 (41)	65 (35)
8-10	352 (32)	1600 (42)	615 (41)	22 (36)	288 (33)	938 (38)	598 (38)	75 (40)
≥ 11	94 (9)	530 (14)	292 (19)	17 (28)	110 (13)	487 (20)	350 (22)	46 (25)
Alcohol intake median (10% and 90% percentiles) (drinks/wk)	2 (0, 14)	3 (0, 12)	3 (0, 13)	3 (0, 15)	12 (1, 45)	12 (2, 35)	10 (2, 35)	11 (1, 42)
Current smokers [n (%)]	704 (64)	2112 (56)	807 (54)	36 (59)	637 (73)	1731 (69)	1010 (63)	101 (54)
Smoking [median (10% and 90% percentiles)]* (pack-years)	18 (5, 38)	15 (4, 33)	14 (4, 34)	16 (2, 45)	30 (12, 60)	27 (9, 53)	23 (7, 51)	19 (4, 54)
Body mass index [median (10% and 90% percentiles)] (kg/m^2)	24 (19, 31)	24 (20, 30)	23 (20, 29)	22 (19, 27)	26 (22, 31)	25 (21, 30)	25 (21, 30)	25 (21, 30)
Diabetes [n (%)]	11 (1)	39 (1)	6 (0)	0 (0)	19 (2)	47 (2)	28 (2)	3 (2)
Hypertension [n (%)]	448 (41)	1403 (37)	496 (33)	12 (20)	429 (50)	1215 (49)	745 (47)	76 (41)
Total cholesterol [median (10% and 90% percentiles)]	6.2 (4.8, 7.8)	6.1 (4.6, 7.8)	5.9 (4.5, 7.7)	5.5 (4.3, 7,3)	5.9 (4.6, 7.4)	5.9 (4.7, 7.3)	5.8 (4.5, 7.3)	5.3 (4.1, 6.9)
Cardiovascular disease [n (%)]	25 (3)	48 (1)	15 (1)	0 (0)	25 (3)	79 (3)	44 (3)	0 (0)

*Among current smoke.

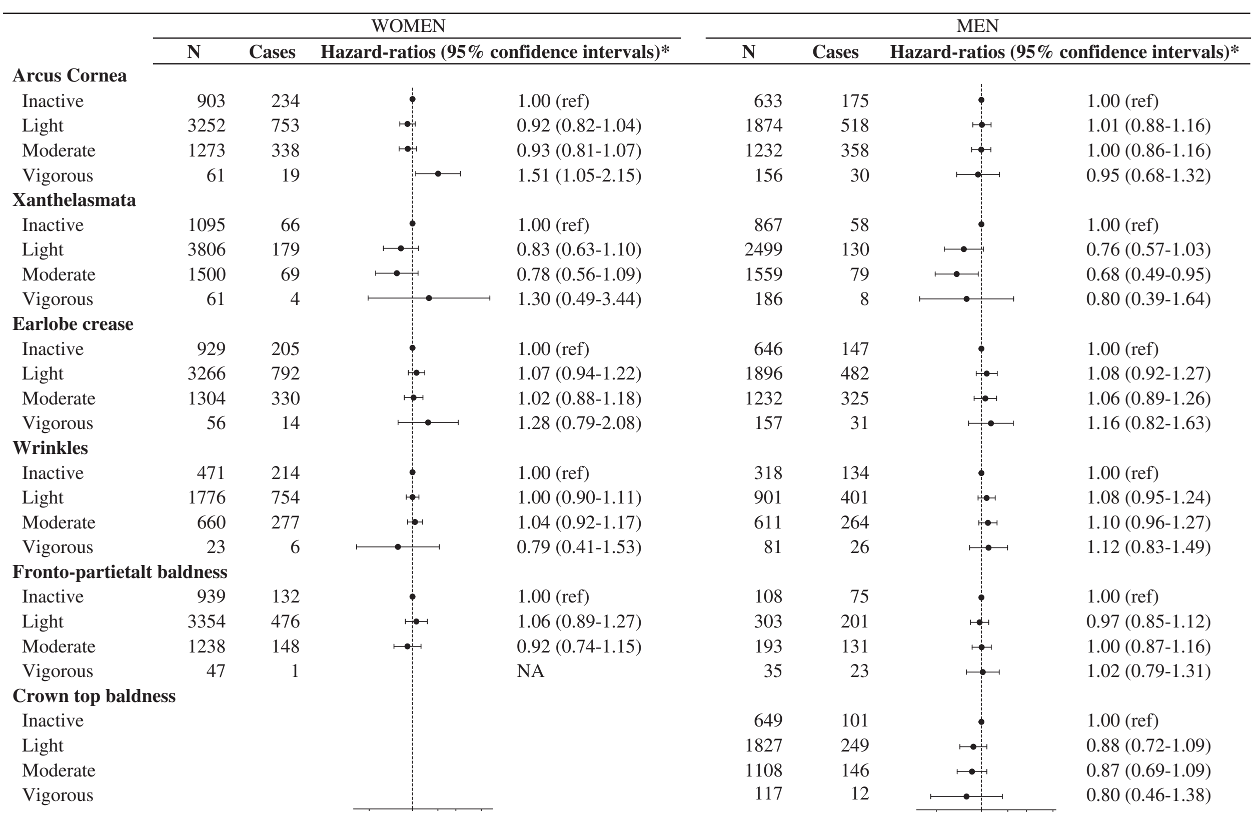

Figure 2. Fully adjusted hazard ratios (95% confidence intervals) for developing visible age-related signs according to physical activity level in leisure time among men and women in the Copenhagen City Heart Study. *Adjusted for age, age^2, year of baseline survey, education, body mass index, alcohol intake, smoking, diabetes, hypertension, cardiovascular disease, and year of baseline survey.

statistical significant associations was seen among women between physical activity and arcus cornea as well as xanthelasmata. The hazards ratios for xanthelasmata among men with moderate physical activity was, 0.68 (95% confidence interval, 0.49–0.95) compared with the inactive individuals. The hazard ratios for arcus cornea among women was 1.51 (95% confidence interval, 1.05–2.15) for vigorous physical activity compared with inactive.

To demonstrate that the risk of developing visible signs of aging in the study cohorts follows established patterns and to test the validity, we included smoking as a positive control of the association with visible signs of aging. The risk of developing arcus corneae, xanthelasmata, and earlobe crease increased stepwise with increased smoking as measured by pack-years. The test for trend was $P < 0.0001$ among women and $P = 0.04$ among men for arcus corneae; $P = 0.002$ among women and 0.03 among men for earlobe crease, and $P < 0.0001$ among women and $P = 0.001$ among men for xanthelasmata. Smoking was not associated to the risk of developing facial wrinkles and pattern baldness. Further, we tested the validity of physical activity in the association to all-cause mortality which showed a step-wise decrease in mortality by an increase in physical activity (Appendix). All analyses were repeated taking competing risk from death into account. For all of the age-related signs, results differed little from main analyses (results not shown).

Discussions

This is the first prospective study in the general population to study physical activity as a risk factor for looking old for your age. The principal finding was that physical activity was not associated with visible age-related signs, measured by development of arcus corneae, facial wrinkles, and pattern baldness. However, independently of chronically age, physical activity was associated to the development of arcus cornea and xanthelasmata although in opposite directions. Compared with an inactive leisure time, moderate physical activity was associated to a lower risk of developing xanthelasmata among men while vigorous physical activity was associated to a higher risk of arcus cornea among women.

The literature in general implies that appearing old for one's age is associated with cardiovascular disease and premature death independently of chronological age[1,2,14–19]. Especially earlobe crease, xanthelasmata and male pattern baldness have previously been found to predict cardiovascular disease and death[1,2,14–19], while there is contradictive evidence to whether arcus corneae is an independent risk factor of cardiovascular disease and death[1,2,20,21]. Given the health benefits of physical activity and that visible age-related signs can be interpreted as a marker for biological age, we hypothesized that a physical activity in leisure time could slow down biological aging and therefore decrease the development of visible age-related signs.

Our finding of an association between moderate physical activity and a decreased risk of xanthelasmata among men may indicate that physical activity slow down the ageing of the body and thereby mediating the risk of cardiovascular disease and early death. This is consistent with the existing literature showing that regular physical activity is associated to longer leukocyte telomere length[8]. In contrast, this association was not seen for women and also physical activity did not predict development of earlobe crease, facial wrinkles or pattern baldness which may indicate that physical activity does not slow down visible aging, even though the risk of cardiovascular disease and mortality is lower in physically active compared with inactive individuals.

To our knowledge, no other observational studies, have previously investigated the development arcus corneae, xanthelasmata, earlobe crease and pattern baldness in relation to physical activity. In mice, physical inactivity has been found to increase baldness and gray hair[9], but this has not been confirmed in human studies. The development of pattern baldness is strongly influenced by genetic predisposition[29] and the androgen pathway[30], which may explain why physical activity is not likely to predict baldness.

We found no association between physical activity and the development of facial wrinkles, which is in correspondence with previous findings[10,11]. It has been hypothesized that physical activity have a beneficial effect on the skin aging due to changes in the structure of the tissue layers[31], but the development of facial wrinkles is also strongly correlated with environmental factors such as sun exposure[32]. We were not able to adjust for the exposure to sunlight in the present study. The sensitivity analysis showed no association between smoking and the development of facial wrinkles. Unmeasured exposure to sunlight may explain this discrepancy and it is likely that sun exposure influenced the differences in skin condition between the physically active and inactive groups.

We observed a positive association between vigorous physical activity and the development of arcus cornea among women. Possibly, long periods of excessive training can put the body under extreme stress resulting in accelerated body aging. However, this needs to be confirmed in other observational and experimental studies.

One of the strengths of this study is the prospective population-based design including a large homogenous sample of both men and women. Initially, the Copenhagen City Heart Study was a random sample of the general population of Copenhagen. In the Copenhagen City Heart study the participants were at baseline asked to complete a detailed questionnaire about several health and lifestyle risk factors, providing researchers with the opportunity of thorough confounder control. In this study we were able to adjust for important confounders such as BMI, diabetes, hypertension, and cardiovascular disease. Trained health professionals examined the participants in regard to visible age-related signs, which ensured a relatively objective collection of outcome information. In addition, we used a method, which took the interval censored nature of the data into account including a robust SE allowing for intragroup correlation.

However, this study has some limitations. First, visual signs of aging is a result of a complex multifactorial aging process and is influences by factors such as diet, exposure to sun light, and genetics which we were not able to account for in this observational design. Second, results should be interpreted given the limitations of the crude and self-reported assessment of physical activity level by questionnaire. However, previous studies have shown that self-reported physical activity is a fairly accurate measure when used in large epidemiological studies[33] and any misclassification is most likely to be nondifferential, as it would be independent from the participant's future development of visible age-related signs. Third, physical activity level was measured at baseline and may change during the follow-up period causing a possible attenuation of associations. Also, the design allows adjusting for effects of several potential confounding factors. Some factors such as hypertension may be regarded as an intermediate factor rather than confounding factor and adjusting for this may have conservatively biased our results. Conversely, cholesterol levels were not included as a confounding factor as this was regarded as an intermediate variable. Unmeasured factors may also influence the association, including inheritance, and dietary habits and other environmental exposures such as sunlight exposure, which were not possible to adjust for. These unmeasured confounders may play an important role of developing visible signs of aging.

Another limitation of this study was the potential introduction of selection bias into the cohort. However, the attendance rate was 74% of those invited, reducing the risk of serious selection bias. Furthermore, only those who participated in at least 2 examinations were included in the analyses. This restriction may also have induced selection bias, as those who participated in a minimum of two examinations may differ from those only participating in one. Finally, competing risk from mortality was a potential source of bias. Because of the intervals censoring, a larger proportion of participants with age-related signs may have died before the follow-up examination. To overcome this, we performed competing risks regression analyses, with the specific date of death obtained from national registers. In these analyses we chose the development of age-related signs to be in the middle of the time interval. The findings from the competing risk regression analyses did not vary from the results presented in this paper.

Conclusions

We show that physical activity is not related to visible age-related signs, measured by development of arcus corneae, facial wrinkles, and pattern baldness. However, among men, being physically active in leisure time was associated to a lower risk of developing xanthelasmata while being vigorous physical activity was associated to a higher risk of arcus cornea among women.

Conflict of interest statement

The authors declare that they have no financial conflict of interest with regard to the content of this report.

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Appendix

Figure A1. Fully adjusted hazard-ratios (95% confidence intervals) for death from all causes according to physical activity level in leisure time among men and women in the Copenhagen City Heart Study. Adjusted for age, age^2, year of baseline survey, education, body mass index, alcohol intake, smoking, diabetes, hypertension, cardiovascular disease, and year of baseline survey.

	WOMEN			MEN		
Physical activity in leisure time	**N**	**Cases**	**Hazard-ratios (95% confidence intervals)**	**N**	**Cases**	**Hazard-ratios (95% confidence intervals)**
Inactive	2622	1917	1.00 (ref)	2100	1710	1.00(ref)
Light	7814	4587	0.78 (0.69-0.87)	5302	3825	0.85 (0.76-0.95)
Moderate	3381	1877	0.72 (0.62-0.83)	3706	2488	0.78 (0.69-0.89)
Vigorous	145	69	0.74 (0.43-1.26)	364	167	0.55 (0.41-0.75)