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

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Abstract

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

Methods: A total of 34,357 adult participants (53.9% women) with a mean age of 51.5 years (SD 15.6 years) from the third Trøndelag Health Study (HUNT) of 2006 to 2008 were observed until January 1, 2018. Cardiorespiratory fitness was estimated from a validated nonexercise algorithm. Data on first hypnotics prescription were obtained through linkage to the National Norwegian Prescription Database. Cox regression with 95% 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 of task increase in CRF was significantly associated with 5% (HR, 0.95; 95% CI, 0.91 to 0.99; *P*=.02) and 4% (HR, 0.96; 95% CI, 0.92 to 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 the reference group, reduced risk was 13% (HR, 0.87; 95% CI, 0.79 to 0.96; *P*=.006) and 15% (HR, 0.85; 95% CI, 0.77 to 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 to 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 a target for preventing sleep problems in adults.

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It is estimated that 50 to 70 million adults in the United States[1] and 45 million adults in Europe[2] have a chronic sleep disorder that affects daily functioning and health.[3] Furthermore, 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 acute or chronic, is the most common sleep disorder. It is characterized by difficulty in initiating sleep, difficulty in maintaining sleep, or early-morning awakenings, resulting in daytime consequences such as tiredness, poor concentration, and impairment in functioning (social, occupational, educational, academic, and behavioral).[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 to extend sleep or to improve the subjective quality of sleep.[14] Recent numbers suggest that the overall consumption of hypnotics has increased in the United States,[15,16] Europe,[17] and Australia.[18] Adverse effects, such as an increased risk of falls and fractures,[19] sleep-related breathing disorder,[20] and serious injuries and death,[21,22] have been reported with long-term use of these

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medications. Moreover, scientific evidence in favor of pharmacologic treatment of chronic insomnia is not strong, and cognitive-behavioral therapy is the mainstay of non-pharmacologic 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 longitudinal study found a bidirectional association between PA and use of psychotropic drugs, including hypnotic drugs.[28]

Physical activity and exercise enhance overall cardiorespiratory fitness (CRF), thus producing many benefits in the primary and secondary prevention of CVD.[29-31] Whereas PA reflects body movements, CRF expresses the ability of the circulatory system to supply and to use 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 PA 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 were obtained from the third wave of the Trøndelag Health Study (HUNT). The HUNT Study is one of the largest population-based studies ever performed; all inhabitants of the Nord-Trøndelag County in Norway 20 years of age or older were invited to HUNT1 (1984-1986),[39] HUNT2 (1995-1997),[40] HUNT3 (2006-2008),[41] and HUNT4 (2017-2019).[42] In this study, we included data from HUNT3. A total of 50,810 individuals (54.1% of those invited) participated in HUNT3. Further details of the HUNT3 study are described elsewhere.[41] Data from all participants in the HUNT Study were 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 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 reporting guideline.[44]

Hypnotic Medication

The NorPD was established on January 1, 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 (N05CD); benzodiazepine-related drugs, hereafter referred to as Z-drugs (N05CF); and melatonin receptor agonists, hereafter referred to as melatonin (N05CH). Further details on medication types included in this study are provided in Supplemental Table 1 (available online at http://www.mayoclinicproceedings.org). We included data on the first registered purchase of hypnotic medication from January 1, 2004, to January 1, 2018, and all subsequent purchases were excluded from the analyses.

Cardiorespiratory Fitness

Cardiorespiratory fitness was estimated on the basis of a previously validated nonexercise prediction model developed with 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 milliliters per kilogram per minute, by 3.5. The MET values were used as a continuous variable in the analyses. Furthermore, by dividing the participants into age (10-year)− and sex-specific tertiles of the CRF distribution, participants were assigned to 3 CRF groups: low (lowest tertile), intermediate (middle tertile), and high (highest tertile).

Other Covariates

Information on age, sex, education (primary, secondary, or tertiary), marital status (unmarried; married; widowed, separated, or divorced), alcohol consumption (once a month or less, 2 to 4 times per month, 2 or 3 times per week, 4 times per week or more), sleep-related problems (no, moderate, or severe; based on 2 questions about how often the participant experiences trouble falling asleep or waking up during the night), symptoms of anxiety and depression (assessed by the validated Hospital Anxiety and Depression Scale[49,50]), long-standing 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 Analyses

In this study, 7476 participants were excluded because their first registered purchase of hypnotics occurred before or within 3 months after their participation in HUNT3. Furthermore, 94 participants were excluded because of the purchase of dementia medication (ATC code N06D) before or within 3 months after participation in HUNT3. Finally, 8883 participants were excluded because of missing values on 1 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% to 31.7%), and this data set 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 during participation in HUNT3. The participants were followed up until their first registered purchase of hypnotic medication, death, emigration, or study end on January 1, 2018, whichever occurred first.

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

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, years	52.2±15.6	51.5±15.6	50.8±15.7
Sex, female	6172 (53.9)	6179 (53.9)	6169 (53.9)
Education			
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			
Unmarried	2867 (25.0)	2753 (24.0)	2777 (24.3)
Married	6739 (58.9)	6950 (60.6)	6947 (60.7)
Widowed, separated, divorced	1830 (16.0)	1740 (15.2)	1702 (14.9)
Alcohol consumption			
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			
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)
HADS-A		3.69±3.00	3.68±2.99
HADS-D	3.32±2.85	2.98±2.70	2.71±2.58
Long-standing limiting illness, yes	4849 (42.4)	3992 (34.8)	3348 (29.2)
Regular shift work, yes	2241 (19.6)	2283 (19.9)	2206 (19.3)
CRF, mL/kg per minute	31.5±6.90	36.8±6.89	41.6±7.60
Hypnotics purchase	2082 (18.2)	1910 (16.7)	1799 (15.7)
BZDs	75 (0.7)	96 (0.8)	58 (0.5)
Z-drugs	1829 (16.0)	1627 (14.2)	1541 (13.5)
Melatonin	487 (4.3)	505 (4.4)	493 (4.3)

[a]BZDs, benzodiazepine derivatives; CRF, cardiorespiratory fitness; HADS-A, Hospital Anxiety and Depression Scale—anxiety symptoms; HADS-D, Hospital Anxiety and Depression Scale—depression symptoms; Z-drugs, benzodiazepine-related drugs.
[b]Data are presented as mean (standard deviation) or number (percentage).
[c]Before multiple imputation.

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 http://www.mayoclinicproceedings.org). In addition, 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 proportional hazards assumption were not a major issue in our analyses (data not shown). All analyses were performed in IBM SPSS software version 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 of 51.5 years (SD 15.6 years), of whom 18,520 (53.9%) were women, were followed up for a mean of 8.9 years (SD 2.6 years). During the follow-up, in which the participants contributed a total of 304,899 person-years, 5791-participants had their first registered purchase of hypnotic medication (incidence rate of 1.90 per 100 person-years), 229 had

TABLE 2. Hazard Ratios and 95% CIs for First Registered Purchase of Prescription Hypnotic Medication by CRF in METs and Tertiles

	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 (reference)		1.00 (reference)	
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

CRF, cardiorespiratory fitness; HR, hazard ratio; METs, metabolic equivalents of task.

Model 1 adjusted for age.

Model 2 adjusted for age, sex, education, marital status, alcohol consumption, sleep problems, symptoms of anxiety and depression assessed by the Hospital Anxiety and Depression Scale, and long-standing limiting illness.

their first registered purchase of benzodiazepine derivatives (incidence rate of 0.08 per 100 person years), 4997 had their first registered purchase of Z-drugs (incidence rate of 1.64 per 100 person years), and 1485 had their first registered purchase of melatonin (incidence rate of 0.49 per 100 person years). Baseline characteristics of the study sample by CRF tertiles are presented in Table 1.

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 long-standing limiting illness (Model 2) found a significantly lower risk of hypnotic medication purchase per 1-MET increment in CRF (HR, 0.96; 95% CI, 0.93 to 0.99; *P*=.004). Compared with those with low CRF, those with intermediate CRF had 5% lower risk (HR, 0.95; 95% CI, 0.89 to 1.01; *P*=.085), whereas those with high CRF had 9% reduced risk of purchasing hypnotics (HR, 0.91; 95% CI, 0.86 to 0.98; *P*=.006). We observed statistically significant interactions for CRF in METs and CRF in tertiles with sex and age (all *P*<.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).

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 to 1.00; *P*=.046]; men: HR, 0.95 [95% CI, 0.91 to 0.99, *P*=.02]). Women in the intermediate and high CRF tertiles did not have a significantly different risk of hypnotic medication purchase compared with women in the low CRF tertile (intermediate: HR, 1.00 [95% CI, 0.91 to 1.08, *P*=.95]; high: HR, 0.95 [95% CI, 0.87 to 1.03; *P*=.22]). Men in the intermediate and high CRF tertiles had significantly lower risk of hypnotic medication purchase compared with men in the low CRF tertile (model 2, intermediate: HR, 0.87 [95% CI, 0.79 to 0.96; *P*=.006]; high: HR, 0.85 [95% CI, 0.77 to 0.95, *P*=.003]).

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

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

TABLE 3. Hazard Ratios and 95% CIs for First Registered Purchase of Prescription Hypnotic Medication by CRF in METs and Tertiles, Stratified by Sex

	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 (reference)		1.00 (reference)		1.84/100	1.00 (reference)		1.00 (reference)	
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

CRF, cardiorespiratory fitness; HR, hazard ratio; METs, metabolic equivalents of task.

Model 1 adjusted for age.

Model 2 adjusted for age, education, marital status, alcohol consumption, sleep problems, symptoms of anxiety and depression assessed by the Hospital Anxiety and Depression Scale, and long-standing limiting illness.

DISCUSSION

To the best of our knowledge, this 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-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 or 3 METs have an 8% to 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 cross-sectional study did not find correlation between CRF and sleep quality in a smaller sample of students.[56] Physical activity and CRF are highly interrelated, 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 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 2 main groups of psychotropic drugs, antidepressants and sleep medication. They also found that 13.5% of those being inactive vs 8.5% of those being described 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 nonpharmacologic treatment of insomnia is recommended for primary treatment of chronic insomnia,[10,23] these findings illustrate that use of hypnotics is also common among those with higher CRF. In fact, purchase of prescribed hypnotics in our large sample is 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 because 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 in women in this

TABLE 4. Hazard Ratios and 95% CIs for First Registered Purchase of Prescription Hypnotic Medication by CRF in METs and Tertiles, Stratified by Age Group

	<65 years old					≥65 years old				
	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 (reference)		1.00 (reference)		3.48/100	1.00 (reference)		1.00 (reference)	
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

CRF, cardiorespiratory fitness; HR, hazard ratio; METs, metabolic equivalents of task.

Model 1 unadjusted.

Model 2 adjusted for sex, education, marital status, alcohol consumption, sleep problems, symptoms of anxiety and depression assessed by the Hospital Anxiety and Depression Scale, and long-standing limiting illness.

study is in line with the inverse relation between treadmill endurance and sleep complaints of people in their 50s reported by Dishman et al.[32] However, an American study on trends in use of benzodiazepines, Z-hypnotics, and serotonergic drugs in 17,255,033 adults found that women, compared with men, had a considerably higher rate of prescriptions for all 3 drug classes.[62] The observed sex difference in insomnia and use of prescribed psychotropic drugs suggests a complicated interplay of biologic, psychological, and social factors[11]; thus, the mechanisms behind our results need further investigation.

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 this 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 received hypnotics only as patients in a clinical setting, our estimates may be too low. We had data from NorPD only 2 to 4 years before participation in HUNT3 (2006-2008); 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 of 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 before baseline and in the first 3 months of follow-up 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.

Cardiorespiratory fitness was estimated from a nonexercise algorithm that is not as precise as values obtained from cardiopulmonary testing. However, nonexercise algorithms have been validated against objectively assessed oxygen uptake[47,64] and have in previous HUNT studies proved 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 country-specific regulations exist for the manufacturing, import, sale, and distribution of medicines,

our results need to be confirmed in other populations.

CONCLUSION

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

POTENTIAL COMPETING INTERESTS

Dr Engstrøm disclosed leadership of the Norwegian Society of Sleep Medicine and consulting for Philips and ResMed at the Nordic sleep conference, May 2019. Dr Bjørn Bjorvatn disclosed leadership of the Norwegian Competence Center for Sleep Disorders, for consulting for Hoffmann-La Roche Ltd and Cura of Sweden, for receiving an honorarium from AGB-Pharma for an invited lecture, and for receiving royalties from a book in Norwegian on cognitive behavioral therapy for insomnia. The others have none to disclose.

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **ATC,** Anatomical Therapeutic Chemical classification system; **CRF,** cardiorespiratory fitness; **CVD,** cardiovascular disease; **HUNT,** Trøndelag Health Study; **HR,** hazard ratio; **MET,** metabolic equivalent of task; **NorPD,** Norwegian Prescription Database; **PA,** physical activity; **rHR,** resting heart rate; **WC,** waist circumference; **Z-drugs,** benzodiazepine-related drugs

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