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Association Between Cardiorespiratory Fitness and Incident Purchase of Hypnotic Drugs in Adults. The HUNT Study.

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Abstract

Study Objectives: To assess if cardiorespiratory fitness (CRF) is associated with first purchase of a prescribed hypnotic drug in the adult population.

Patients and Methods: A total of 34,357 adult participants (53.9% women) with a mean (SD) age of 51.5 (15.6) from the third Trøndelag Health Study (HUNT) in 2007-09 were followed until 1 January 2018. CRF was estimated from a validated non-exercise algorithm. Data on first hypnotics prescription was obtained through linkage to the National Norwegian Prescription Database. Cox regression with 95% confidence intervals (CIs) was used to estimate hazard ratios (HRs).

Results: After 304,899 person-years of follow-up 5791 participants had their first registered purchase of prescribed hypnotics corresponding to an incidence rate of 1.90 per 100 person years. Each 1-metabolic equivalent increase in CRF was significantly associated with 5% (HR 0.95; 95% CI, 0.91-0.99, *P*=.02) and 4% (HR 0.96, 95% CI, 0.92-1.00, *P*=.046) risk reduction for incident use of hypnotics in men and women, respectively. When CRF was categorized into tertiles with lowest CRF as reference group, reduced risk was 13% (HR 0.87, 95% CI, 0.79-0.96, *P*=.006) and 15% (HR 0.85, 95% CI, 0.77-0.95, *P*=.003) for men in the intermediate and highest CRF category, respectively. In women with highest CRF the reduced risk was 5% (HR 0.95, 95% CI, 0.87-1.03, *P*=.22).

Conclusion: Cardiorespiratory fitness in adulthood is associated with incident purchase of prescription medication commonly used for sleep problems. These findings suggest that fitness should be considered as a target for preventing sleep problems in adults.

ABBREVIATIONS

ATC= Anatomical Therapeutic Chemical Classification System

BZDs= benzodiazepine derivatives

CI= confidence interval

CRF= cardiorespiratory fitness

CVD= cardiovascular disease

HADS-A= Hospital Anxiety and Depression Scale- anxiety symptoms

HADS-D= Hospital Anxiety and Depression Scale - depressive symptoms

HUNT= Trøndelag Health Study

HR= hazard ratio

MET= metabolic equivalent

NorPD= Norwegian Presecription Database

PA= physical activity

Z-drugs= benzodiazepine-related drugs

Introduction

It is estimated that 50 to 70 million adults in the U.S[1] and 45 million adults in Europe[2] have a chronic sleep disorder that impacts daily functioning and health[3]. Further, sleep problems are associated with health conditions such as diabetes[4], hypertension and cardiovascular disease (CVD)[5, 6], depression[7], and dementia.[8] Insomnia, whether short-term or chronic, is the most common sleep disorder, and is characterized by difficulty initiating sleep, maintaining sleep or early-morning awakenings, resulting in daytime consequences such as tiredness, poor concentration and impairment in social, occupational, educational, academic, and behavioral functioning.[9, 10] Prevalence of insomnia is reported to vary between 5.8% and 43% in the general population[10-12], and 5-year incidence of insomnia is found to be 13.9%.[13] Hypnotics are medications used to induce or extend sleep, or improve the subjective quality of sleep.[14] Recent numbers suggest that the overall consumption of hypnotics has increased in the US[15, 16], Europe[17], and Australia.[18] Long-term use of these medications has shown negative side-effects such as an increased risk of; falls and fractures[19], sleep related breathing disorder[20], and serious injuries and death.[21, 22] Moreover, scientific evidence in favor of pharmacological treatment of chronic insomnia is not strong, and cognitive behavioral therapy is the mainstay of non-pharmacological treatment of chronic insomnia.[10, 23]

Meta-analyses support that both aerobic physical activity (PA)[24, 25] and strength training[26] are associated with improved sleep and less use of sleep medication. Exercise advice is also included as a behavioral component for optimal sleep hygiene[27] and a recent longitudinal study found a bidirectional association between PA and use of psychotropic drugs, including hypnotic drugs.[28]

PA and exercise enhance overall cardiorespiratory fitness (CRF), thus producing many benefits in the primary and secondary prevention of CVD.[29-31] While PA reflects bodily movements, CRF expresses the ability of the circulatory system to supply and utilize oxygen.[29] Several studies also support an association between CRF and brain health (ie, sleep complaints[32], depression[33-35], brain volumes[36], and dementia risk[37]) indicating a neuroprotective effect. Reduced physical activity and increased prevalence of obesity suggest that CRF levels in the adult population have decreased lately.[38] However, the association between CRF and use of prescribed sleep medication has not been evaluated. Thus, the aim of this study was to assess the prospective relationship between CRF and incident use of prescribed hypnotic medications, as a proxy for sleep problems, in a sample of adults from the general population.

METHODS

Study Design and Participants

Data was obtained from the third wave of the Trøndelag Health Study (HUNT). The HUNT Study is one of the largest population-based studies ever performed, where all inhabitants of the Nord-Trøndelag County in Norway aged ≥20 years were invited to HUNT1 (1984-1986) [39], HUNT2 (1995-1997)[40], HUNT3 (2006-2008)[41], and HUNT4 (2017-2019).[42] In the present study, we included data from HUNT3. A total of 50,810 individuals (54.1% of those invited) participated in HUNT3. Further details on the HUNT3 study are described elsewhere.[41] Data from all participants in the HUNT Study was linked to the Norwegian Prescription Database (NorPD)[43] through their unique Norwegian personal identification numbers to obtain information on purchases of prescribed hypnotic medication. All participants in the HUNT study provided informed consent. The current study was approved by the Regional Committee for Ethics in Medical Research in Norway (no. 2017/382 REK sør øst D) and followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.[44]

Hypnotic Medication

NorPD was established on January 1st 2004 at the Norwegian Institute of Public Health, and contains data on all drugs approved by the Norwegian Medicines Agency dispensed in Norwegian pharmacies.[43, 45] Purchases of prescribed drugs used for sleep problems were classified as hypnotics (N05) according to the Anatomical Therapeutic Chemical classification system (ATC).[46] These included Benzodiazepine derivatives (BZDs) (N05CD), Benzodiazepine-related drugs, hereafter referred to as Z-drugs (N05CF), and melatonin receptor agonists, hereafter melatonin (N05CH). Further details on medication types included in this study are provided in Supplemental Table 1 (available online). We included data on the first registered purchase of hypnotic medication from January 1st 2004 to January 1st 2018, and all subsequent purchases were excluded from the analyses.

*Insert Table 1 here

Cardiorespiratory Fitness

CRF in ml/kg/min was estimated based on a previously validated non-exercise prediction model developed using data from the HUNT Study.[47] The CRF prediction model is based on sex, age, waist circumference (WC), resting heart rate (rHR), and self-reported PA. WC and rHR were assessed at the clinical examinations at HUNT3, whereas information on self-reported PA was obtained from validated questions.[48] Further details on the CRF prediction model and calculation of the PA index used in the model have been described elsewhere.[47] The sex-specific prediction models are as follows:

*Men: 100.27 – (0.296 * age) – (0.369 * WC) – (0.155 * rHR) + (0.226 * PA index)*

*Women: 74.74 – (0.247 * age) – (0.259 * WC) – (0.114 * rHR) + (0.198 * PA index)*

We calculated metabolic equivalent of task (MET) values by dividing CRF in ml/kg/min by 3.5. The MET values were used as a continuous variable in the analyses. Further, by dividing the participants into age (10-year)- and sex-specific tertiles of the CRF distribution, participants were categorized into three CRF groups: low (lowest tertile), intermediate (middle tertile), or high (highest tertile).

Other Covariates

Information on age, sex, education (primary, secondary, or tertiary), marital status (unmarried, married, or widowed/separated/divorced), alcohol consumption (once a month or less, 2-4 times per month, 2-3 times per week, 4 times per week or more), sleep-related problems (no, moderate, or severe; based on two questions regarding how often the participant experiences trouble falling asleep or waking up during the night), symptoms of anxiety and depression (assessed using the validated Hospital Anxiety and Depression Scale[49, 50]), longstanding limiting illness of physical or psychological nature (no or yes), and regular shift work or graveyard shifts (no or yes) was obtained from the HUNT3 questionnaires.

Statistical Analysis

In the present study, 7476 participants were excluded because their first registered purchase of hypnotics occurred before or within 3 months after their participation in HUNT3. Further, 94 participants were excluded due to the purchase of dementia medication (ATC code N06D) prior to or within 3 months after participation in HUNT3. Finally, 8883 participants were excluded due to missing values on one or more variables included in the CRF equation. A multivariate multiple imputation procedure with 10 imputations was used to replace missing values on possible confounders (0.2%-31.7%) and this dataset was used for the multivariable analyses. The final study sample comprised 34,357 participants from HUNT3. Start of follow-up was 3 months after participation in HUNT3 to decrease the likelihood of a prescription of hypnotic medication while participating in HUNT3. The participants were followed up until their first registered purchase of hypnotic medication, death, emigration, or study end on January 1st 2018, whichever occurred first.

Baseline characteristics were obtained using descriptive statistics and frequencies. We used Cox proportional hazards models to obtain hazard ratios (HR) with corresponding 95% confidence intervals (CIs) for the association of CRF with first registered purchase of hypnotic medication. The analyses were performed in a two-step manner, where the first step (Model 1) was adjusted for age, whereas the second step (Model 2) was adjusted for age, sex, education, marital status, alcohol consumption, sleep problems, symptoms of anxiety and depression, and longstanding limiting illness.

Statistical interaction with age, sex, and regular shift work was assessed by including an interaction term (eg, CRF * sex) in Model 2. If the interaction term was statistically significant, we performed stratified analyses to further assess effect modification of the association between CRF and first registered purchase of hypnotic medication. When stratified by age, the analyses were carried out for young-to-middle-aged adults (< 65 years) and older adults (≥ 65 years) separately, as studies indicate that older adults have higher prevalence of insomnia symptoms and insomnia disorder.[51]

The proportional hazards assumption was investigated by running Cox models with time-dependent variables (interactions between the variable and time).[52] If the proportional hazards assumption was violated, we included the time-dependent variable in the final Cox model.[53] Several violations of the proportionality assumption were observed (Supplemental Table 2, available online at). Additionally, we performed sensitivity analyses to assess whether the association between CRF and purchase of hypnotic medication differs according to follow-up time. Changing the follow-up time had marginal effects on the estimates, indicating that observed violations of the PH assumption were not a major issue in our analyses (data not shown). All analyses were performed in IBM SPSS v. 26, and a *P* value below .05 was considered an indicator of statistical significance.

RESULTS

Sample Characteristics

The 34,357 participants, with a mean age 51.5 years (SD 15.6 years), of which 53.9% were women, were followed up for a mean of 8.9 years (SD 2.6 years). During the follow-up where the participant contributed a total of 304,899 person years, 5791 participants had their first registered purchase of hypnotic medication (incidence rate 1.90 per 100 person years), 229 had their first registered purchase of BZDs (incidence rate 0.08 per 100 person years), 4997 had their first registered purchase of Z-drugs (incidence rate 1.64 per 100 person years), and 1485 had their first registered purchase of melatonin (incidence rate 0.49 per 100 person years). Baseline characteristics of the study sample by CRF tertiles are presented in **Table 1.**

*****Insert Table 1 here

CRF and Hypnotic Medication

Cox regression analyses (**Table 2**) adjusted for age, sex, education, marital status, alcohol consumption, sleep problems, symptoms of anxiety and depression, and longstanding limiting illness (Model 2) showed a significantly lower risk of hypnotic medication purchase per 1-MET increment in CRF (HR 0.96, 95% CI 0.93-0.99, *P*=.004). When compared to those with low CRF, those with intermediate CRF had 5% lower risk (HR 0.95, 95% CI 0.89-1.01, *P*=.085), while those with high CRF had 9% reduced risk of purchasing hypnotics (HR 0.91, 95% CI 0.86-0.98, *P*=.006). We observed statistically significant interactions for CRF in METs and CRF in tertiles with sex and age (all *P* values<.05) thus the main analyses were stratified by sex and age. No statistically significant interaction was observed for CRF in METs and shift work (*P*=.18) or CRF in tertiles and shift work (*P*=.98).

*Insert Table 2 here

Analyses stratified by sex (**Table 3**) indicated that each 1-MET increment in CRF was significantly associated with a decreased risk of hypnotic medication purchase for both women and men (Model 2: women HR 0.96, 95% CI 0.92-1.00, *P*=.046; men HR 0.95, 95% CI 0.91-0.99, *P*=.02). Women in the intermediate and high CRF tertiles did not have a significantly different risk of hypnotic medication purchase when compared to women in the low CRF tertile (intermediate HR 1.00, 95% CI 0.91-1.08, *P*=.95; high HR 0.95, 95% CI 0.87-1.03, *P*=.22) . Men in the intermediate and high CRF tertiles had significantly lower risk of hypnotic medication purchase when compared to men in the low CRF tertile (Model 2: intermediate HR 0.87, 95% CI 0.79-0.96, *P*=.006; high HR 0.85, 95% CI 0.77-0.95, *P*=.003).

*Insert Table 3 here

When stratified by age (< 65 years old or ≥ 65 years old; **Table 4**), results from the fully adjusted (Model 2) showed that each 1-MET increment in CRF was significantly associated with lower risk of hypnotic medication purchase in both age groups (< 65 y/o HR 0.93, 95% CI 0.90-0.96, *P*<.001; ≥ 65 y/o HR 0.89, 95% CI 0.85-0.94, *P*<.001).

*Insert Table 4 here

Participants in both age groups who were in the high CRF tertile had significantly lower risk of hypnotic medication purchase compared to participants in the low CRF tertile, and the association was slightly stronger in the oldest age group (Model 2: < 65 y/o HR 0.92, 95% CI 0.86-1.00, *P*=.046; ≥ 65 y/o HR 0.89, 95% CI 0.79-1.00, *P*=.04).

DISCUSSION

To the best of our knowledge, the current study is the first to assess the association between CRF and the purchase of prescribed hypnotic drugs. Results from our large population-based study include 34,357 participants and found higher baseline CRF to be associated with lower risk for incident purchase of prescribed hypnotics. This association seems to be stronger in men and in older adults. When CRF was analyzed as a continuous variable we found that each 1 metabolic equivalent (1-MET) increase in CRF was associated with a reduced risk of incident purchase of prescribed hypnotics by 4% in women, the corresponding risk reduction in men was 5%. In turn this implies that women and men with an increase in CRF corresponding to 2-3 METs have a 8-15% lower likelihood of receiving a prescription of hypnotics.

Our results are in line with prospective[32] and cross-sectional findings on the association between CRF and sleep problems.[54, 55] However, a recent cross-sectional study did not find correlation between CRF and sleep quality in a smaller sample of students.[56] PA and CRF are highly inter-related, and PA is the main modifiable determinant of CRF. In general, the greater the activity amount or intensity, the greater the increase in CRF.[29] A recent meta-analysis[57] also found aerobic exercise interventions to have a significant positive influence on primary insomnia, especially in older patients.

Our findings correspond to findings on the relation between PA and use of prescribed psychotropic medication.[28, 58] Lahti et al.[58] found that the associations were similar for the two main groups of psychotropic drugs; antidepressants and sleep medication. They also found that 13.5% of those being inactive versus 8.5% of those being categorized as most active purchased sleep medication. The corresponding numbers were higher in our sample as 18.2% of those with lowest CRF and 15.7% of those with highest CRF purchased hypnotics during follow-up. Nevertheless, given that non-pharmacological treatment of insomnia is recommended as primary treatment for chronic insomnia[10, 23], these findings illustrate that use of hypnotics is common, also among those with higher CRF. In fact, purchase of prescribed hypnotics in our large sample is quite similar to self-reported use of hypnotics in a Norwegian study of 1346 patients visiting their general practitioner.[59] The slightly stronger associations between CRF and use of hypnotics in older adults in our study might be expected since prevalence of insomnia and use of sleep medication is found to be higher in older individuals than in the younger population.[11, 60, 61]

A stronger association between CRF and hypnotics in men than women in this study is in line with the inverse relation between treadmill endurance and sleep complaints among people in their fifties shown by Dishman et al.[32] However, a recent American study on trends in use of Benzodiazepines, Z-hypnotics and Serotonergic Drugs in 17,244 millions of adults, found that women, compared to men, had a considerably higher rate of prescriptions for all 3 drugs classes.[62] The observed sex-difference in insomnia and use of prescribed psychotropic drugs suggest a complicated interplay of biological, psychological, and social factors[11], thus the mechanisms behind our results need further investigation.

Strengths and Limitations

The large sample size with participants from the general population and the long-term follow up with linkage to the national registry NorPD with information about all individual purchased hypnotic drugs in Norway constitute considerable strengths of the current study. However, several limitations should be noted. Drug use in hospitals and nursing homes is not registered at an individual level in NorPD[43], meaning that if many participants in HUNT3 only received hypnotics as patients in a clinical setting our estimates may be too low. We only had data from NorPD two to four years prior to participation in HUNT3(2006-08), thus we were not able to take prescriptions of drugs used for sleep problems in earlier life into account. Importantly, major depressive disorders and anxiety disorders often overlap, and insomnia is prevalent in both conditions.[63] We did not have access to medical records or indication for prescription, thus specific medical diagnoses under medical treatment at baseline such as cancer as well as substance use and some sleep disorders may have influenced CRF through decreased PA level, thereby causing a further need for medical treatment for sleep problems, suggesting that CRF may not be directly related to incident use of prescribed hypnotics. Nevertheless, we believe that the exclusion of participants purchasing hypnotics several years prior to baseline and the first three months of follow-up have reduced the risk for reverse causality. Still, drugs from other ATC groups can be prescribed in relation to sleep problems meaning that our definition of hypnotics may have underestimated the real use.

CRF was estimated from a non-exercise algorithm which is not as precise as values obtained from cardiopulmonary testing. However, non-exercise algorithms have been validated against objectively assessed oxygen uptake[47, 64] and have in previous HUNT studies proven to be significantly associated with myocardial infarction[65], CVD mortality[64], depressive symptoms[34], brain volumes[36], and dementia risk.[66] Still, as CRF is suggested to be region- or country-specific[67], and that country-specific regulations exist regarding the manufacturing, import, sale and distribution of medicines, our results need to be confirmed in other populations.

CONCLUSIONS

In summary, we found that baseline CRF was associated with incident purchase of hypnotics, and that this association seemed to be slightly stronger in men and in those aged 65 years and older, as compared to women and lower age, respectively. In a public health perspective these findings are important for preventive purposes as prevalence of sleep problems are high and that use of prescribed hypnotics with potential harmful side-effects are widespread.

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SUPPLEMENTAL ONLINE MATERIAL

Supplementary material can be found online at. Supplemental material attached to journal articles has not been edited, and the authors take the responsibility for the accuracy of all data.

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TABLE 1. Baseline Characteristics of Study Participants by CRF level (N=34,357)[a,b,c]

	Low (n=11,448)	Intermediate (n=11,462)	High (n=11,447)
Age, mean (SD), y	52.2 ± 15.6	51.5 ± 15.6	50.8 ± 15.7
Sex, n (% women)	6172 (53.9)	6179 (53.9)	6169 (53.9)
Education, n (%)			
Primary	2628 (23.0)	2230 (19.5)	1750 (15.3)
Secondary	3912 (34.2)	3938 (34.4)	3643 (31.8)
Tertiary	1501 (13.1)	1973 (17.2)	2652 (23.2)
Marital status, n (%)			
Unmarried	2867 (25.0)	2753 (24.0)	2777 (24.3)
Married	6739 (58.9)	6950 (60.6)	6947 (60.7)
Widow(er)/separated/divorced	1830 (16.0)	1,740 (15.2)	1,702 (14.9)
Alcohol consumption, n (%)			
Once a month or less	5080 (44.4)	4194 (36.6)	3807 (33.3)
2-4 times per month	4768 (41.6)	5307 (46.3)	5392 (47.1)
2-3 times per week	1196 (10.4)	1554 (13.6)	1819 (15.9)
4 times per week or more	235 (2.1)	278 (2.4)	314 (2.7)

Sleep problems, n (%)			
No	9596 (83.8)	9833 (85.8)	9917 (86.6)
Moderate	1423 (12.4)	1287 (11.2)	1217 (10.6)
Severe	429 (3.7)	342 (3.0)	313 (2.7)
[d]HADS-A, mean (SD)	3.76 ± 3.16	3.69 ± 3.00	3.68 ± 2.99
[e]HADS-D, mean (SD)	3.32 ± 2.85	2.98 ± 2.70	2.71 ± 2.58
Longstanding limiting illness, yes, n (%)	4849 (42.4)	3992 (34.8)	3348 (29.2)
Regular shift work, yes, n (%)	2241 (19.6)	2283 (19.9)	2206 (19.3)
CRF, ml/kg/min, mean (SD)	31.5 ± 6.90	36.8 ± 6.89	41.6 ± 7.60
Hypnotics purchase, n (%)	2082 (18.2)	1910 (16.7)	1799 (15.7)
[f]BZDs	75 (0.7)	96 (0.8)	58 (0.5)
[g]Z-drugs	1829 (16.0)	1627 (14.2)	1541 (13.5)
Melatonin	487 (4.3)	505 (4.4)	493 (4.3)

[a]Before multiple imputation.
[b]CRF, cardiorespiratory fitnesss.
[c]Data are presented as mean (SD) or as No. (percentage).
[d]HADS-A, Hospital Anxiety and Depression Scale-anxiety symptoms.
[e]HADS-D, Hospital Anxiety and Depression Scale-depression symptoms
[f]BZDs, benzodiazepine derivatives.
[g]Z-drugs, benzodiazepine-related drugs.

TABLE 2. Hazard ratios (HR) and 95% confidence intervals (CI) for first registered purchase of prescription hypnotic medication by CRF in METs and tertiles[a]

	Cases/100 person years	Model 1 HR (95% CI)	*P*	Model 2 HR (95% CI)	*P*
CRF (METs)	1.90/100	0.89 (0.87-0.91)	<.001	0.96 (0.93-0.99)	.004
CRF tertiles					
Low	2.08/100	1.00 (ref.)		1.00 (ref.)	
Intermediate	1.87/100	0.91 (0.86-0.97)	.003	0.95 (0.89-1.01)	.09
High	1.75/100	0.86 (0.81-0.92)	<.001	0.91 (0.86-0.98)	.006

[a]Hazard ratio, HR, confidence interval, CI, metabolic equivalent, MET, CRF, cardiorespiratory fitness.

Model 1 adjusted for age.

Model 2 adjusted for age, sex, education, marital status, alcohol consumption, sleep problems, HADS-A, anxiety symptoms, HADS-D, depressive symptoms, and longstanding limiting illness.

TABLE 3. Hazard ratios (HR) and 95% confidence intervals (CI) for first registered purchase of prescription hypnotic medication by CRF in METs and tertiles, stratified by sex[a]

	Women					Men				
	Cases/100 person years	Model 1 HR (95% CI)	*P*	Model 2 HR (95% CI)	*P*	Cases/100 person years	Model 1 HR (95% CI)	*P*	Model 2 HR (95% CI)	*P*
CRF (METs)	2.18/100	0.93 (0.90-0.97)	.001	0.96 (0.92-1.00)	.046	1.58/100	0.91 (0.88-0.95)	<.001	0.95 (0.91-0.99)	.02
CRF tertiles										
Low	2.30/100	1.00 (ref.)		1.00 (ref.)		1.84/100	1.00 (ref.)		1.00 (ref.)	
Intermediate	2.20/100	0.97 (0.90-1.05)	.51	1.00 (0.92-1.08)	.95	1.49/100	0.83 (0.75-0.91)	<.001	0.87 (0.79-0.96)	.006
High	2.03/100	0.91 (0.83-0.99)	.02	0.95 (0.87-1.03)	.22	1.42/100	0.80 (0.72-0.88)	<.001	0.85 (0.77-0.95)	.003

[a]Hazard ratio, HR, confidence interval, CI, metabolic equivalent, MET, CRF, cardiorespiratory fitness.

Model 1 adjusted for age.

Model 2 adjusted for age, education, marital status, alcohol consumption, sleep problems, HADS-A, anxiety symptoms, HADS-D, depressive symptoms, and longstanding limiting illness.

TABLE 4. Hazard ratios (HR) and 95% confidence intervals (CI) for first registered purchase of prescription hypnotic medication by CRF in METs and tertiles, stratified by age group[a]

	< 65 y/o					≥ 65 y/o				
	Cases/100 person years	Model 1 HR (95% CI)	*P*	Model 2 HR (95% CI)	*P*	Cases/100 person years	Model 1 HR (95% CI)	*P*	Model 2 HR (95% CI)	*P*
CRF (METs)	1.61/100	0.85 (0.83-0.88)	<.001	0.93 (0.90-0.96)	<.001	3.22/100	0.87 (0.83-0.91)	<.001	0.89 (0.85-0.94)	<.001
CRF tertiles										
Low	1.75/100	1.00 (ref.)		1.00 (ref.)		3.48/100	1.00 (ref.)		1.00 (ref.)	
Intermediate	1.57/100	0.90 (0.84-0.97)	.006	0.94 (0.87-1.01)	.10	3.24/100	0.93 (0.83-1.04)	.21	0.96 (0.86-1.08)	.51
High	1.50/100	0.86 (0.80-0.93)	<.001	0.92 (0.86-1.00)	.046	2.91/100	0.84 (0.75-0.94)	.03	0.89 (0.79-1.00)	.04

[a]Hazard ratio, HR, confidence interval, CI, metabolic equivalent, MET, CRF, cardiorespiratory fitness.

Model 1 unadjusted.

Model 2 adjusted for sex, education, marital status, alcohol consumption, sleep problems, HADS-A, anxiety symptoms, HADS-D, depressive symptoms, and longstanding limiting illness.