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The combined influence of leisure-time physical activity and weekly alcohol intake on fatal ischaemic heart disease and all-cause mortality

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Aims To determine the combined influence of leisure-time physical activity and weekly alcohol intake on the risk of subsequent fatal ischaemic heart disease (IHD) and all-cause mortality.

Methods and results Prospective cohort study of 11 914 Danes aged 20 years or older and without pre-existing IHD. During ~20 years of follow-up, 1242 cases of fatal IHD occurred and 5901 died from all causes. Within both genders, being physically active was associated with lower hazard ratios (HR) of both fatal IHD and all-cause mortality than being physically inactive. Further, weekly alcohol intake was inversely associated with fatal IHD and had a U-shaped association with all-cause mortality. Within level of physical activity, non-drinkers had the highest HR of fatal IHD, whereas both non-drinkers and heavy drinkers had the highest HR of all-cause mortality. Further, the physically inactive had the highest HR of both fatal IHD and all-cause mortality within each category of weekly alcohol intake. Thus, the HR of both fatal IHD and all-cause mortality were low among the physically active who had a moderate alcohol intake.

Conclusion Leisure-time physical activity and a moderate weekly alcohol intake are both important to lower the risk of fatal IHD and all-cause mortality.

Keywords Physical activity • Alcohol intake • Ischaemic heart disease • All-cause mortality • Survival analysis

Introduction

A large number of prospective population studies have found beneficial effects of physical activity on the risk of cardiovascular disease and all-cause mortality.[1–7] Physical inactivity is of major importance in public health because it is highly prevalent and potentially modifiable.[8] Another large number of prospective studies have documented a lower risk of both cardiovascular disease and all-cause mortality associated with a light to moderate alcohol intake.[9–13] Several of the potentially causal mechanisms for the beneficial effects of physical activity and alcohol intake on the circulatory system have been proposed. Some of these mechanisms may be shared, e.g. the beneficial effects on lipoprotein metabolism, inflammation, endothelial health, and insulin resistance.[14–17] Although alcohol intake is a modifiable risk factor as well, it may seem inappropriate to advise non-drinkers to start drinking, as reasons for not drinking may include religious believes, previous alcoholism, or pregnancy. Whether one of these two modifiable factors may compensate for the effect of the other, or whether both of them are important for cardiovascular health and health in general is not yet clarified. The aim of our study was to estimate the combined influence of leisure-time physical activity and weekly alcohol intake on the risk of subsequent fatal ischaemic heart disease (IHD) and all-cause mortality.

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Methods

In the Copenhagen City Heart Study, an age-stratified sample of 19 329 men and women from a distinct area of Copenhagen were randomly drawn from the Danish civil registration system and invited to participate in the first examination in 1976–78. They were drawn among ~90 000 eligible inhabitants aged 20 years or older in 1976–78, and they were re-invited in 1981–83 along with additionally 500 newly invited persons. The response proportion at the first examination was 74% and 70% at the second examination.

The participants were invited to the Copenhagen University Hospital and were asked to complete a self-administered questionnaire regarding various health-related issues including questions about leisure-time physical activity and weekly alcohol intake, before a physical examination was performed. The staff checked the responses to the questionnaires during the examination with regard to potential non-response or inconsistent responses.

We used information from the second examination where 13 095 persons participated. Of these, 491 participants were excluded due to incomplete information on the exposure variables and covariates, and further 690 participants were excluded due to pre-existing IHD in 1981–83. In our analyses, information from the remaining 11 914 participants was used, and, of these, the vast majority were Caucasians. The Copenhagen City Heart Study complies with the Declaration of Helsinki, which the Ethics Committee of Copenhagen and Frederiksberg Municipality, Denmark has approved (#01-144/01). A detailed description of the Copenhagen City Heart Study has been published previously.[18]

Leisure-time physical activity

Leisure-time physical activity was assessed as the mean level each week during the last year graded in four levels based on a questionnaire constructed by Saltin and Grimby,[19] with modifications. The four levels were: (i) being almost entirely inactive or engaging in light physical activity <2 h per week (e.g. reading, watching television, cinemagoer); (ii) engaging in light physical activity for 2–4 h per week (e.g. walking, cycling, light gardening, light physical exercise); (iii) engaging in light physical activity for >4 h per week or more vigorous activity for 2–4 h per week (e.g. brisk walking, fast cycling, heavy gardening, sports that cause perspiration or exhaustion); and (iv) engaging in vigorous physical activity for >4 h per week, regular heavy exercise, or competitive sports several times per week. Level 1 was considered physically inactive, level 2 was considered a low level of physical activity, and levels 3 and 4 together were considered a moderate to high level of physical activity. The two highest levels of physical activity were combined, as there was only 2% of the population, who reported to perform the highest level of physical activity.

Alcohol intake

The subjects were classified according to their reported total weekly intake of alcohol, where one drink corresponds to one bottle of beer, one glass of wine, and one unit of spirit: non-drinkers, below one drink per week (none); moderate drinkers, one to 14 drinks per week (moderate); and heavy drinkers, 15 or more drinks per week (high).

Covariates

The following set of potential confounders was identified according to the methods of causal diagrams developed by Greenland *et al.*:[20] age, gender, smoking habits (never-smoker, ex-smoker, smoker of 1–14 g/day, and >14 g/day. One cigarette was equivalent to 1 g, a cheroot to 3 g, and a cigar to 5 g of tobacco), body mass index (kg/m^2, continuous), education (<8 years, 8–11 years, or at least 12 years), marital status (married or cohabiting, divorced or widowed, and single), and pre-existing diabetes. Possible intermediating effect of high-density lipoprotein cholesterol (HDL-C) on the pathway between physical activity or alcohol intake and fatal IHD were estimated by including HDL-C in the multi-adjusted model.

Follow-up

Using the unique person identification number in the Danish civil registration system, the participants were followed from date of entry into the study, until date of death, loss to follow-up, emigration, or until 31 December 2001 in the analyses of fatal IHD and until 11 March 2004 in the analyses of all-cause mortality.[21] These identification numbers encode date of birth, gender, and a record linkage with complete hospital discharge history for each individual. As a result of emigration or disappearance, 55 persons (0.5%) were lost to follow-up before 31 December 2001 and 75 (0.6%) were lost to follow-up before 11 March 2004. Identification of deaths due to IHD in the Danish Causes of Death Registry was based on the international classification of diseases, eighth and 10th revision (ICD-8 codes; 410–414, ICD-10 codes; I20–I25) published by the World Health Organization.

Statistical analyses

We calculated hazard ratios (HR) with 95% confidence intervals for fatal IHD and all-cause mortality using Cox's proportional hazards regression analysis with age as the underlying time variable and delayed entrance, accordingly, which ensured optimal adjustment for age.

Analyses were repeated with adjustment for the confounders and for the analyses of the risk of fatal IHD an additional model also included HDL-C concentrations. The percent of change in the regression coefficient between these two multivariable models was used to measure the mediating effect of HDL-C. Gender specific analyses were performed when estimating the effect of leisure-time physical activity and weekly alcohol intake. Men and women were combined in the analyses of the combined influence of physical activity and alcohol intake, as the gender separate analyses showed the same tendency. Alcohol intake was included as a cubic spline variable in the analyses of leisure-time physical activity and elsewhere as a discrete variable. Body mass index was included as a cubic spline variable in all analyses. In the analyses of the combined influence of physical activity and alcohol intake, the reference group was the physically inactive non-drinkers, but we also performed additional tests within the same model using other groups as reference. We used a joint reference group to ensure that the HR for the different levels of alcohol intake combined with physical activity status were estimated with reference to a common baseline risk.

The analyses included 5272 men and 6642 women who provided information about the variables of interest and who were free of an IHD diagnosis in 1981–83. For every Cox model, the proportional hazard assumption was controlled with a smoothed plot of scaled Schoenfeld residuals vs. time. All analyses were two-sided and performed using STATA version 9.

Results

Of the 5272 men and 6642 women included in the analyses, 822 men (16%) and 1156 women (17%) classified themselves as physically inactive and 807 men (15%) and 2842 women (43%) reported that they consume <1 drink per week. Within both

genders, the physically inactive tended to be older, less educated, included more smokers, and diabetics, and were less likely to cohabit than the physically active (Table 1). Additionally, those who consumed the majority of alcohol as wine were more likely to be women and physically active than men and inactive (Table 1). Physically inactive men had a median alcohol intake of 10 drinks per week, whereas men who reported either a low or a moderate to high level of physical activity drank nine drinks per week (data not shown). Among women, physically inactive had a median alcohol intake of zero drinks per week, whereas those who reported a low level of physical activity drank two drinks per week and moderate to highly active women drank 10 drinks per week (data not shown). Within both genders, non-drinkers tended to be older, less educated, and included fewer smokers, but more diabetics than moderate and heavy drinkers (Table 1).

During the ~20 years of follow-up, 5901 participants died, and, of these, 724 men and 534 women died of IHD.

Leisure-time physical activity and weekly alcohol intake

Within both genders, being physically active was associated with significant lower HR for both fatal IHD and all-cause mortality than being physically inactive (*Table 2* and 3). HDL-C did not mediate the risk of fatal IHD among the physically active groups (*Table 2*).

Alcohol intake was inversely associated with fatal IHD among both men and women (*Table 2*). HDL-C was a mediator of 29–58% of this risk in men and 15–32% in women (*Table 2*). A weekly moderate alcohol intake reduced the risk of all-cause mortality among both men and women, whereas the risk among heavy drinkers was similar to non-drinkers (*Table 3*).

Ischaemic heart disease

Figure 1 shows the HR of fatal IHD for combinations of physical activity level and weekly alcohol intake. Within each level of physical activity, non-drinkers had the highest HR of fatal IHD, i.e. compared with moderate drinkers on each physical activity level, the HR was 1.30 (1.04–1.63) among the physically inactive non-drinkers, 1.31 (1.08–1.59) among non-drinkers with a low level of physical activity, and 1.30 (1.04–1.63) among non-drinkers with a moderate to high level of physical activity. Further, within each category of weekly alcohol intake, the physically inactive had the highest HR of fatal IHD. Thus, the lowest HR of fatal IHD were observed among the physically active moderate or heavy drinkers (range 0.50–0.56) and the highest HR among the physically inactive non-drinkers (reference group) (*Figure 1*).

Compared with physically inactive non-drinkers, being physically active was associated with a 31–33% lower HR of fatal IHD, and drinking at least one drink weekly was associated with a 30–32% lower HR, whereas being both physically active and drinking at least one drink weekly was associated with a 44–50% lower HR of fatal IHD (calculated from *Figure 1*). Further, the HR of fatal IHD did not differ between non-drinkers who reported either a low level (0.98, 0.77–1.25) or a moderate to high level of physical activity (0.95, 0.73–1.23) compared with physically inactive moderate drinkers. Thus, both physical activity and alcohol intake lowered the risk of fatal IHD.

All-cause mortality

Figure 2 shows the HR of all-cause mortality for combinations of physical activity level and weekly alcohol intake. Within each category of weekly alcohol intake, the physically inactive had the highest HR of all-cause mortality and within each level of physical activity, moderate drinkers had the lowest HR of all-cause mortality. Compared to non-drinkers on a similar physical activity level, a moderate alcohol intake lowered the HR for all-cause mortality both among persons with a low level of physical activity (0.87, 0.78–0.97) and among those with a moderate to high level of physical activity (0.90, 0.82–0.98), but not among physically inactive (0.96, 0.84–1.09).

Compared with physically inactive non-drinkers, being physically active was associated with 23% lower HR of all-cause mortality, whereas a moderate alcohol intake did not lower the HR significantly, but being both physically active and drinking at least one drink weekly was associated with a 12–33% lower HR of all-cause mortality (calculated from *Figure 2*). Thus, the lowest HR of all-cause mortality were observed among the physically active moderate drinkers and the highest HR among the physically inactive non- and heavy drinkers (*Figure 2*). Further, the HR of all-cause mortality were significantly lower among non-drinkers who reported either a low level (0.80, 0.72–0.90) or a moderate to high level of physical activity (0.81, 0.71–0.91) compared with physically inactive moderate drinkers.

Discussion

Our study shows that being both physically active and drinking a moderate amount of alcohol is important to lower the risk of both fatal IHD and all-cause mortality. As there might be good reasons for alcohol abstention, it is important that physical activity can reverse some of the adverse health effects associated with alcohol abstention.

Leisure-time physical activity and weekly alcohol intake

Our results show that being physical active in leisure-time was associated with low risk of death due to IHD and all-causes, which is in line with numerous other studies.[1–7] Additionally, we found beneficial effects of a moderate weekly alcohol intake on the risk of fatal IHD and all-cause mortality (*Table 2* and *3*), which is also well-known from other studies.[9–13]

Ischaemic heart disease

Non-drinkers who were physically inactive were at high risk of developing fatal IHD, potentially because they might not obtain the beneficial effects from neither physical activity nor alcohol intake on the circulatory system. Numerous studies have shown beneficial effects of both physical activity and alcohol intake on lipoprotein metabolism, inflammatory markers, insulin resistance, and endothelial function.[11,16,17,22–31]

Table 1 Baseline characteristics of men and women aged at least 20 years (n = 11 914) according to weekly alcohol intake and leisure time physical activity (1981–1983), Copenhagen City Heart Study

	Alcohol intake and physical activity								
	None[a]			Moderate[a]			High[a]		
	Inactive[b]	Low[b]	Moderate/high[b]	Inactive[b]	Low[b]	Moderate/high[b]	Inactive[b]	Low[b]	Moderate/high[b]
Men									
Number	153	313	341	365	1198	1127	304	738	733
Alcohol (drinks per week)[c]	0 (0–0)	0 (0–0)	0 (0–0)	7 (4–10)	7 (4–10)	7 (4–10)	28 (20–41)	24 (19–35)	24 (19–33)
Age (years)[c]	60 (49–68)	60 (50–67)	60 (50–68)	59 (51–68)	57 (48–65)	56 (44–64)	56 (48–62)	55 (46–62)	54 (45–62)
HDL-C[d] (mmol/L)[c]	0.89 (0.77–1.05)	0.92 (0.80–1.04)	0.93 (0.80–1.06)	0.96 (0.80–1.15)	0.98 (0.84–1.14)	1.00 (0.86–1.17)	1.00 (0.85–1.26)	1.06 (0.91–1.30)	1.08 (0.92–1.30)
Body mass index[c,e]	25.6 (22.9–27.8)	25.6 (23.0–28.3)	25.5 (23.4–28.1)	26.0 (23.5–28.6)	25.4 (23.3–27.8)	25.1 (23.0–27.5)	26.5 (24.0–29.4)	26.0 (23.4–28.7)	25.9 (23.7–28.4)
Non-smokers (%)	35	42	44	34	37	43	18	27	33
Diabetes (%)	6.5	3.5	4.4	4.7	2.8	2.5	3.9	2.0	3.3
Low level of education (%)	65	55	54	58	41	35	56	42	40
Cohabiting (%)	65	71	69	70	81	76	61	70	72
Wine-drinkers (%)[f]	—	—	—	11	22	23	9	11	12
Women									
Number	619	1430	793	454	1858	1036	83	233	136
Alcohol (drinks per week)[c]	0 (0–0)	0 (0–0)	0 (0–0)	5 (2–7)	4 (2–8)	4 (2–7)	20 (16–30)	20 (16–25)	21 (17–26)
Age (years)[c]	62 (54–70)	60 (52–65)	60 (52–66)	58 (50–65)	55 (46–62)	55 (44–63)	53 (46–62)	54 (46–61)	55 (43–61)
HDL-C[d] (mmol/L)[c]	1.11 (0.94–1.33)	1.16 (0.99–1.36)	1.18 (1.02–1.37)	1.21 (1.05–1.46)	1.24 (1.04–1.45)	1.25 (1.08–1.48)	1.35 (1.17–1.62)	1.31 (1.11–1.56)	1.41 (1.15–1.70)
Body mass index[c,e]	25.0 (22.0–28.8)	24.9 (22.2–28.4)	24.5 (22.0–27.3)	24.5 (22.0–27.3)	23.7 (21.6–26.4)	23.2 (21.5–25.7)	23.9 (21.7–27.1)	23.5 (21.4–25.5)	23.4 (21.5–25.7)
Non-smokers (%)	48	50	49	35	46	50	24	29	42
Diabetes (%)	3.9	2.7	1.5	1.8	0.9	0.7	1.2	0.9	0.7
Low level of education (%)	73	57	59	51	34	35	43	18	24
Cohabiting (%)	42	52	50	51	60	59	43	66	58
Wine-drinkers (%)[f]	—	—	—	43	58	58	34	49	51

[a]None, below one drink per week; Moderate, 1–14 drinks per week; High, above 14 drinks per week.
[b]Inactive: physically inactive; low: light physical activity for 2–4 h per week; moderate/high: at least light physical activity for >4 h per week or more vigorous activity for 2–4 h per week.
[c]Median (lower—upper quartile).
[d]HDL-C, high-density lipoprotein cholesterol.
[e]Weight (kg)/height^2 (m)^2.
[f]Percent of the group where wine contribute to >50% of the weekly alcohol intake.

Table 2 **Hazard ratios (HR) and 95% confidence intervals (CI) for fatal ischaemic heart disease associated with leisure-time physically activity and weekly alcohol intake among 5272 men and 6642 women in the Copenhagen City Heart Study (1981–1983)**

	HR (95% CI)					
	Physical activity			Alcohol intake		
	Inactive[a]	Low[a]	Moderate/high[a]	None[b]	Moderate[b]	High[b]
Men						
Age-adjusted ($n = 5272$, cases = 710)	1.00 (reference)	0.62 (0.51–0.76)	0.64 (0.52–0.78)	1.00 (reference)	0.77 (0.63–0.93)	0.86 (0.70–1.06)
Multi-adjusted[c] ($n = 5272$, cases = 710)	1.00 (reference)	0.67 (0.54–0.82)	0.71 (0.58–0.87)	1.00 (reference)	0.77 (0.64–0.94)	0.79 (0.63–0.98)
Multi-adjusted[c] + HDL-C[d] ($n = 5272$, cases = 710)	1.00 (reference)	0.68 (0.55–0.83)	0.71 (0.58–0.87)	1.00 (reference)	0.83 (0.68–1.01)	0.90 (0.72–1.13)
Effect of HDL-C[d]		3%	3%		29%	58%
Women						
Age-adjusted ($n = 6642$, cases = 532)	1.00 (reference)	0.68 (0.55–0.84)	0.61 (0.48–0.78)	1.00 (reference)	0.69 (0.58–0.83)	0.68 (0.44–1.05)
Multi-adjusted[c] ($n = 6642$, cases = 532)	1.00 (reference)	0.76 (0.61–0.94)	0.72 (0.56–0.92)	1.00 (reference)	0.72 (0.60–0.87)	0.65 (0.42–1.01)
Multi-adjusted[c] + HDL-C[d] ($n = 6642$, cases = 532)	1.00 (reference)	0.75 (0.60–0.92)	0.72 (0.57–0.92)	1.00 (reference)	0.76 (0.63–0.92)	0.75 (0.48–1.16)
Effect of HDL-C[d]		−6%	2%		15%	32%

[a]Inactive: physically inactive; low: light physical activity for 2–4 h per week; moderate/high: at least light physical activity for >4 h per week or more vigorous activity for 2–4 h per week.
[b]None: below one drink per week; moderate: 1–14 drinks per week; high: above 14 drinks per week.
[c]Adjusted for age, smoking habits, body mass index, education, marital status, known diabetes, and physical activity or alcohol intake.
[d]HDL-C, high-density lipoprotein cholesterol. The percent change in the regression coefficient between the multivariable model with and without HDL-C was used to measure the mediating effect of HDL-C.

Table 3 Hazard ratios (HR) and 95% confidence intervals (CI) for all-cause mortality associated with leisure-time physically activity and weekly alcohol intake among 5272 men and 6642 women in the Copenhagen City Heart Study (1981–1983)

	HR (95% CI)					
	Physical activity			Alcohol intake		
	Inactive[a]	Low[a]	Moderate/high[a]	None[b]	Moderate[b]	High[b]
Men						
Age-adjusted ($n = 5272$, cases = 2971	1.00 (reference)	0.72 (0.65–0.79)	0.64 (0.58–0.71)	1.00 (reference)	0.85 (0.77–0.94)	1.13 (1.02–1.26)
Multi-adjusted[c] ($n = 5272$, cases = 2971)	1.00 (reference)	0.79 (0.72–0.88)	0.73 (0.66–0.81)	1.00 (reference)	0.87 (0.78–0.96)	1.05 (0.94–1.17)
Women						
Age-adjusted ($n = 6642$, cases = 2930)	1.00 (reference)	0.68 (0.62–0.75)	0.67 (0.61–0.75)	1.00 (reference)	0.89 (0.82–0.96)	1.07 (0.92–1.25)
Multi-adjusted[c] ($n = 6642$, cases = 2930)	1.00 (reference)	0.74 (0.68–0.81)	0.75 (0.68–0.83)	1.00 (reference)	0.93 (0.86–1.00)	1.03 (0.88–1.20)

[a]Inactive: physically inactive; low: light physical activity for 2–4 h per week, moderate/high: at least light physical activity for >4 h per week or more vigorous activity for 2–4 h per week.
[b]None: below one drink per week; moderate: 1–14 drinks per week; high: above 14 drinks per week.
[c]Adjusted for age, smoking habits, body mass index, education, marital status, known diabetes, and physical activity or alcohol intake.

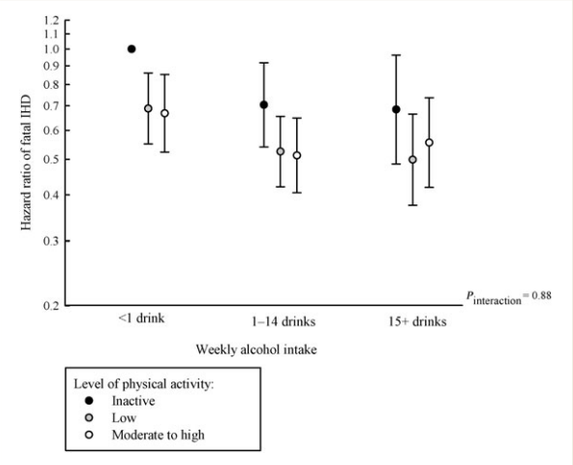

Figure 1 Hazard ratios (95% confidence intervals) for fatal ischaemic heart disease associated with the combined influence of leisure-time physical activity level and weekly alcohol intake among 11 914 men and women (1242 cases). Adjusted for age, smoking habits, body mass index, education, marital status, and pre-existing diabetes. The reference group is those who are physically inactive and non-drinkers

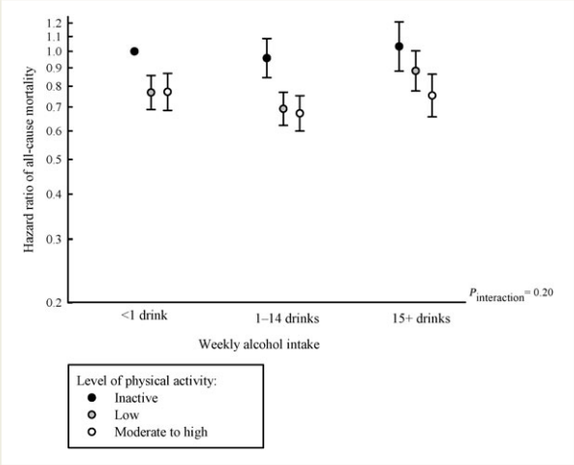

Figure 2 Hazard ratios (95% confidence intervals) for all-cause mortality associated with the combined influence of leisure-time physical activity level and weekly alcohol intake among 11 914 men and women (5901 cases). Adjusted for age, smoking habits, body mass index, education, marital status, and pre-existing diabetes. The reference group is those who are physically inactive and non-drinkers

In men, HDL-C was a mediator of 29–58% of the effect of alcohol intake on fatal IHD and 15–32% in women. This is to some extent in line with the previously suggested 40–60%.[27,32,33] HDL-C did not mediate the effect of physical activity on fatal IHD in this study (*Table 2*). Several studies have reported a dose–response relationship between physical activity and HDL-C changes, suggesting that exercise can favourably alter blood lipids when certain exercise thresholds are met.[34] Due to a very low prevalence of highly active participants, we had to combine those who reported a moderate and a high level of activity, and this may explain the missing mediating effect of HDL-C in our study.

Body mass index could be an intermediate variable between physical activity and mortality and thus explain why HDL-C is not important in the analyses of the risk of fatal IHD. However, the regression coefficients were essentially similar in the multivariable model with and without the adjustment for body mass index, which suggests that body mass index in these settings did not mediate the effect of physical activity on the risk of fatal IHD (data not shown). The risk lowering effect of physical activity among non-drinkers may therefore be due to other beneficial effects of physical activity, as previously described. Further, we expected that the effect of alcohol on the risk of fatal IHD would be minimized among highly active participants, but the results indicate that physical activity cannot compensate for weekly alcohol intake among the group of moderate to highly physically active persons (*Figure 1*). We might have seen the expected effect if the population included a sufficient number of persons who achieved the highest level of physical activity. It might also be due to overreporting of the level of physical activity or simply that a weekly alcohol intake has other important risk lowering effects on the circulatory system than those achieved by physical activity.

Although the inactive non-drinkers can benefit from both physical activity and alcohol intake, there might be a specific reason for alcohol abstention such as religion, previous alcoholism, or pregnancy. Therefore, it is important that non-drinkers can reduce their risk of fatal IHD by being physically active.

All-cause mortality

The physically active had a significant risk lowering effect of a moderate weekly alcohol intake and this was in contrast to the physically inactive, who did not have this effect of a moderate weekly alcohol intake (*Figure 2*). Drinking pattern in terms of type of alcohol consumed and steady or binge drinking might explain this difference between the physically active and inactive. A larger proportion of the physically active preferred to drink wine compared to the physically inactive (*Table 1*), but information on whether the alcohol was consumed dispersed during the week or congregated on few days was not obtained through the questionnaire. It has been suggested that substances present in wine, but not in beer and spirits, are responsible for the lower mortality among wine drinkers.[35–38] Hence, the preventive effect of a moderate alcohol intake on all-cause mortality among the physically active may be due to a healthy drinking pattern.

Limitations

Although the size, the prospective design, and the long follow-up time strengthen this study, accuracy of the registers, confounding, and misclassification are potential limitations.

The cause of death may not be accurately registered due to the low percentage of autopsy, but it is improbable that participants suffered unrecognized deaths.[39]

We stratified by gender and adjusted for age, smoking, body mass index, education, marital status, and diabetes, but confounding may still be possible, especially as this cohort has no information on dietary intake. The physically active potentially have a healthier diet than the inactive, and those who drink moderately potentially have a healthier diet than non-drinkers, which may have confounded our results. The preventive effect of physical activity and alcohol intake may, instead, be due to a healthier diet or to effects of diet in interaction with physical activity or alcohol intake.

Further, we dichotomized the level of physical activity and categorized alcohol intake in order to perform the analyses of the combined effects, which have resulted in loss of information. Level of physical activity and alcohol intake obtained through a questionnaire could be subject to misclassification. Overreporting of physical activity level would result in lower beneficial effects of physical activity and may have attenuated our results with the consequence that the real difference between the physical active and inactive would be greater.

The physical activity question used in this population study has revealed associations between the level of leisure-time physical activity and mortality in other population studies.[40,41] Additionally, the question has been shown to discriminate sedentary persons from their more active counterparts with respect to maximal oxygen uptake.[42] It is likely that some of those participants grouped as physically inactive are active at work. However, when we adjusted for physical activity at work, our results did not change.

The group of non-drinkers is a mixture of never drinkers and rare drinkers and may also be a mixture of former heavy drinkers, drinkers who underreport, and people who are ill and therefore have stopped drinking.[43] If non-drinkers in the present study were actually heavy drinkers or recent heavy drinkers, the risk of mortality related to heavy drinking would be higher and the risk among non-drinkers lower than observed. However, one of our endpoints were fatal IHD, an illness not particularly related to heavy drinking and the real difference between the non-drinkers and moderate drinkers may be even greater.

Further, we excluded participants who had an IHD diagnose before the examination in 1981–83, as they had a high risk for relapse and, as a consequence, may have changed their lifestyle. Some participants may have had undiagnosed symptoms of IHD prior to the examination in 1981–83. If this has caused lifestyle changes regarding alcohol intake and physical activity, this could bias our results. However, when cases that occurred during the first 5 years of follow-up were excluded, the results were essentially similar in both the analyses on the risk of fatal IHD and all-cause mortality. Excluding diabetics at baseline instead of adjusting for diabetes did not alter the results either.

In this study, 70% of the original invited cohort participated. It cannot be excluded that a decision not to participate could be related to alcohol consumption and maybe physical inactivity. Heavy alcohol consumption could be associated with social prejudices making heavy drinkers feel disinclined to participate in health surveys. Thus, the results of this study cannot necessarily be generalized to groups with extremely heavy alcohol consumption. This is probably not a problem with physical activity, as 17% of the population reported that they were physical inactive, but we might have captured the healthiest of the physically inactive.

In conclusion, non-drinkers who are physically inactive are a high-risk group for fatal IHD and all-cause mortality. Physical activity and a moderate alcohol intake can lower the risk of fatal IHD and all-cause mortality. Hence, as there might be reasons for alcohol abstention, it is important that physical activity can

reverse some of the adverse health effects associated with alcohol abstention. But neither physical activity alone nor alcohol intake can completely reverse the increased risk associated with physical inactivity and alcohol abstention. Thus, both physical activity and alcohol intake are important to lower the risk of fatal IHD and all-cause mortality.

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CLINICAL VIGNETTE

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Atrial enhancement by cardiovascular magnetic resonance in cardiac amyloidosis

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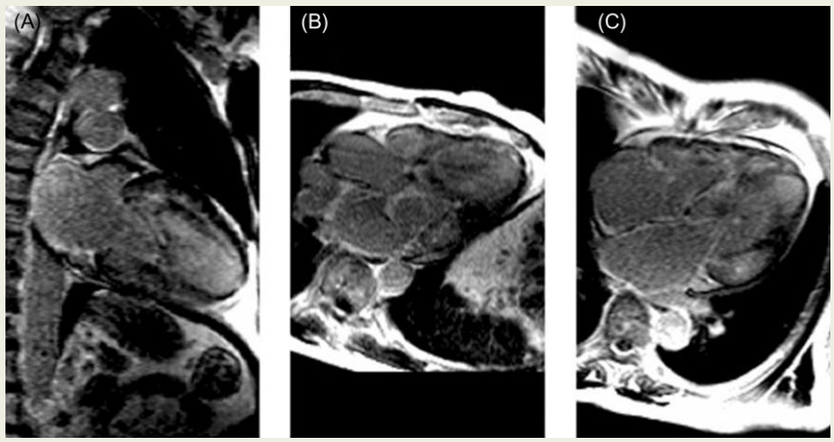
A 78-year-old man was referred for cardiovascular magnetic resonance (CMR) to investigate symmetrical left ventricular hypertrophy identified by echocardiography. Electrocardiography showed first-degree heart block with a long duration (140 ms), low-voltage P wave, and atrial arrhythmia identified on 48 h Holter monitoring. CMR showed biatrial dilatation, severe left ventricular hypertrophy, and globally impaired systolic function. Following intravenous gadolinium, there was early myocardial enhancement of the left ventricle, with a prominent subendocardial pattern. However, enhancement was also clearly seen in both atrial walls (Panels A–C).



CMR is a well-established diagnostic investigation for cardiac amyloidosis. It has been shown that there is a high myocardial gadolinium concentration early after injection typically with subendocardial late enhancement, which correlates with morphological markers of increased cardiac amyloid load. The atrial morphology and the endocardial accumulation of amyloid are consistent with the electrocardiographic findings. Iatrogenic left atrial enhancement has been described following pulmonary vein isolation; however, we believe this to be the first description of atrial gadolinium enhancement in a disease state. The accumulation of gadolinium in atria suggests that some of the cardiac manifestations of amyloidosis may not be due to ventricular infiltration alone. The CMR assessment of this abnormal interstitial protein in atrial myocardium may potentially correlate better with the occurrence of atrial arrhythmia and conduction defects than with ventricular enhancement alone.

Panel A Cardiovascular magnetic resonance identifying atrial involvement in the patient with amyloidosis: vertical long axis.

Panel B Cardiovascular magnetic resonance identifying atrial involvement in the patient with amyloidosis: left ventricular outflow tract.

Panel C Cardiovascular magnetic resonance identifying atrial involvement in the patient with amyloidosis: four-chamber view.