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Research paper

Cardiorespiratory fitness and incident use of anxiolytics and antidepressants in adults. A linkage study between HUNT and the Norwegian Prescription Database

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ABSTRACT

Background: We investigated the association between cardiorespiratory fitness (CRF) and incident use of antidepressants or anxiolytics in the general adult population.
Methods: A non-exercise prediction model was used to estimate CRF in 32,603 participants in the third wave of the Trøndelag Health Study (HUNT3; 2006–08). Data on first purchase of antidepressants and anxiolytics were obtained from the Norwegian Prescription Database. Cox regression was used to estimate hazard ratios (HRs).
Results: Each 1- metabolic equivalent of task (MET) increase in CRF was associated with 4 % reduced risk of purchasing antidepressant or anxiolytic medication during follow-up (HR 0.96, 95 % Confidence interval [CI] 0.94–0.98). Compared to the low CRF tertile, participants in intermediate (HR 0.93, 95 % CI 0.87–0.98) and high (HR 0.92, 95 % CI 0.86–0.98) CRF tertiles had reduced risk of medication purchase. Men in intermediate and high CRF tertile had lower risk of medication purchase (intermediate HR 0.87, 95 % CI 0.79–0.96; high HR 0.87, 95 % CI 0.78–0.96). Intermediate and high CRF tertiles were associated with reduced risk of medication use for younger adults (20 to <30 years old; intermediate HR 0.74, 95 % CI 0.61–0.91, high HR 0.78, 95 % CI 0.64–0.95) and middle-aged adults (30 to <65 years old; intermediate HR 0.90, 95 % CI 0.83–0.97, high HR 0.90, 95 % CI 0.84–0.98), but not in older adults (≥65 years old).
Limitations: Only information about medication purchase and not actual use was available.
Conclusion: Increased CRF is associated with reduced risk of anxiolytics and antidepressants purchase, with stronger effects for men and younger adults.

1. Introduction

Anxiety and depression are among the most prevalent psychiatric disorders in the general population (Baxter et al., 2013; Ferrari et al., 2013). The 12-month prevalence of anxiety disorders and major depressive disorder (MDD) in adults in the US has been estimated to be around 18 % and 7 %, respectively (Kessler et al., 2005). Psychological interventions like cognitive behavioral therapy are recommended as treatment for both anxiety disorders and MDD (APA Presidential Task Force on Evidence-Based Practice, 2006), and studies also show that pharmacological treatment may be equally effective as psychotherapy in the treatment of these disorders (Cuijpers et al., 2013). Antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), are recommended in the clinical guidelines for several anxiety disorders and MDD (National Institute for Health and Care Excellence, 2022). Although antidepressants are effective, side effects such as headaches, insomnia, anxiety, sexual dysfunction and weight gain are reported (Santarsieri and Schwartz, 2015). Anxiolytics like benzodiazepine are not recommended as routine treatment of anxiety disorders because of the risk of dependence, but may be used as short-term treatment of anxiety

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disorders (National Institute for Health and Care Excellence, 2014). It is expected that many individuals suffering from symptoms of anxiety and depression will have received prescriptions of anxiolytics or antidepressants, and medication use has been reported to be increasing in Europe (Estrela et al., 2020) and the USA (Olfson et al., 2019).

Studies suggest that physical activity is an effective treatment for MDD and depressive symptoms (Ashdown-Franks et al., 2020; Kvam et al., 2016; Rethorst et al., 2009). The effect of physical activity on anxiety disorders is less clear. Meta-analyses have found a small effect of physical activity on anxiety (Ashdown-Franks et al., 2020; Rebar et al., 2015), but as data from large randomized controlled trials are scarce, this association needs further investigation. Large-scale population-based studies may also inform the understanding of the possible anxiolytic effect of physical activity.

Physical activity is bodily movements that require energy exposure, whereas cardiorespiratory fitness (CRF) reflects how well the circulatory, respiratory and muscular systems provide sufficient oxygen during prolonged exercise. Increased physical activity is associated with increased CRF, and studies show an association between higher CRF and reduced risk of depression (Baumeister et al., 2017; Dishman et al., 2012; Kandola et al., 2019; Loprinzi et al., 2017) and to some degree anxiety symptoms (Shigdel et al., 2019). Individuals with low and intermediate CRF are at an increased risk of developing depression compared to individuals with high CRF (Schuch et al., 2016). The association between increased CRF and reduced risk of psychological symptoms indicates that improved CRF may potentially reduce the need for pharmacological treatment of mental health problems. Physical activity may therefore be promoted as a low cost and highly accessible alternative both in the prevention and treatment of mental illness. Indeed, register based studies show that physical activity is associated with decreased risk of psychotropic medication prescriptions, including antidepressants and sleep medication (Lahti et al., 2013; Stubbs et al., 2017; Waller et al., 2016). However, despite the robust positive association between physical activity and mental health, the relationship between CRF and use of psychotropic medication based on register data has received less attention.

The aim of the current study was to investigate the prospective relationship between CRF at baseline and incident use of anxiolytics and antidepressants over more than ten years in a large adult sample from the general population.

2. Methods

2.1. Population

The Trøndelag Health Study (HUNT) is one of the largest population-based studies ever performed, where all inhabitants of the Nord-Trøndelag County in Norway aged 20 years and older were invited to participate in HUNT1 (1984–86) (Holmen et al., 1990), HUNT2 (1995–97) (Holmen et al., 2003), HUNT3 (2006–08) (Krokstad et al., 2013), and HUNT4 (2017–2019) (Åsvold et al., 2022). This study included data from HUNT3, where 50,810 individuals participated (54.1 % participation rate). The participants attended a clinical examination and filled out comprehensive questionnaires on health-related factors. Details on the HUNT3 study have been described previously (Krokstad et al., 2013).

Each participant in the HUNT Study has a unique Norwegian personal identification number, which allows linkage of data from all participants to national and international registries (Krokstad et al., 2013). We linked data from HUNT3 participants to data from the Norwegian Prescription Database (NorPD) to obtain information on purchases of prescribed anxiolytic and antidepressant medication.

2.2. Anxiolytic and antidepressant medication

NorPD was established on January 1st 2004 at the Norwegian Institute of Public Health (2021), and aims at collecting and processing data on drug consumption by humans and animals in Norway. We obtained data on purchases of prescribed anxiolytic and antidepressant medication from January 1st 2004 to January 1st 2018 for all participants of the HUNT3 study from NorPD. Purchases of anxiolytic and antidepressant medication were classified according to the Anatomical Therapeutic Chemical (ATC) classification system (WHO Collaborating Centre for Drug Statistics Methodology, 2021). For anxiolytics, we included all medications with the ATC code N05B, with the exception of N05BA06 (Lorazepam) and N05BA09 (Clobazam), as anxiety treatment is not the main indication of these drugs in Norway. For antidepressants, all medications with the ATC code N06A were included, with the exception of N06AX27 (Esketamine) which primarily has been used as an anesthetic in Norway. The primary outcome in the current study was the first registered purchase of anxiolytic or antidepressant medication between 3 months after participation in HUNT3 to January 1st 2018, meaning that all subsequent purchases were excluded from the analyses.

2.3. Cardiorespiratory fitness

We used a previously validated non-exercise prediction model based on sex, age, waist circumference (WC), resting heart rate (rHR), and self-reported physical activity to estimate CRF in milliliters per kilogram per minute (Nes et al., 2011). Information on self-reported physical activity was obtained from validated questions (Kurtze et al., 2008). WC and rHR were measured at the clinical examinations, whereas self-reported physical activity was assessed in questionnaires. Self-reported physical activity was recoded into a physical activity index which was used in the models. Further details on the physical activity index and on the CRF prediction model are provided elsewhere (Nes et al., 2011). The sex-specific models are as follows (Nes et al., 2011):

$$\text{Men}: 100.27 - (0.296^{*}\ \text{age}) - (0.369^{*}\ \text{WC}) - (0.155^{*}\ \text{rHR}) + (0.226^{*}\ \text{physical activity index})$$

$$\text{Women}: 74.74 - (0.247^{*}\ \text{age}) - (0.259^{*}\ \text{WC}) - (0.114^{*}\ \text{rHR}) + (0.198^{*}\ \text{physical activity index})$$

To increase comparability with previous studies, CRF in milliliters per kilogram per minute was divided by 3.5 to obtain metabolic equivalent of task (MET) values, which were used in further analyses. We also created a categorical CRF variable with three levels by dividing the participants into age (10-year)- and sex-specific tertiles of the CRF distribution: “low” (bottom tertile), “intermediate” (middle tertile), and “high” (top tertile).

2.4. 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 high; 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 Hospital Anxiety and Depression Scale (Zigmond and Snaith, 1983), and long-standing limiting illness of physical or psychological nature (participants are not asked to list specific disorders) was obtained from the HUNT3 questionnaires.

2.5. Statistical analyses

We excluded 9804 participants who had their first registered purchase of anxiolytics or antidepressants before or within 3 months after participation in HUNT3 to reduce the risk of reverse causation, as physical inactivity due to mental health problems may have led to reduced eCRF in this period, and that non-pharmacological treatments are recommended to be considered first for new episodes of less severe depression (National Institute for Health and Care Excellence, 2022). In addition, we excluded 87 participants who purchased dementia medication prior to or within 3 months after participation in HUNT3, and 8316 participants who had missing values on one or more variables included in the CRF prediction model. Missing values on possible confounders (0.1–29.2 %) were imputed using a multivariate multiple imputation procedure with 10 imputations. A total of 32,603 participants (53.2 % women) with a mean age of 52.0 years (SD 16.0 years) were included in the final study sample and in all statistical analyses. The participants were followed-up from 3 months after participation in HUNT3 until their first registered purchase of anxiolytic or antidepressant medication, death, emigration, or study end on January 1st 2018, whichever occurred first.

Descriptive statistics and frequencies were used to obtain baseline characteristics of the study sample. We used Cox proportional hazards models to obtain hazard ratios (HR) of the association of CRF with the first registered purchase of anxiolytic or antidepressant medication. The precision of the HR was assessed by 95 % confidence intervals (CIs). The proportional hazards assumption was investigated by running Cox proportional hazards models with time-dependent variables by including an interaction term between time and variable separately for each variable in the analysis. A statistically significant interaction term indicated violation of the proportional hazards assumption, and the time-dependent variable was thus included in the main analyses. A list of violations of the proportionality assumption is included in the appendix. In analyses where CRF tertiles were used as the exposure variable, the low CRF group served as the reference category. We performed the analyses in two steps. In the first step (model 1), we included age at HUNT3 in the model. In the second step (model 2), sex, education, marital status, alcohol consumption, sleep problems, symptoms of anxiety and depression, and longstanding limiting illness were added to the model.

We assessed statistical interaction of CRF with age and sex by adding an interaction term to model 2. In the case of a statistically significant interaction term, we performed stratified analyses. In analyses stratified by age, age was categorized into three groups: young adults (20 to <30 years old), adults (≥30 to <65 years old), and older adults (≥65 years old) as several studies indicate heightened prevalence of depressive and anxiety disorders in younger adults (Kessler et al., 2010; McDougall et al., 2007) as well as in women (Kuehner, 2003; McLean et al., 2011). We calculated population attributable fraction (PAF) by the Mantel-Haenszel approach (Benichou, 2001) to estimate the number of cases of anxiolytics or antidepressants purchase attributable to being in the low CRF tertile.

Additionally, we performed a sensitivity analysis where we compared the risk of first registered purchase of anxiolytic or antidepressant medication in the top and bottom CRF quintiles. This was done to reduce the risk of potential overlap between the CRF tertiles caused by the limited predictive value of the CRF estimation model (Nes et al., 2011).

All analyses were performed in IBM SPSS v. 26, and a *p*-value below 0.05 was considered an indicator of statistical significance.

3. Results

The 32,603 participants were followed up for a mean of 8.7 years (SD 2.8 years, range 0–11), contributing with a total of 284,403 person-years to the analyses. During the follow-up, 6176 participants (18.9 %) had their first registered purchase of anxiolytic or antidepressant medication. Baseline characteristics of the study sample by CRF tertiles are presented in Table 1.

3.1. CRF and anxiolytic or antidepressant medication

The results from the Cox proportional hazards models for the association of CRF with first registered purchase of anxiolytic or

Table 1
Baseline characteristics of study population by CRF tertiles before multiple imputation.

	Low (n = 10,864)	Intermediate (n = 10,874)	High (n = 10,865)
Age, years, mean (SD)	52.7 ± 15.9	52.0 ± 15.9	51.3 ± 16.0
Sex, n (%) women	5782 (53.2)	5788 (53.2)	5782 (53.2)
Education, n (%)			
Primary	2474 (22.8)	2100 (19.3)	1649 (15.2)
Secondary	3694 (34.0)	3687 (33.9)	3444 (31.7)
Tertiary	1481 (13.6)	1950 (17.9)	2592 (23.9)
Marital status, n (%)			
Unmarried	2678 (24.7)	2590 (23.8)	2628 (24.2)
Married	6434 (59.2)	6591 (60.6)	6577 (60.5)
Widow(er)/separated/divorced	1742 (16.0)	1677 (15.4)	1638 (15.1)
Alcohol consumption, n (%)			
Once a month or less	4732 (43.6)	3908 (35.9)	3599 (33.1)
2–4 times per month	4586 (42.2)	5057 (46.5)	5117 (47.1)
2–3 times per week	1161 (10.7)	1512 (13.9)	1726 (15.9)
4 times per week or more	232 (2.1)	271 (2.5)	310 (2.9)
Problems sleeping, n (%)			
No	9071 (83.5)	9213 (84.7)	9350 (86.1)
Moderate	1337 (12.3)	1276 (11.7)	1153 (10.6)
High	456 (4.2)	385 (3.5)	362 (3.3)
HADS-A, mean (SD)	3.49 ± 2.92	3.52 ± 2.85	3.51 ± 2.80
HADS-D, mean (SD)	3.16 ± 2.71	2.92 ± 2.62	2.64 ± 2.51
Longstanding limiting illness, n (%)	4304 (39.6)	3636 (33.4)	3094 (28.5)
CRF, METs, mean (SD)	9.03 ± 2.00	10.5 ± 2.01	11.9 ± 2.21
Anxiolytics/antidepressant purchase, n (%)	2246 (20.7)	2015 (18.5)	1915 (17.6)
Benzodiazepine derivatives	1083 (10.0)	1001 (9.2)	948 (8.7)
SSRI	728 (6.7)	661 (6.1)	645 (5.9)
Time from baseline to first purchase of anxiolytics/antidepressants, years, mean (SD)	4.25 ± 2.89	4.40 ± 2.93	4.43 ± 2.92

HADS-D: Hospital Anxiety and Depression Scale: Depression subscale; HADS-A: Hospital Anxiety and Depression Scale: Anxiety subscale.

Table 2
Hazard ratios (HR) and 95 % confidence intervals (CI) for first registered purchase of prescription anxiolytic or antidepressant medication by CRF in METs and tertiles. Bold numbers indicate statistically significant associations at $p < 0.05$.

	Cases/person-years	Model 1[a] HR (95 % CI)	Model 2[b] HR (95 % CI)
CRF (METs)	6176/284403	**0.89 (0.87–0.90)**	**0.96 (0.94–0.98)**
CRF tertiles			
Low	2246/92812	1.00 (ref.)	1.00 (ref.)
Intermediate	2015/95374	**0.88 (0.83–0.94)**	**0.93 (0.87–0.98)**
High	1915/96217	**0.84 (0.79–0.89)**	**0.92 (0.86–0.98)**

[a] Adjusted for age.
[b] Adjusted for age, sex, education, marital status, alcohol consumption, sleep problems, symptoms of anxiety and depression, and longstanding limiting illness.

antidepressant medication are presented in Table 2. Each 1-MET increment in CRF was associated with a 11 % lower risk of purchasing anxiolytic or antidepressant medication during the follow-up in model 1 (HR 0.89, 95 % CI 0.87–0.90), and a 4 % lower risk in model 2 (HR 0.96, 95 % CI 0.94–0.98). CRF in tertiles was also associated with the risk of purchasing anxiolytic or antidepressant medication. Compared to the low CRF tertile, participants in both the intermediate and high CRF tertiles had lower risk of purchasing anxiolytic or antidepressant medication during the follow-up in both model 1 (intermediate HR 0.88, 95 % CI 0.83–0.94; high HR 0.84, 95 % CI 0.79–0.89) and the fully adjusted model 2 (intermediate HR 0.93, 95 % CI 0.87–0.98; high HR 0.92, 95 % CI 0.86–0.98) (Table 2). Tests for interaction with age and sex revealed a significant interaction between CRF in METs and sex ($p < 0.001$), CRF tertiles and age ($p = 0.018$), CRF in METs and age in groups (young adult, adult, older adult; $p = 0.01$), and CRF tertiles and age in groups ($p = 0.009$). Adjusted PAF attributable to being in the low CRF tertile was 0.027.

3.2. Sex- and age-stratified analyses

When analyses were stratified by sex (Table 3), we found that each 1-MET increment in CRF was associated with a 6–7 % decreased risk of purchasing anxiolytic or antidepressant medication in both women and men in model 1. This association was somewhat attenuated after further adjustment (model 2) for both women (HR 0.97, 95 % CI 0.95–1.00) and men (HR 0.95, 95 % CI 0.93–0.98). Women and men in the intermediate and high CRF tertile had lower risk of purchasing anxiolytic or antidepressant medication when compared to women and men in the low CRF tertile in model 1. However, further adjustment (model 2) attenuated the association in women, and the association only remained statistically significant for men (intermediate HR 0.87, 95 % CI 0.79–0.96; high HR 0.87, 95 % CI 0.78–0.96) (Table 4).

Analyses stratified by age (young adult, adult, and older adult; Table 4) revealed that, in young and older adults, each 1-MET increase in CRF was significantly associated with a decreased risk of purchasing anxiolytics or antidepressants during the follow-up time in the fully adjusted model (young adults HR 0.90, 95 % CI 0.85–0.95; older adults HR 0.94, 95 % CI 0.91–0.97). CRF in METs was associated with a decreased risk of purchasing anxiolytics or antidepressants in adults in the unadjusted model, but the association was attenuated and no longer present in the fully adjusted model (Table 4). In young adults and adults, both intermediate and high CRF was significantly associated with a lower risk of purchasing anxiolytic or antidepressant medication compared to participants with low CRF in the fully adjusted model (young adults: intermediate HR 0.74, 95 % CI 0.61–0.91, high HR 0.78, 95 % CI 0.64–0.95; adults: intermediate HR 0.90, 95 % CI 0.83–0.97, high HR 0.90, 95 % CI 0.84–0.98). There was no significant association between CRF in tertiles and purchase of anxiolytic or antidepressant medication in older adults (Table 4).

3.3. Sensitivity analyses

In analyses comparing the top and bottom CRF quintiles, participants in the top CRF quintile had a 12 % reduced risk of purchasing anxiolytic or antidepressant medication compared to participants in the bottom CRF quintile in the fully adjusted model (HR 0.88, 95 % CI 0.81–0.96).

4. Discussion

This study aimed to investigate the association between CRF and incident prescription of anxiolytics and antidepressants in a large sample of 32,603 participants from the general adult population. We found that higher CRF was associated with lower risk of purchasing prescribed anxiolytics or antidepressants, and that the association was particularly evident in men. The same association was found for younger and middle-aged adults in the intermediate and high CRF tertiles, and for older adults when CRF was measured in METs, regardless of sex.

Participants in the intermediate and high CRF tertiles had lower risk of incident use of anxiolytics or antidepressants compared to those in the low tertile. This finding was supported by the sensitivity analysis comparing the top and bottom CRF quintiles, which showed that participants in the top CRF quintile had a 12 % reduced risk of purchasing anxiolytic or antidepressant medication compared to participants in the bottom CRF quintile. Moreover, each 1-MET increase in CRF was associated with reduced risk of medication prescription. This may indicate a protective dose-response relationship between CRF and psychotropic drugs. In keeping with this observation, a recent intervention study found an exercise intensity trend for reduced anxiety symptoms among patients in primary care, independent of depressive symptoms, but effect sizes were rather similar at low and higher intensities (Henriksson et al., 2022). This is further supported by our findings showing that the largest difference in risk of medication prescription was observed between the low and intermediate CRF tertiles, with high CRF providing little additional risk reduction. In a public health perspective this is promising, given that it may take less effort to help individuals to increase their CRF level from low to intermediate compared to the effort needed to reach a

Table 3
Hazard ratios (HR) and 95 % confidence intervals (CI) for first registered purchase of prescription anxiolytic or antidepressant medication by CRF in METs and tertiles, stratified by sex. Bold numbers indicate statistically significant associations at $p < 0.05$.

	Women			Men		
	Cases/person years	Model 1[a] HR (95 % CI)	Model 2[b] HR (95 % CI)	Cases/person years	Model 1[a] HR (95 % CI)	Model 2[b] HR (95 % CI)
CRF (METs)	3873/149288	**0.94 (0.91–0.96)**	0.97 (0.95–1.00)	2303/135115	**0.93 (0.90–0.95)**	**0.95 (0.93–0.98)**
CRF tertiles						
Low	1379/48944	1.00 (ref.)	1.00 (ref.)	867/43868	1.00 (ref.)	1.00 (ref.)
Intermediate	1283/49988	**0.92 (0.95–0.99)**	0.96 (0.89–1.03)	732/45386	**0.83 (0.75–0.91)**	**0.87 (0.79–0.96)**
High	1211/50355	**0.87 (0.80–0.94)**	0.95 (0.88–1.03)	704/45861	**0.79 (0.72–0.87)**	**0.87 (0.78–0.96)**

[a] Adjusted for age.
[b] Adjusted for age, education, marital status, alcohol consumption, sleep problems, symptoms of anxiety and depression, and longstanding limiting illness.

Table 4
Hazard ratios (HR) and 95 % confidence intervals (CI) for first registered purchase of prescription anxiolytic or antidepressant medication by CRF in METs and tertiles, stratified by age. Bold numbers indicate statistically significant associations at $p < 0.05$.

	Young adults			Adults			Older adults		
	Cases/ person years	Unadjusted HR (95 % CI)	Fully adjusted[a] HR (95 % CI)	Cases/ person years	Unadjusted HR (95 % CI)	Fully adjusted[a] HR (95 % CI)	Cases/ person years	Unadjusted HR (95 % CI)	Fully adjusted[a] HR (95 % CI)
CRF (METs)	567/30086	**0.87 (0.84–0.90)**	**0.90 (0.85–0.95)**	3815/ 197123	**0.90 (0.89–0.92)**	1.00 (0.97–1.02)	1794/57194	**0.89 (0.87–0.92)**	**0.94 (0.91–0.97)**
CRF tertiles									
Low	220/9448	1.00 (ref.)	1.00 (ref.)	1380/63261	1.00 (ref.)	1.00 (ref.)	646/20103	1.00 (ref.)	1.00 (ref.)
Intermediate	164/9968	**0.71 (0.58–0.87)**	**0.74 (0.61–0.91)**	1245/66534	**0.86 (0.80–0.93)**	**0.90 (0.83–0.97)**	606/18872	1.00 (0.90–1.12)	1.04 (0.93–1.17)
High	183/10670	**0.74 (0.61–0.90)**	**0.78 (0.64–0.95)**	1190/67328	**0.81 (0.75–0.88)**	**0.90 (0.84–0.98)**	542/18218	0.93 (0.83–1.04)	1.00 (0.89–1.12)

[a] Adjusted for sex, education, marital status, alcohol consumption, sleep problems, symptoms of anxiety and depression, and longstanding limiting illness.

high level. The results of the current study support earlier research that found moderately and vigorously active persons to have reduced risk of using psychotropic medication, including antidepressants, sedatives and sleep medication (Lahti et al., 2013). The results also mirror those of a study which found that adults using antidepressant medication were less physically active than individuals without medication (St-Amour et al., 2021).

Persons who have been prescribed antidepressants or anxiolytics are likely to suffer from diagnosed mental disorder(s), and prescriptions of psychotropic medication may thus also be seen as a marker for help-seeking for psychiatric problems. Prospective cohort studies show a reduced risk of common mental health disorders with higher CRF levels (Kandola et al., 2019), and the current study is in line with these findings. Furthermore, CRF is related to assessment of physical activity level, although CRF is a multifaceted measure that takes several variables into account. Increased physical activity is associated with increased estimates of CRF, which is true both for non-clinical populations as well as populations with severe mental illness (Vancampfort et al., 2017). The results of this study therefore support the protective effect of physical activity on symptoms of anxiety and depression, which has been demonstrated in several cross-sectional and longitudinal studies (Kvam et al., 2016; Rebar et al., 2015).

Although the sex-stratified analysis showed a clearer association between higher CRF and reduced risk of anxiolytics and antidepressants for men, the same tendency was found for women, although statistical evidence was weaker. Previous research has found physical activity to be associated with reduced risk of symptoms of anxiety and depression in middle-aged and older women (Griffiths et al., 2014). Furthermore, previous studies have not found sex differences in the association between physical activity or CRF and psychotropic medication use (Lahti et al., 2013; Stubbs et al., 2017; Waller et al., 2016). Hence, the results from the present study may also be clinically relevant for women, although sex differences in the association of CRF and the use of psychotropic drugs may require further investigation.

The results revealed some unexpected findings regarding age differences; higher CRF measured in METs was associated with reduced risk of medication prescription in young and older adults, and the same tendency was found for middle-aged adults. For CRF measured in tertiles, young adults and adults in the intermediate and high CRF tertiles had reduced risk of anxiolytics or antidepressants purchase, but not older adults. It is not clear why age effects differed depending on how CRF was assessed. However, this finding may be due to overadjustment, since the estimation of CRF was adjusted for age and the CRF categories were stratified by age. Previous register based studies have shown support for reduced risk of psychotropic medication in physically active middle-aged adults (Lahti et al., 2013; Stubbs et al., 2017; Waller et al., 2016), but in these studies middle-aged were not compared to younger adults or older adults and thus not directly comparable to the results of the present study. Although our results vary according to the way CRF was measured, the findings of reduced risk of antidepressant or anxiolytics purchase in older adults with higher MET-assessed CRF are promising, considering that as many as 20 % of community dwelling older adults are reported to receive prescriptions of psychotropic drugs (Du et al., 2016; Merel and Paauw, 2017). In addition, the results showed that younger adults had the largest reduction in risk of prescription of anxiolytics and antidepressants both when CRF was measured in tertiles as well as in MET. This is an encouraging finding, as previous research shows that increased CRF during youth is associated with reduced risk of both general health and mental health problems later in life (García-Hermoso et al., 2020; Kandola et al., 2019), and that depression and anxiety disorders are among the top ten causes of years lived with disability in younger adults (Vos et al., 2020).

The results are also highly relevant in a cost-effectiveness perspective. The population attributable fraction showed that about 3 % of the sample, corresponding to 185 cases, could have avoided prescriptions of medication if they had increased their CRF from low to intermediate or high. A large Norwegian register study (Ruths et al., 2021) of community health care for patients diagnosed with MDD by their general practitioner reported that >25 % received prescription for antidepressants, which means that a reduced need for mental healthcare in those with higher CRF could have substantial societal impact in terms of reduced cost. At the individual level this would imply less personal suffering due to improved mental health and reduced risk of common side effects of psychotropic drugs.

There are several proposed mechanisms to explain the association between CRF and use of psychopharmacological drugs. At a psychological level, CRF has been linked to improved emotion regulation strategies (Bernstein and McNally, 2018) which may lead to less psychological symptoms. At a biological level, higher CRF is associated with improved heart rate variability (Chen et al., 2019), favorable changes in serotonin and endorphin transmission (Brosse et al., 2002; Parise et al., 2001), all of which have been associated with improved mental health.

4.1. Strengths and limitations

A major strength of the present study is the large sample representative of the Norwegian adult population. Furthermore, the possibility to link health information with NorPD constitutes a unique combination of data sources. This database includes a complete list of all prescriptions for all participants, which is rare internationally. Since NorPD contains prescriptions from two to four years prior to participating in the HUNT study, this allowed a long observation time before baseline, which is a considerable strength of the study. However, several limitations should be noted. NorPD provides data on purchase of prescription drugs in outpatient pharmacies. However, only a very small number of participants in the HUNT study are likely to be inpatients. Further, it does not provide information about actual medication use, thus there is a risk that anxiolytic and antidepressant medications were purchased but not used - or used incorrectly. In order to prevent the risk of reverse causality we excluded participants with first registered purchase of anxiolytics or

antidepressant before or within 3 months after participation in HUNT3, but as we did not have access to medical records, we cannot rule out the possibility that participants may have been suffering from mental illness. Furthermore, symptoms of anxiety and depression which were used as an adjustment variable in the analyses were self-reported and not registered through clinical assessment. This method is, however, widely used and the only feasible approach in large scale studies such as the HUNT study. CRF was based on a non-exercise algorithm which is less accurate than exercise measures of maximal oxygen consumption, however, the non-exercise algorithm has been validated in previous studies (Nauman et al., 2017; Nes et al., 2011). CRF was only measured at baseline, thus we cannot rule out the possibility that change in CRF over time has affected the results. Lastly, this is an observational study and unmeasured confounders may exist, which represents a risk that the observed associations are influenced by residual confounding and therefore do not represent a causal relationship.

5. Conclusion

We found that higher levels of CRF were associated with lower risk of purchasing anxiolytic or antidepressant medication. Intermediate and high CRF tertiles were associated with reduced risk of anxiolytics or antidepressant purchase in both women and men, although stronger associations were observed in men, younger adults aged 20 to 29 years and adults aged 30 to 64. This association was not found for older adults (aged 65 or older). The results have important implications for the general public as they suggest that increasing the level of CRF in the general population may reduce the need for pharmacological treatment of common mental health problems.

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Ethical standards

The Regional Committees for Medical and Health Ethics approved the study. This study was performed in line with the principles of the Declaration of Helsinki.

Consent to participate

Respondents had to provide written informed consent participate.

Consent for publication

Not applicable.

Code availability

Not applicable.

CRediT authorship contribution statement

All authors contributed to the study conception and design. AH wrote the first draft of the manuscript. EZ conducted statistical analyses. All authors contributed to the interpretation of the results and revised the original manuscript. All authors read and approved the final manuscript.

Declaration of competing interest

The authors report no conflict of interest.

Data availability

Data from the Trøndelag Health Study (HUNT) used in research projects is available upon reasonable request to the HUNT data access committee (hunt@medisin.ntnu.no). The HUNT data access information (www.ntnu.edu/hunt/data) describes in detail the policy about data availability.

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