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Cardiovascular fitness and risk of migraine: a large, prospective population-based study of Swedish young adult men

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ABSTRACT

Objectives: To examine the relationship between cardiovascular fitness in young adult men and future risk of migraine, and to study eventual differential effects on migraine risks in categories of BMI and blood pressure.

Design: National prospective population-based cohort study

Setting: Sweden 1968-2014

Participants Swedish 18-year-old men (n= 1 819 828) participating in mandatory military conscription between 1968-2005.

Primary and secondary outcomes: Primary outcome was first dispensation of prescribed migraine-specific medication, identified using the Swedish Prescribed Drug Register between ages 20-60. Secondary outcome was migraine diagnosis from the Swedish National Hospital Register.

Results: During follow-up, 22 533 men filled a prescription for migraine-specific medication. Compared to high cardiovascular fitness, low and medium fitness increased the risk of migraine-specific medication with adjusted RR 1.29, 95% Cl 1.24-1.35 and RR 1.15, 95% Cl 1.12-1.19, respectively. Stratified analyses of this association by levels of BMI, systolic, or diastolic blood pressure showed that lower fitness levels increased risk of migraine in all groups except for underweight men or men with high diastolic blood pressure.

Conclusions: Young men with a lower cardiovascular fitness have a higher long-term risk of developing pharmacological prescription-requiring migraine. This study contributes with information regarding risk factors for migraine in men, an understudied population in migraine research.

Key words: migraine, cardiovascular fitness, prospective, risk factor, men, cohort

Strengths and limitations of this study

- This is a large, longitudinal study based on a nearly total population sample of young men in Sweden between 1969 and 2005 (n=1 819 828), employing objective measurements of cardiovascular fitness at baseline.
- The study has a long follow-up time (2-46 years) and relies on high quality national register data to identify men, an understudied population in migraine research, who later develop migraine.
- The incidence of migraine is likely underestimated since men with undiagnosed migraine or those only using over-the-counter migraine medication are not captured in the available data.
- Although analyses were adjusted for several potential confounding variables, sources of residual and unmeasured confounding (such as smoking and alcohol consumption) may still be present.

INTRODUCTION

Migraine is an intermittent neurological disorder with strong influences on the vascular system.[1] Cardiovascular fitness, a state indicating overall capacity of the cardiovascular and respiratory systems and the ability to carry out prolonged strenuous exercise, is specifically associated with positive effects on vascular health as well as a reduced incidence of several neurological and cardiovascular disorders.[2-4] However, data on the relationship between cardiovascular fitness and the development of migraine are lacking. Higher levels of *physical activity,* a behavior in which body movement produced by muscle action increases the energy expenditure and enhances or maintains cardiovascular fitness[2], is prospectively associated with a reduced risk of migraine.[5] Physical activity is strongly correlated to but not interchangeable with cardiovascular fitness, the latter also depending on other components such as genetic makeup.[2]

Although not informative regarding direction of causality, cross-sectional data show that peak oxygen uptake is inversely associated with migraine[6] whereas cross-sectional studies of migraine and physical activity show discordant findings.[7-10] In patients with migraine, regular physical activity appears to have alleviating effects on migraine symptoms such as frequency and intensity.[11] However, acute physical exercise may also be a trigger of migraine episodes[12] and individuals with migraine or severe headaches might therefore be more reluctant to exercise. There is also a high comorbidity between migraine and cardiovascular conditions.[13] While factors affecting cardiovascular health, such as weight and blood pressure have also been shown to influence migraine prevalence,[14 15] the long-term risk of migraine, with respect to cardiovascular fitness, across strata of BMI and blood pressure remains to be clarified. Migraine is two to three times more prevalent in women, and data on factors influencing migraine in men are scarce.[16] Focusing on men only means that possible effects of menstruation, pregnancy and lactation do not need to be taken into consideration.

The primary aim of this study was to investigate whether baseline cardiovascular fitness in young adult men affects the long-term risk of migraine in a large, prospective population-based cohort with objective measures of cardiovascular fitness at baseline and a long follow-up time. Secondary aims were to evaluate whether the relationship between cardiovascular fitness and future risk of migraine is modified by baseline levels of BMI or blood pressure.

METODS

We performed a population-based prospective study of young Swedish men enlisting for military service. Exposure variables were obtained at conscription (baseline) from records in the Swedish Military Service Conscription Register. Data from this register were linked to the Swedish Prescribed Drug Register, the National Hospital Registers, the Longitudinal Integration Database for Health Insurance and Labour Market Studies and the Swedish Cause of Death Register. Linkage of individual data was made possible by the unique personal identification number assigned to each registered person in Sweden. After linkage, all data were anonymized and coded by Statistics Sweden in order to maintain the confidentiality for the included men.

During follow-up, use of migraine-specific medication identified through the Swedish Prescribed Drug Register served as a marker of migraine. Further, in a secondary analysis, hospital diagnoses of migraine, identified in the National Hospital Register, were recorded as outcomes. The Ethics Committee of the University of Gothenburg and Confidentiality Clearance at Statistics Sweden approved this study (Dnr 462-14).

Study population

The source population of the study comprised all men (n=1 819 828) who enlisted for military service during 1968–2005, who were 16-25 years old and had a specified test center location. Enlistment was mandatory during this period for all Swedish men. Only individuals with severe

chronic medical or mental conditions, serious disabilities or incarceration were granted exemption (in all, 2–3% of the male population per year). The vast majority were 18 years old at time of conscription (mean age 18.2, SD=0.7). To reduce the risk of possible reverse causation, men with a migraine diagnosis prior to or during the two years after conscription (identified through the National Hospital Register and Conscription Register) were excluded from the analyses, as were men who died or emigrated within two years after conscription and men who lacked data on cardiovascular fitness (Figure 1). For analyses using the Prescribed Drug Register, men who died or emigrated prior to the start of the register (2005) were excluded (Figure 1).

Ascertainment of exposure: cardiovascular fitness

All men underwent a 2-day examination at one of six conscription centers (Southern, Western, Eastern, Central/Bergslagen, Northern lower and Northern upper). Cardiovascular fitness was evaluated at all centers throughout the entire study period. Cardiovascular fitness was objectively measured by a physician using a standardized cycle ergometric maximal test. The test started with submaximal exercise and work rate was continuously increased until exhaustion. The final work rate (Wmax) was recorded and divided by body weight and converted into stanine scores that served as a measure of cardiovascular fitness. We have previously observed that the frequency distribution of cardiovascular fitness in the dataset is right-skewed and not normally distributed. Therefore, as in other studies,[17] cardiovascular fitness categories were trichotomized as low (score 1–4), medium (score 5–7) and high (score 8–9). Although the protocol for the ergometer test has changed over the years, average cardiovascular fitness scores have remained stable (<1% change). The conscription cardiovascular fitness test has been shown to have good reliability and validity.[18]

Covariates

Weight, height, and systolic and diastolic blood pressures were measured by a physician, according to a written standard protocol. Systolic and diastolic blood pressures were measured on the first conscription day after 5-10 minutes rest in the supine position. One measurement was generally performed, although when systolic blood pressure was over 145 mmHg or diastolic blood pressure was outside the range of 50-85 mmHg, a second measurement was made the following day and included in the register instead. Weight (kg) and height (m) were measured and BMI was calculated as (kg/m^2). BMI values < 10 and > 60 km/m^2 were treated as extreme values and excluded. BMI was categorized as low (< 18.5 kg/m^2), normal (18.5-24.9 kg/m^2) and high (> 25.0 kg/m^2). Systolic and diastolic blood pressures were divided into three groups; systolic blood pressure: ≥ 140, 120-139 and ≤ 119 mmHg and diastolic blood pressure: ≥ 80, 66-79 and ≤ 65 mmHg. Data on conscription test center, conscription year, age at conscription and parental education were also included since they are plausible covariates. Differences among regions and test centres could introduce confounding. There might also be effects of variation in diagnosis frequency and differences in conscription procedures depending on what year the subject enlisted. Socioeconomic status affects level of cardiovascular fitness in the current dataset and is associated with migraine risk.[19] Therefore, parental education was included as a measure of the socioeconomic status and adjusted for. Information on parental education (80% coverage), as well as emigration, were collected from the Longitudinal Integration Database for Health Insurance and Labour Market Studies (Swedish acronym LISA; http://www.scb.se/Pages/List____257743.aspx) at Statistics Sweden. The LISA database includes data from all Swedish residents aged 16 years and older and is annually updated. Parental education (maternal and paternal education treated separately) was graded in 3 levels: pre-high school education (up to 9 years), high school education and university/postgraduate education.

Outcome variables

The outcome of migraine between age 20 and 60 was obtained using first recorded dispensing of prescribed migraine-specific medication, identified using the Swedish Prescribed Drug Register. This national register started in 2005 and includes detailed information on all prescription drugs (from primary care and hospital-based care) that are dispensed by all pharmacies in Sweden.[20] The Prescribed Drug Register is updated monthly and grouped according to the Anatomical Therapeutic Chemical (ATC) classification (WHO). The following migraine-specific medication were included: Sumatriptan (N02CC01), Naratriptan (N02CC02), Zolmitriptan (N02CC03), Rizatriptan (N02CC04), Almotriptan (N02CC05), Eletriptan (N02CC06), Frovatriptan (N02CC07), Dihydroergotamine (N02CA01) and Ergotamine (N02CA02). As these medications are also indicated for cluster headache, men with this diagnosis (ICD-10: G44.0; ICD-9: 346C; ICD-8: 346.01) in the National Hospital Register were excluded from the analyses.

Additional secondary analyses were also performed using ICD-codes for migraine diagnosis from the Swedish National Hospital Register as an outcome (ICD-10: G43; ICD-9: 346A,B,X,W; ICD-8: 346.09). This register contains both inpatient and outpatient diagnoses recorded in a hospital setting including referrals to neurologists/migraine specialists and emergency visits. In Sweden, it is mandatory for all private and publicly funded hospitals to register one principal discharge diagnosis and up to thirty contributory diagnoses. Register coverage for all inpatient care increased gradually during 1968-1986 and diagnoses from hospital outpatient care have been recorded since 2001. The Swedish National Hospital Register is a national, population-based register with high coverage; it is validated with positive predictive values of (85%–95%) for most ICD diagnoses.[21]

Statistical analyses

In order to address the primary aim i.e. how cardiovascular fitness at baseline affects risk of migraine during follow-up, we calculated risk ratios and 95% confidence intervals using

Poisson regressions with offset to correct for differences in exposure time robust standard errors. From these models, we also calculated model-based population attributable fractions (PAF) with corresponding 95% CIs.[22] The PAFs are interpreted as the estimated percentage of all cases during follow-up that could have been prevented if the men of specified cardiovascular fitness group instead had belonged to the group with high cardiovascular fitness. The rationale for choosing risk ratio analyses was the aggregation of both new and older records in the Prescribed Drug Register at register initiation, rendering it not possible to establish the time of first prescription. Cox proportional hazards models were thus not suitable. All analyses were adjusted for age at conscription, conscription region, conscription decade and parental education (Model 1). Given that BMI might affect both cardiovascular fitness and migraine, we also performed an additional model (Model 2) also adjusting for BMI.[23] To address the secondary aim i.e. whether the relationship of cardiovascular fitness and migraine was modified by levels of BMI or blood pressure, we stratified the risk estimates by categories of baseline BMI, as well as systolic and diastolic blood pressure, applying the above mentioned categories. We also performed secondary analyses to evaluate the relationship between cardiovascular fitness and risk of hospital-based migraine diagnosis, which likely addresses the most severe migraine cases. Cox proportional hazards models were performed to estimate hazard ratios and 95% confidence intervals. Separate analyses were performed for outpatient migraine diagnoses only, as well as outpatient and inpatient diagnoses, together. By removing the inpatient diagnoses, individuals with the highest degree of psychiatric and somatic comorbidity, medication overuse and highest pain scores were excluded [24] rendering the patient group more homogenous. We also performed separate analyses of only primary diagnoses of migraine. The follow-up period began at conscription (baseline), and person-time was included until time of 1) first record of migraine in the National Hospital Register, 2) death, 3) emigration or 4) at the end of follow-up, i.e. on December 31, 2014 whichever happened first (minimum 2 years and

maximum 46 years follow-up). Death dates were obtained from the Swedish Cause of Death Register, which has kept record of virtually all deaths in Sweden since 1961.

Men with missing data for parental education were included as a separate category in all analyses. High cardiovascular fitness was used as the reference category and all P-values are 2-tailed. The statistical calculations were performed with SAS version 9.4 (SAS Institute, NC).

RESULTS

Baseline characteristics by levels of cardiovascular fitness in the study population are shown in Table 1. Men with lower cardiovascular fitness were more likely to have lower parental education, higher BMI and higher systolic blood pressure than men with higher fitness. After exclusion criteria were applied, analyses of dispensed migraine-specific medication were based on a total of 1 143 832 subjects, and secondary analyses of migraine diagnoses in the National Hospital Register were based on 1 213 104 subjects (Figure 1).

Table 1 Baseline characteristics by cardiovascular fitness level in a cohort of 1 143 833 male conscripts used to analyse prescription of migraine-specific medication before age 60.

		Level of cardiovascular fitness		
	All, n (%)	High, n (%)	Medium, n (%)	Low, n (%)
Total	1 143 833 (100.0)	316 115 (100.0)	673 536 (100.0)	154 182 (100.0)
Migraine-specific medication	22 677 (2.0)	55 632 (1.8)	13 520 (2.0)	3595 (2.3)
Decade of conscription				
1968-1969	2920 (0.9)	2920 (0.9)	5169 (0.8)	1530 (1.0)
1970s	123 367 (39.0)	123 367 (39.0)	198 357 (29.5)	53 399 (34.6)
1980s	104 762 (33.1)	104 762 (33.1)	252 082 (37.4)	76 103 (49.4)
1990s	65 057 (20.6)	65 057 (20.6)	161 868 (24.0)	20 154 (13.1)
2000s	20 099 (6.4)	20 099 (6.4)	56 060 (8.3)	2996 (1.9)
Place of conscription				
South	70 546 (22.3)	70 546 (22.3)	158 784 (23.6)	34 535(22.4)
West	62 247 (19.7)	62 247 (19.7)	145 540 (21.6)	37 758 (24.5)
East	68 731 (21.7)	68 731 (21.7)	140 660 (20.9)	37 058 (24.0)
Bergslagen	63 472 (20.1)	63 472 (20.1)	130 994 (19.4)	30 580 (19.8)
Lower Norrland	31 232 (9.9)	31 232 (9.9)	64 667 (9.6)	9912 (6.4)
Upper Norrland	19 887 (6.3)	19 887 (6.3)	32 891 (4.9)	4339 (2.8)
Parental education				
Pre–high school	83 976 (26.6)	83 976 (26.6)	199 592 (29.6)	61 910 (40.2)
High school	124 718 (39.5)	124 718 (39.5)	289 883(43.0)	63 424 (41.1)
University or higher	100 633 (31.8)	100 633 (31.8)	166 772 (24.8)	23 388 (15.2)
Missing	6788 (2.1)	6788 (2.1)	17 289 (2.6)	5460 (3.5)

BMI				
High (≥ 25.0)	6344 (2.0)	6344 (2.0)	52 873 (7.9)	29 856 (19.4)
Normal (18.5-24.9)	283 599 (89.7)	283 599 (89.7)	549 055 (81.5)	97 578 (63.3)
Low (<18.5)	25 703 (8.1)	25 703 (8.1)	69 896(10.4)	26 071 (16.9)
Missing	469 (0.1)	469 (0.1)	1712 (0.3)	677 (0.4)
Systolic blood pressure				
≥ 140 mmHg	50 693 (16.0)	50 693 (16.0)	128 388 (19.1)	32 465 (21.1)
120-139 mmHg	199 747 (63.2)	199 747 (63.2)	424 041 (63.0)	96 678 (62.7)
≤119 mmHg	64 170 (20.3)	64 170 (20.3)	117 757(17.5)	24 360 (15.8)
Missing	1505 (0.5)	1505 (0.5)	3350 (0.5)	675 (0.4)
Diastolic blood pressure				
≥ 80 mmHg	130 451 (41.3)	130 451 (41.3)	283 226 (42.1)	63 204 (41.0)
66-79 mmHg	140 125 (44.3)	140 125 (44.3)	297 911 (44.2)	68 564 (44.5)
≤ 65 mmHg	43 959 (13.9)	43 959 (13.9)	88 962 (13.2)	21 710 (14.1)
Missing	1580 (0.5)	1580 (0.5)	3437 (0.5)	704 (0.5)

Abbreviations: BMI, body mass index
[1]Performance was trichotomized as low (score 1–4), medium (score 5–7) and high (score 8–9).

Cardiovascular fitness and future migraine-specific medication

Prescriptions for migraine-specific medication were filled by 22 533 men (2.0%). Compared to the high cardiovascular fitness level, both low and medium levels increased the risk for use of migraine-specific medication (RR 1.29, 95% Cl 1.24-1.35 and RR 1.15, 95% Cl 1.12-1.19, respectively) during follow-up (Table 2). PAF of medium cardiovascular fitness (8.0%) for migraine-specific medication was higher than that of low fitness (3.6%). Including BMI as an additional confounder to the multivariable models did not change the RRs or PAFs significantly. The proportion of men with missing values for cardiovascular fitness was 31.6% for men with migraine-specific medication and 32.4% for men without.

Table 2 Risk ratios of prescribed migraine-specific medication before age 60 in relation to cardiovascular fitness levels in young adult men.

	Model 1[2] n= 1 143 833			Model 2[3] n= 1 136 786		
Cardiovascular fitness[1]	Migraine/ Total No.	RR (95% CI)	P	Migraine/ Total No.	RR (95% CI)	P
High	55 632 / 316 115	1.00 (reference)		5554 / 315 646	1.00 (reference)	
Medium	13 520 / 673 536	1.15 (1.12-1.19)	<0.001	13 483 / 671 824	1.14 (1.11-1.18)	<0.001
Low	3595 / 154 182	1.29 (1.24-1.35)	<0.001	3572 / 153 505	1.27 (1.21-1.32)	<0.001

Abbreviations: BMI, body mass index; CI, confidence interval; No., number of events; RR, risk ratio
[1] High level= reference category
[2]Adjusted for age, conscription calendar year and region and parental education.
[3]Adjusted for age, conscription calendar year and region, parental education and BMI

Risks stratified by categories of BMI and blood pressure

The association of cardiovascular fitness and future migraine-specific medication was analysed in separate strata of BMI and blood pressure groups (Figure 2). Low and medium fitness increased the risk for migraine medication in men with high and normal BMI, but had no effect in underweight men. For systolic blood pressure, low and medium fitness had similar associations with future migraine medication in all three categories. Fitness was not associated with future migraine medication in men with diastolic blood pressure ≥ 80 mmHg, but increased the risk of medication in men with diastolic blood pressures 66-79 mmHg as well as ≤65 mmHg

Cardiovascular fitness and future migraine diagnosis

Migraine diagnoses were recorded in the National Hospital Register for 10 043 men (0,8% of the entire study population). Most (82%) were primary diagnoses. Approximately one third of the men with a migraine diagnosis in the National Hospital Register were also observed with migraine medication in the Prescribed Drug Register. Lower cardiovascular fitness increased the risk of a first-time migraine outpatient diagnosis (Table 3). Adding migraine codes for inpatient migraine to the outpatient codes did not result in a statistically significant association. Associations were similar when analysing primary migraine diagnoses only. For primary outpatient diagnoses, HR for low and medium cardiovascular fitness were 1.15, 95% CI 1.05-1.26 (P=0.002) and 1.07, 95% CI 1.01-1.14 (P=0.035), respectively. For combined primary outpatient and inpatient diagnoses, HR for low fitness was 0.98, 95% CI 0.91-1.09 (P=0.21) and HR for medium fitness was 1.03, 95% CI 0.98-1.09 (P=0.26).

Table 3 Hazard ratios of migraine diagnoses, recorded in the National Hospital Register, in relation to cardiovascular fitness levels in young adult men followed for up to 46 years.

Outpatient migraine diagnoses only			
Cardiovascular fitness[1]	Migraine / Total No.	HR (95% CI)[2]	P
High	1759/ 338 295	1.00 (reference)	

Medium	4060/ 710 865	1.08 (1.02-1.15)	0.007
Low	1044/ 163 946	1.18 (1.08-1.28)	<0.001
All migraine diagnoses (inpatient and outpatient)			
Cardiovascular fitness[1]	Migraine / Total No.	HR (95% CI)[2]	P
High	2655/ 338 295	1.00 (reference)	
Medium	5852/ 710 865	1.05 (1.00-1.12)	0.14
Low	1536/ 163 946	1.05 (0.98-1.12)	0.30

Abbreviations: BMI, body mass index; CI, confidence interval; No., number of events; HR, hazard ratio
[1] High level= reference category
[2]Adjusted for age, conscription calendar year and region and parental education.

DISCUSSION

In this large, prospective cohort of young adult men, cardiovascular fitness was inversely associated with future migraine. Though quite similar, the risks were somewhat larger for filled migraine-specific drug prescriptions than for outpatient migraine diagnosis. The increased risk of migraine among those with a low level of cardiovascular fitness was higher than for those with a medium level fitness. However, more new migraine cases detected in this study were attributable to medium cardiovascular fitness rather than to low cardiovascular fitness, given that medium cardiovascular fitness is more common in the population.

Comparisons with other studies

This population-based longitudinal study provides new insights into the effects of cardiovascular fitness on migraine risk. While not directly comparable with cardiovascular fitness, there are two prospective studies evaluating the relationships between physical activity and migraine with inconsistent results.[5 8] However, it is important to distinguish the terms cardiovascular fitness and physical activity. Cardiovascular fitness is more strongly related to health outcomes than physical activity, and activity not resulting in an increase in fitness level may not provide protective effects against adverse health outcomes.[25] Hence, studies of cardiovascular fitness in addition to physical activity are of great importance. A cross-sectional study found an inverse relationship of peak oxygen uptake and migraine in adults younger than 50,[6] but given its cross-sectional study design, no conclusions can be made regarding the direction of the observed effect.

Effect modification by BMI and blood pressure

The association of cardiovascular fitness and migraine was only apparent in men with normal and high BMI but not in those with low BMI. Prospective studies of BMI and later risk of migraine appear to be lacking, but a meta-analysis of cross-sectional studies concluded that the risk of migraine appears to be moderately increased in both obese and underweight individuals.[14] Our results suggest that there is no additional beneficial effect of having a higher cardiovascular fitness in men with a low BMI at baseline, but it should be noted that the number of men in this category was limited and there may have been a problem with study power. It is also possible that there might be a common underlying factor influencing both BMI and migraine.

While an association between cardiovascular fitness and migraine was observed in all categories of systolic blood pressure, this was not the case for the group with a diastolic blood pressure of ≥ 80 mmHg. This observation may partly be explained by the previously reported relationship between higher blood pressures and hypoalgesia.[26] It could also reflect an unknown, underlying cause in young men with deviant blood pressures. Further studies are needed to elucidate the effects of BMI and blood pressure on migraine and its interrelationship with cardiovascular fitness.

Possible mechanisms

The increased risk of migraine with lower cardiovascular fitness observed in this study may be explained by a combination of several factors. There might be an unknown, common predisposing factor for both low cardiovascular fitness and migraine given the clear association of migraine with unfavourable cardiovascular risk factor profiles.[27] An association between migraine and cardiovascular risk comorbidities could be explained by a common pathology underlying both conditions and migraine might be a local manifestation of a systemic, rather that neurological, phenomenon.[27] Our research findings expand on previous studies linking

migraine to cardiovascular risk factor profiles, highlighting the long-term association between cardiovascular fitness and migraine.

Several areas of the brain are still developing during late adolescence, and it is also possible that cardiovascular fitness during this period has long-term effects on brain health that might reduce susceptibility to migraine. Low cardiovascular fitness increases the risk of several other neurological and psychiatric disorders such as stroke,[3] epilepsy,[4] and depression.[28] It could be that a common mechanism affecting neuroprotection, neurogenesis, synaptic plasticity, neuroinflammation, and neurotrophic factors such as brain-derived neurotrophic factor (BDNF) may be involved.[29] Hence, higher cardiovascular fitness might result in a greater "brain reserve" that may act as a compensatory buffer of brain plasticity and neural resources and better enable the brain to cope with neuropathology, resulting in long-lasting beneficial effects on brain health.[30] Indeed, there is increasing evidence suggesting that behavioural interventions such as physical activity during critical stages of development can have such long-lasting and robust effects on the brain.[30]

Cardiovascular fitness may also influence migraine burden such as pain. Several studies report lower migraine burden with more physical activity[31] and a recent randomized study of exercise in migraine patients showed decreased migraine pain, intensity and frequency after the training intervention.[32] Neuroadaptive changes with pain are well-known[33] and decreased levels of BDNF have been reported in patients with migraine.[34] Higher fitness level during adolescence could induce long-lasting structural and/or biochemical changes to the brain, generating a higher threshold for migraine pain. Further, although we excluded men with migraine prior to or for two years after conscription, it is possible that some men with undiagnosed migraine were included in the study. Men burdened with undiagnosed migraine at baseline might exercise less, which could result in lower cardiovascular fitness at conscription.

Strengths and limitations

Strengths of this study include the population-based design, its large size and the objective measurements of cardiovascular fitness at baseline. Other strengths are available information on a large number of important covariates, the long follow-up time and the use of national register data to identify conscripts who later developed migraine. Further, this study focuses on men, an understudied population in migraine research.

Several limitations should be considered when interpreting our results. The incidence of migraine is likely underestimated since our outcome measurements only captures men who seek health care. Thus, we are unable to identify men using over the counter migraine medication only. Altogether, these definitions likely select for men with more severe migraine episodes, which cannot be handled by the patient himself. Although we excluded men who died or emigrated before the Prescribed Drug Register started in 2005, we may have missed men who enlisted during the earlier years and had migraine that later resolved (or men who did not seek treatment for migraine later). Boys with an early migraine diagnosis that resolved prior to conscription might have been misclassified as having migraine at baseline and would hence be wrongfully excluded from the analyses.

The hospital register does not include codes from primary care; therefore, men without hospital-based care could only be identified through the Prescribed Drug Register. By removing inpatient diagnoses of migraine from the analyses, we might also introduce a selection bias. In Sweden, migraine or cluster headache are the only indications for triptans and ergotamide (FASS; https://www.fass.se/). We have excluded men with prescribed migraine-specific medication at baseline as well as men diagnosed with cluster headache. However, there is still a small possibility that these medications could be prescribed for other indications and such subjects would be included in our study. The migraine diagnosis based on ICD codes has not been formally validated. However, we have no reason to believe that the generally high positive

predictive values observed for other ICD codes in the National Hospital Register would not apply to migraine.

Although we have controlled for confounding by adjusting for information on several covariates, residual and unmeasurable confounding may still be present as our study is observational. In particular, we had no information on smoking and alcohol consumption. Our research goal was to estimate the effect of baseline cardiovascular fitness on long-term risk of migraine. Therefore, we do not include data on cardiovascular fitness or other health-related risk factors at later stages in life. We have no information regarding changes over time. Our findings should not be interpreted as explanatory regarding the causal chain leading to the onset of migraine. Moreover, the amount of missing values for cardiovascular fitness could have biased the results. However, since proportions with missing values were very similar among men with and without migraine-specific medication, it is unlikely that this would affect the associations. The main purpose of the Swedish Conscription Register was for military use and detailed descriptions of causes for missing data are classified. Although we have no reason to believe that our findings cannot be extrapolated to women, our study only included men.

CONCLUSION

Lower cardiovascular fitness in adult young men increases the risk of future migraine. Our study calls for targeted research to test whether interventions to improve cardiovascular fitness result in reduced risk of developing migraine among men with low cardiovascular fitness levels. In addition, studies that explore possible mediators of the effect of cardiovascular fitness on the later development of migraine may provide insights into the biological understanding of migraine, informing the development of further preventive strategies.

Authors contribution JN, SG, ML, DÅ, MÅ, MW and GK conceptualized the study. JN, SG, DÅ, MÅ, MW and GK contributed to data acquisition. JN, SG, JLR and TK designed the analyses, and JN and SG performed the analyses. All co-authors contributed to interpretation of as well as drafting and critically revising the manuscript for important intellectual content. JN, SG and GK are the guarantors."

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Competing interests TK has received honoraria from Lilly for providing methodological advice and from Novartis for a lecture on neuroepidemiology. He further has received honoraria from The BMJ for editorial services and serves as a consultant on US National Institutes of Health grants on migraine. The other authors have no conflicts of interest.

Patient consent Not required

Ethics approval: The Ethics Committee of the University of Gothenburg and Confidentiality Clearance at Statistics Sweden approved this study (Dnr 462-14).

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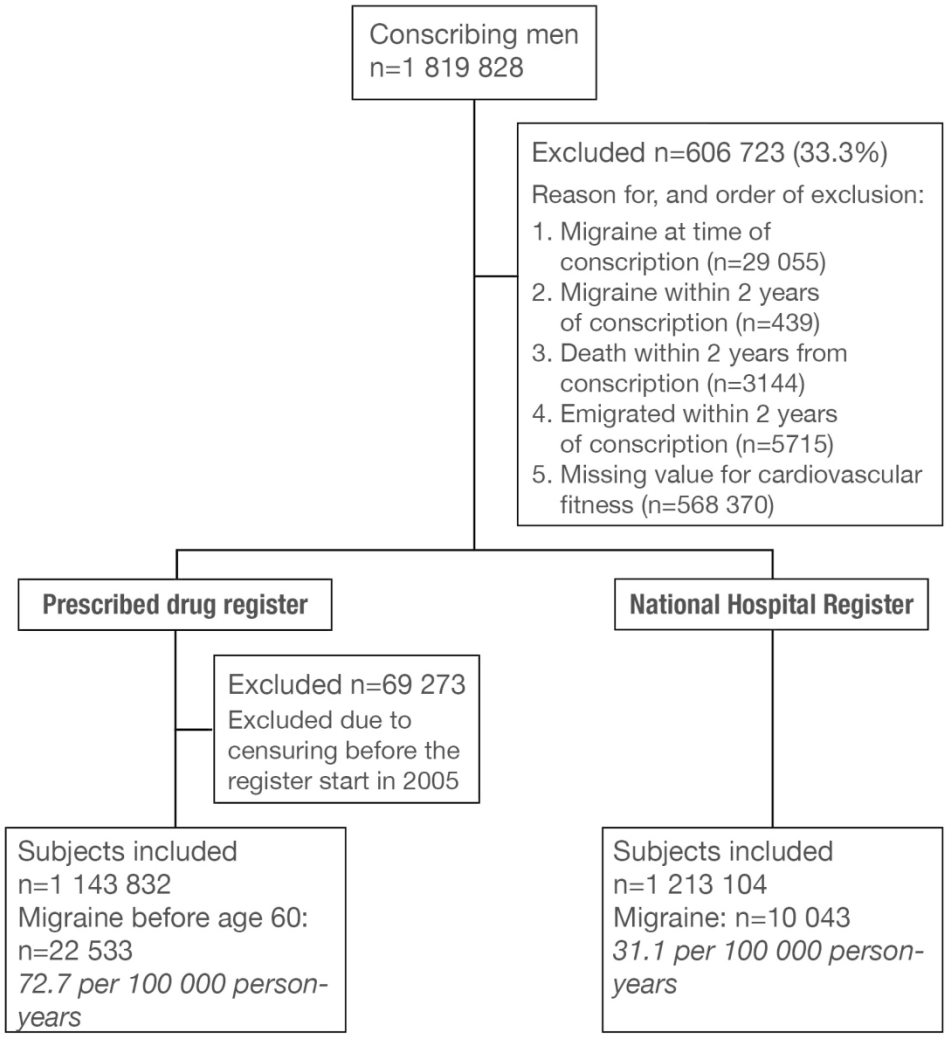

Figure 1 Flowchart of the study populations showing included and excluded subjects and number of outcomes.

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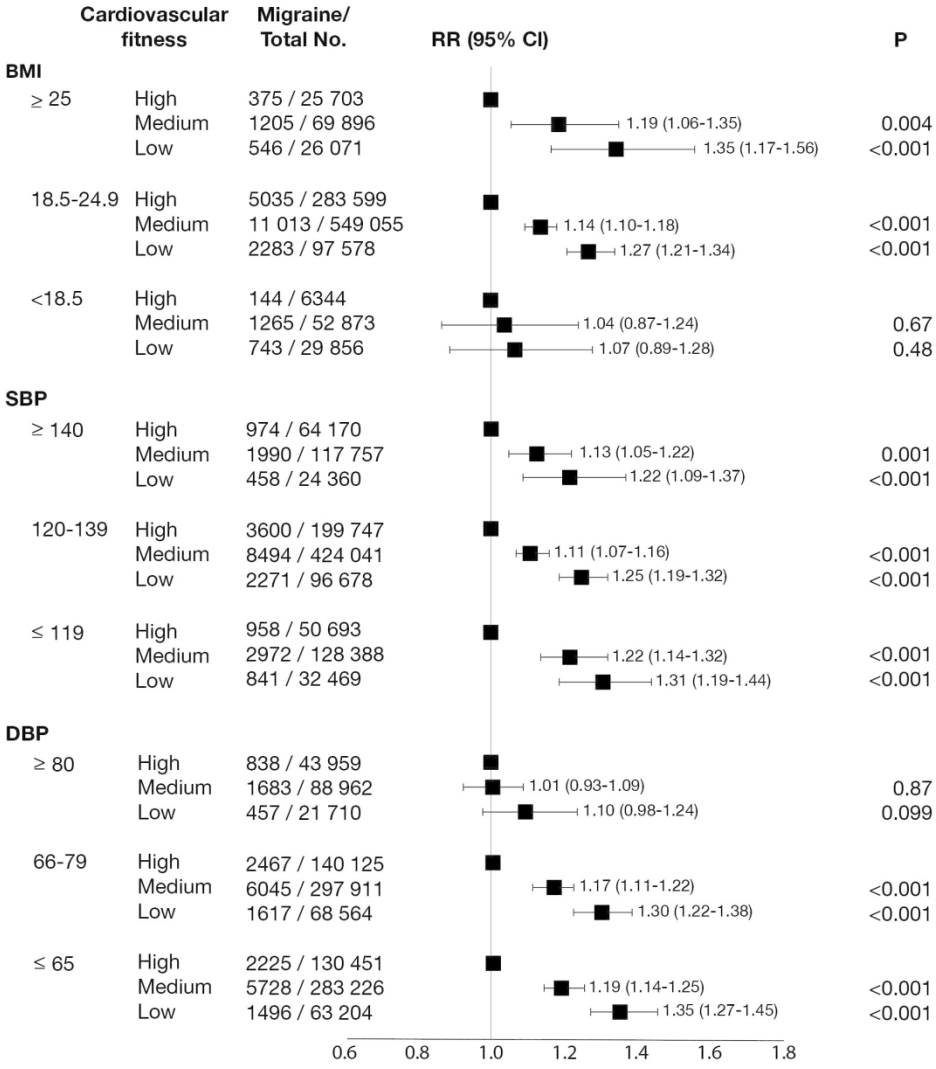

Figure 2 Risk ratios of prescribed migraine-specific medication in relation to cardiovascular fitness levels stratified by categories of body mass index, systolic and diastolic blood pressure at baseline.

Footnote Figure 2:
Abbreviations: BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; No., number of events; RR, risk ratio; SBP, systolic blood pressure.
RR adjusted for age, conscription calendar year and region parental education.

170x182mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	*(a)* Indicate the study's design with a commonly used term in the title or the abstract **The title describes the study as a "prospective population-based study".**
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found **The abstract describes Objectives, Design, Setting, Participants, Outcomes, Results and Conclusion.**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **The background and rationale questions are described in the Introduction (p. 4-5).**
Objectives	3	State specific objectives, including any prespecified hypotheses **Objectives/research questions are stated in the Introduction (p. 5).**
Methods		
Study design	4	Present key elements of study design early in the paper **Key elements of the study design are presented in the Introduction (p.5) and Method (p.5) section. The study design is further described throughout the whole Method section.**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **The setting is described in the Method section (p.5-6). Location and dates are described on p. 6, 8-10.**
Participants	6	*(a)* Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **A description of the study population is described in the Method section (p.5-6). Methods of follow-up are described on p. 7-10.**
		(b) For matched studies, give matching criteria and number of exposed and unexposed **n/a**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Outcomes are discussed on p.8, exposure on p. 6, confounders and covariates on p. 7 and effect modifiers on p. 9.** **Exposure is level of cardiovascular fitness at age 18. The outcome of migraine is defined as a recorded dispensing of prescribed migraine-specific medication (between age 20 and 60), identified using the Swedish Prescribed Drug Register. Confounders are conscription test region, year and age as well as parental education and BMI. Effect modifiers are BMI and blood pressure.**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **Measure of the exposure are described in the Method section (p. 6), of covariates (p. 7) and of outcome variables (p. 8).**
Bias	9	Describe any efforts to address potential sources of bias

		Potential sources of bias are discussed under Limitation in the Discussion section (p. 16-17).
Study size	10	Explain how the study size was arrived at **Study size is described in the Method section (p. 5), the Result section (p. 10) and Figure 1.**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **Description of quantitative variables and groupings are described in the Method section (p. 6-7).**
Statistical methods	12	*(a)* Describe all statistical methods, including those used to control for confounding **All statistical methods are described in the Statistical analyses subsection.**
		(b) Describe any methods used to examine subgroups and interactions **Description of subgroup analysis and effect modification are described in the Statistical analyses subsection.**
		(c) Explain how missing data were addressed **Missing data are reported in Table 1 and addressed in the Method section (p. 10) and in the Strengths and limitation subsection (p. 17).**
		(d) If applicable, explain how loss to follow-up was addressed **Loss to follow-up due to deaths and emigrations are described in the Method section (p.6).**
		(e) Describe any sensitivity analyses **A subanalysis is described in the Method section (p. 8-11).**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **The numbers are presented in Figure 1.**
		(b) Give reasons for non-participation at each stage **Reasons are described in Figure 1.**
		(c) Consider use of a flow diagram **Figure 1 is a flow diagram.**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **Baseline characteristics of the population are described in Table 1.**
		(b) Indicate number of participants with missing data for each variable of interest **Missing data are shown in Table 1.**
		(c) Summarise follow-up time (eg, average and total amount) **Follow-up time is shown in Figure 1.**
Outcome data	15*	Report numbers of outcome events or summary measures over time **Number of outcomes are shown in Figure 1, Table 2 and in the Result section (p.10).**
Main results	16	*(a)* Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **Adjusted estimates and 95% confidence intervals are presented for all outcomes. Confounders are described in the Method section (p.7, 9).**
		(b) Report category boundaries when continuous variables were categorized **n/a**

		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **n/a**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **Subanalyses are described in the Statistical analyses subsection (p.8-11).**
Discussion		
Key results	18	Summarise key results with reference to study objectives **Key results are summarised in the Discussion section (p. 13).**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **Limitations are discussed in the Strengths and limitations subsection (p.16-17).**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **Conclusions are included as a final subsection to the Discussion section (p. 17-18).**
Generalisability	21	Discuss the generalisability (external validity) of the study results **This is discussed in the Strengths and limitations subsection (p.16-17).**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **Funding is reported in a separate section (p.18).**

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Cardiovascular fitness and risk of migraine: a large, prospective population-based study of Swedish young adult men

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Cardiovascular fitness and risk of migraine: a large, prospective population-based study of Swedish young adult men

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ABSTRACT

Objectives: To examine the relationship between cardiovascular fitness by cycle ergometric test, in young adult men and future risk of migraine, and to study eventual differential effects on migraine risks in categories of BMI and blood pressure.

Design: National prospective population-based cohort study

Setting: Sweden 1968-2014

Participants Swedish 18-year-old men (n= 1 819 828) participating in mandatory military conscription between 1968-2005.

Primary and secondary outcomes: Primary outcome was first dispensation of prescribed migraine-specific medication, identified using the Swedish Prescribed Drug Register between ages 20-60. Secondary outcome was migraine diagnosis from the Swedish National Hospital Register.

Results: During follow-up, 22 533 men filled a prescription for migraine-specific medication. Compared to high cardiovascular fitness, low and medium fitness increased the risk of migraine-specific medication with adjusted RR 1.29, 95% Cl 1.24-1.35 (population attributable fraction of 3.6% 95% Cl 1.7-5.3) and RR 1.15, 95% Cl 1.12-1.19 (population attributable fraction of 8.0% 95% Cl 4.0-11.7), respectively. Stratified analyses of this association by levels of BMI, systolic, or diastolic blood pressure showed that lower fitness levels increased risk of migraine in all groups except for underweight men or men with high diastolic blood pressure.

Conclusions: Young men with a lower cardiovascular fitness have a higher long-term risk of developing pharmacological prescription-requiring migraine. This study contributes with information regarding risk factors for migraine in men, an understudied population in migraine research.

Key words: migraine, cardiovascular fitness, prospective, risk factor, men, cohort

Strengths and limitations of this study

- This is a large, longitudinal study based on a nearly total population sample of young men in Sweden between 1969 and 2005 (n=1 819 828), employing objective measurements of cardiovascular fitness at baseline.
- The study has a long follow-up time (2-46 years) and relies on high quality national register data to identify men, an understudied population in migraine research, who later develop migraine.
- The incidence of migraine is likely underestimated since men with undiagnosed migraine or those only using over-the-counter or preventative migraine medication are not captured in the available data.
- Although analyses were adjusted for several potential confounding variables, sources of residual and unmeasured confounding (such as smoking and alcohol consumption) may still be present.

INTRODUCTION

Migraine is an intermittent neurological disorder with strong influences on the vascular system.[1] Cardiovascular fitness, a state indicating overall capacity of the cardiovascular and respiratory systems and the ability to carry out prolonged strenuous exercise, is specifically associated with positive effects on vascular health as well as a reduced incidence of several neurological and cardiovascular disorders.[2-4] However, data on the relationship between cardiovascular fitness and the development of migraine are lacking. Higher levels of *physical activity,* a behavior in which body movement produced by muscle action increases the energy expenditure and enhances or maintains cardiovascular fitness[2], is prospectively associated with a reduced risk of migraine.[5] Physical activity is strongly correlated to but not interchangeable with cardiovascular fitness, the latter also depending on other components such as genetic makeup.[2]

Although not informative regarding direction of causality, cross-sectional data show that peak oxygen uptake is inversely associated with migraine[6] whereas cross-sectional studies of migraine and physical activity show discordant findings.[7-10] In patients with migraine, regular physical activity appears to have alleviating effects on migraine symptoms such as frequency and intensity.[11] However, acute physical exercise may also be a trigger of migraine episodes[12] and individuals with migraine or severe headaches might therefore be more reluctant to exercise. There is also a high comorbidity between migraine and cardiovascular conditions.[13] While factors affecting cardiovascular health, such as weight and blood pressure have also been shown to influence migraine prevalence,[14 15] the long-term risk of migraine, with respect to cardiovascular fitness, across strata of BMI and blood pressure remains to be clarified. Migraine is two to three times more prevalent in women, and data on factors influencing migraine in men are scarce.[16] Focusing on men only means that possible effects of menstruation, pregnancy and lactation do not need to be taken into consideration.

The primary aim of this study was to investigate whether baseline cardiovascular fitness in young adult men affects the long-term risk of migraine in a large, prospective population-based cohort with objective measures of cardiovascular fitness at baseline and a long follow-up time. Secondary aims were to evaluate whether the relationship between cardiovascular fitness and future risk of migraine is modified by baseline levels of BMI or blood pressure.

METODS

We performed a population-based prospective study of young Swedish men enlisting for military service. Exposure variables were obtained at conscription (baseline) from records in the Swedish Military Service Conscription Register. Data from this register were linked to the Swedish Prescribed Drug Register, the National Hospital Registers, the Longitudinal Integration Database for Health Insurance and Labour Market Studies and the Swedish Cause of Death Register. Linkage of individual data was made possible by the unique personal identification number assigned to each registered person in Sweden. After linkage, all data were anonymized and coded by Statistics Sweden in order to maintain the confidentiality for the included men.

During follow-up, use of migraine-specific medication identified through the Swedish Prescribed Drug Register served as a marker of migraine. Further, in a secondary analysis, hospital diagnoses of migraine, identified in the National Hospital Register, were recorded as outcomes. The Ethics Committee of the University of Gothenburg and Confidentiality Clearance at Statistics Sweden approved this study (Dnr 462-14).

Study population

The source population of the study comprised all men (n=1 819 828) who enlisted for military service during 1968–2005, who were 16-25 years old and had a specified test center location. Enlistment was mandatory during this period for all Swedish men. Only individuals with severe

chronic medical or mental conditions, serious disabilities or incarceration were granted exemption (in all, 2–3% of the male population per year). The vast majority were 18 years old at time of conscription (mean age 18.2, SD=0.7). To reduce the risk of possible reverse causation, men with a prescribed migraine-specific medication or migraine diagnosis prior to or during the two years after conscription (identified through the National Hospital Register and Conscription Register) were excluded from the analyses, as were men who died or emigrated within two years after conscription and men who lacked data on cardiovascular fitness (Figure 1). For analyses using the Prescribed Drug Register, men who died or emigrated prior to the start of the register (2005) were excluded (Figure 1).

Ascertainment of exposure: cardiovascular fitness

All men underwent a 2-day examination at one of six conscription centers (Southern, Western, Eastern, Central/Bergslagen, Northern lower and Northern upper). Cardiovascular fitness was evaluated at all centers throughout the entire study period. Cardiovascular fitness was objectively measured by a physician using a standardized cycle ergometric maximal test. The test started with submaximal exercise and work rate was continuously increased until exhaustion. The final work rate (Wmax) was recorded and divided by body weight and converted into stanine scores that served as a measure of cardiovascular fitness. We have previously observed that the frequency distribution of cardiovascular fitness in the dataset is right-skewed and not normally distributed. Therefore, as in other studies,[17] cardiovascular fitness categories were trichotomized as low (score 1–4), medium (score 5–7) and high (score 8–9). Although the protocol for the ergometer test has changed over the years, average cardiovascular fitness scores have remained stable (<1% change). The conscription cardiovascular fitness test has been shown to have good reliability and validity.[18]

Covariates

Weight, height, and systolic and diastolic blood pressures were measured by a physician, according to a written standard protocol. Systolic and diastolic blood pressures were measured on the first conscription day after 5-10 minutes rest in the supine position. One measurement was generally performed, although when systolic blood pressure was over 145 mmHg or diastolic blood pressure was outside the range of 50-85 mmHg, a second measurement was made the following day and included in the register instead. Weight (kg) and height (m) were measured and BMI was calculated as (kg/m^2). BMI values < 10 and > 60 km/m^2 were treated as extreme values and excluded. BMI was categorized as low (< 18.5 kg/m^2), normal (18.5-24.9 kg/m^2) and high (> 25.0 kg/m^2). Systolic and diastolic blood pressures were divided into three groups; systolic blood pressure: ≥ 140, 120-139 and ≤ 119 mmHg and diastolic blood pressure: ≥ 80, 66-79 and ≤ 65 mmHg. Data on conscription test center, conscription year, age at conscription and parental education were also included since they are plausible covariates. Differences among regions and test centres could introduce confounding. There might also be effects of variation in diagnosis frequency and differences in conscription procedures depending on what year the subject enlisted. Socioeconomic status affects level of cardiovascular fitness in the current dataset and is associated with migraine risk.[19] Therefore, parental education was included as a measure of the socioeconomic status and adjusted for. Information on parental education (80% coverage), as well as emigration, were collected from the Longitudinal Integration Database for Health Insurance and Labour Market Studies (Swedish acronym LISA; http://www.scb.se/Pages/List____257743.aspx) at Statistics Sweden. The LISA database includes data from all Swedish residents aged 16 years and older and is annually updated. Parental education (maternal and paternal education treated separately) was graded in 3 levels: pre-high school education (up to 9 years), high school education and university/postgraduate education.

Outcome variables

The outcome of migraine between age 20 and 60 was obtained using first recorded dispensing of prescribed migraine-specific medication, identified using the Swedish Prescribed Drug Register. This national register started in 2005 and includes detailed information on all prescription drugs (from primary care and hospital-based care) that are dispensed by all pharmacies in Sweden.[20] The Prescribed Drug Register is updated monthly and grouped according to the Anatomical Therapeutic Chemical (ATC) classification (WHO). The following migraine-specific medication were included: Sumatriptan (N02CC01), Naratriptan (N02CC02), Zolmitriptan (N02CC03), Rizatriptan (N02CC04), Almotriptan (N02CC05), Eletriptan (N02CC06), Frovatriptan (N02CC07), Dihydroergotamine (N02CA01) and Ergotamine (N02CA02). As these medications are also indicated for cluster headache, men with this diagnosis (ICD-10: G44.0; ICD-9: 346C; ICD-8: 346.01) in the National Hospital Register were excluded from the analyses.

Additional secondary analyses were also performed using ICD-codes for migraine diagnosis from the Swedish National Hospital Register as an outcome (ICD-10: G43; ICD-9: 346A,B,X,W; ICD-8: 346.09). This register contains both inpatient and outpatient diagnoses recorded in a hospital setting including referrals to neurologists/migraine specialists and emergency visits. In Sweden, it is mandatory for all private and publicly funded hospitals to register one principal discharge diagnosis and up to thirty contributory diagnoses. Register coverage for all inpatient care increased gradually during 1968-1986 and diagnoses from hospital outpatient care have been recorded since 2001. The Swedish National Hospital Register is a national, population-based register with high coverage; it is validated with positive predictive values of (85%–95%) for most ICD diagnoses.[21]

Statistical analyses

In order to address the primary aim i.e. how cardiovascular fitness at baseline affects risk of migraine during follow-up, we calculated risk ratios and 95% confidence intervals using

Poisson regressions, with exposure time as offset to correct for differences in exposure time, and robust standard errors. Based on the obtained models, we also calculated the maximum likelihood estimations for the adjusted population attributable fractions (PAF), with corresponding 95% CIs.[22 23] The PAFs are interpreted as the estimated percentage of all cases during follow-up that could have been prevented if the men of specified cardiovascular fitness group instead had belonged to the group with high cardiovascular fitness. The rationale for choosing risk ratio analyses was the aggregation of both new and older records in the Prescribed Drug Register at register initiation, rendering it not possible to establish the time of first prescription. Cox proportional hazards models were thus not suitable. All analyses were adjusted for age at conscription, conscription region, conscription decade and parental education (Model 1). Given that BMI might affect both cardiovascular fitness and migraine, we also performed an additional model (Model 2) also adjusting for BMI.[24] To address the secondary aim i.e. whether the relationship of cardiovascular fitness and migraine was modified by levels of BMI or blood pressure, we stratified the risk estimates by categories of baseline BMI, as well as systolic and diastolic blood pressure, applying the above mentioned categories. We also performed secondary analyses to evaluate the relationship between cardiovascular fitness and risk of hospital-based migraine diagnosis, which likely addresses the most severe migraine cases. Cox proportional hazards models were performed to estimate hazard ratios and 95% confidence intervals. Separate analyses were performed for outpatient migraine diagnoses only, as well as outpatient and inpatient diagnoses, together. By removing the inpatient diagnoses, individuals with the highest degree of psychiatric and somatic comorbidity, medication overuse and highest pain scores were excluded [25] rendering the patient group more homogenous. We also performed separate analyses of only primary diagnoses of migraine. The follow-up period began at conscription (baseline), and person-time was included until time of 1) first record of migraine in the National Hospital Register, 2) death, 3) emigration or 4) at the

end of follow-up, i.e. on December 31, 2014 whichever happened first (minimum 2 years and maximum 46 years follow-up). Death dates were obtained from the Swedish Cause of Death Register, which has kept record of virtually all deaths in Sweden since 1961.

Men with missing data for parental education were included as a separate category in all analyses. High cardiovascular fitness was used as the reference category and all P-values are 2-tailed and we consider a P-value of less than 0.05 as statistically significant. The statistical calculations were performed with SAS version 9.4 (SAS Institute, NC).

Patient and public involvement

There was no patient involvement in this study.

RESULTS

Baseline characteristics by levels of cardiovascular fitness in the study population are shown in Table 1. Men with lower cardiovascular fitness were more likely to have lower parental education, higher BMI and higher systolic blood pressure than men with higher fitness. After exclusion criteria were applied, analyses of dispensed migraine-specific medication were based on a total of 1 143 831 subjects, and secondary analyses of migraine diagnoses in the National Hospital Register were based on 1 213 104 subjects (Figure 1).

Table 1 Baseline characteristics by cardiovascular fitness level in a cohort of 1 142 831 male conscripts used to analyse prescription of migraine-specific medication before age 60.

		Level of cardiovascular fitness		
	All, n (%)	High, n (%)	Medium, n (%)	Low, n (%)
Total	1 143 831 (100.0)	316 113 (100.0)	673 536 (100.0)	154 182 (100.0)
Migraine-specific medication	22 533 (2.0)	5 525 (1.7)	13 448 (2.0)	3 560 (2.3)
Decade of conscription				
1968-1969	9619 (0.8)	2920 (0.9)	5169 (0.8)	1 530 (1.0)
1970s	357 123 (32.8)	123 367 (39.0)	198 357 (29.5)	53 399 (34.6)
1980s	432 857 (37.8)	104 672 (33.1)	252 082 (37.4)	76 103 (49.4)
1990s	247 079 (21.6)	65 057 (20.6)	161 868 (24.0)	20 154 (13.1)
2000s	79 153 (6.9)	20 097 (6.4)	56 060 (8.3)	2 996 (1.9)
Place of conscription				

South	263 865 (23.1)	70 546 (22.3)	158 784 (23.6)	34 535 (22.4)
West	245 545 (21.5)	62 247 (19.7)	145 540 (21.6)	37 758 (24.5)
East	246 449 (21.5)	68 731 (21.7)	140 660 (20.9)	37 058 (24.0)
Bergslagen	225 046 (19.7)	63 472 (20.1)	130 994 (19.4)	30 580 (19.8)
Lower Norrland	105 809 (9.3)	31 230 (9.9)	64 667 (9.6)	9 912 (6.4)
Upper Norrland	57 117 (5.0)	19 887 (6.3)	32 891 (4.9)	4 339 (2.8)
Parental education				
Pre–high school	345 478 (30.2)	83 976 (26.6)	199 592 (29.6)	61 910 (40.2)
High school	478 024 (41.8)	124 718 (39.5)	289 883 (43.0)	63 424 (41.1)
University or higher	290 792 (25.4)	100 633 (31.8)	166 772 (24.8)	23 388 (15.2)
Missing	29 537 (2.6)	6 788 (2.1)	17 289 (2.6)	5 460 (3.5)
BMI				
High (≥ 25.0)	89 073 (7.8)	6344 (2.0)	52 873 (7.9)	29 856 (19.4)
Normal (18.5-24.9)	930 230 (81.3)	283 599 (89.7)	549 055 (81.5)	97 578 (63.3)
Low (<18.5)	121 670 (10.6)	25 703 (8.1)	69 896 (10.4)	26 071 (16.9)
Missing	2 858 (0.2)	469 (0.1)	1 712 (0.3)	677 (0.4)
Systolic blood pressure				
≥ 140 mmHg	211 550 (18.5)	50 693 (16.0)	128 388 (19.1)	32 469 (21.1)
120-139 mmHg	720 456 (63.0)	199 746 (63.2)	424 041 (63.0)	96 678 (62.7)
≤119 mmHg	206 286 (18.0)	64 170 (20.3)	117 757 (17.5)	24 360 (15.8)
Missing	5 530 (0.5)	1 505 (0.5)	3 350 (0.5)	675 (0.4)
Diastolic blood pressure				
≥ 80 mmHg	476 880 (41.7)	130 450 (41.3)	283 226 (42.1)	63 204 (41.0)
66-79 mmHg	506 599 (44.3)	140 125 (44.3)	297 911 (44.2)	68 564 (44.5)
≤ 65 mmHg	154 631 (13.5)	43 959 (13.9)	88 962 (13.2)	21 710 (14.1)
Missing	5721 (0.5)	1580 (0.5)	3437 (0.5)	704 (0.5)

Abbreviations: BMI, body mass index
[1]Performance was trichotomized as low (score 1–4), medium (score 5–7) and high (score 8–9).

Cardiovascular fitness and future migraine-specific medication

Prescriptions for migraine-specific medication were filled by 22 533 men (2.0%). Compared to the high cardiovascular fitness level, both low and medium levels increased the risk for use of migraine-specific medication (adjusted RR 1.29, 95% Cl 1.24-1.35 and 1.15, 95% Cl 1.12-1.19, respectively) during follow-up (Table 2). PAF of medium cardiovascular fitness (8.0%) for migraine-specific medication was higher than that of low fitness (3.6%). Including BMI as an additional confounder to the multivariable models did not change the RRs or PAFs substantially. The proportion of men with missing values for cardiovascular fitness was 31.6% for men with migraine-specific medication and 32.4% for men without.

Table 2 Risk ratios and population attributable fractions of prescribed migraine-specific medication before age 60 in relation to cardiovascular fitness levels in young adult men.

	Model 1[2], n= 1 143 831			
Cardiovascular fitness[1]	Migraine / Total No.	RR (95% Cl)	P	PAF (95% Cl)

High	5 525 / 316 113	1.00 (reference)		
Medium	13 448 / 673 536	1.15 (1.12-1.19)	<0.001	8.0% (4.0-11.7)
Low	3 550 / 154 182	1.29 (1.24-1.35)	<0.001	3.6% (1.7- 5.3)
Model 2[3], n= 1 140 973				
Cardiovascular fitness[1]	Migraine / Total No.	RR (95% CI)	P	PAF (95% CI)
High	5 517 / 315 644	1.00 (reference)		
Medium	13 411 / 671 824	1.14 (1.11-1.18)	<0.001	7.5% (3.2-11.4)
Low	3 537 / 153 505	1.27 (1.21-1.32)	<0.001	3.3% (1.2- 5.2)

Abbreviations: BMI, body mass index; CI, confidence interval; PAF, population attributable fraction; No., number of events; RR, risk ratio

[1] High level= reference category

[2]Adjusted for age, conscription calendar year and region and parental education.

[3]Adjusted for age, conscription calendar year and region, parental education and BMI

Risks stratified by categories of BMI and blood pressure

The association of cardiovascular fitness and future migraine-specific medication was analysed in separate strata of BMI and blood pressure groups (Figure 2). Low and medium fitness increased the risk for migraine medication in men with high and normal BMI, but had no effect in underweight men. For systolic blood pressure, low and medium fitness had similar associations with future migraine medication in all three categories. Fitness was not associated with future migraine medication in men with diastolic blood pressure ≥ 80 mmHg, but increased the risk of medication in men with diastolic blood pressures 66-79 mmHg as well as ≤65 mmHg

Cardiovascular fitness and future migraine diagnosis

Migraine diagnoses were recorded in the National Hospital Register for 10 043 men (0.8% of the entire study population). Most (82%) were primary diagnoses. Approximately one third of the men with a migraine diagnosis in the National Hospital Register were also observed with migraine medication in the Prescribed Drug Register. Lower cardiovascular fitness increased the risk of a first-time migraine outpatient diagnosis (Table 3). Adding migraine codes for inpatient migraine to the outpatient codes did not result in a statistically significant association. Associations were similar when analysing primary migraine diagnoses only. For primary outpatient diagnoses, HR for low and medium cardiovascular fitness were 1.15, 95% CI 1.05-1.26 (P=0.002) and 1.07, 95% CI 1.01-1.14 (P=0.035), respectively. For combined primary

outpatient and inpatient diagnoses, HR for low fitness was 0.98, 95% Cl 0.91-1.09 (P=0.21) and HR for medium fitness was 1.03, 95% Cl 0.98-1.09 (P=0.26).

Table 3 Hazard ratios of migraine diagnoses, recorded in the National Hospital Register, in relation to cardiovascular fitness levels in young adult men followed for up to 46 years.

Outpatient migraine diagnoses only			
Cardiovascular fitness[1]	Migraine / Total No.	HR (95% CI)[2]	P
High	1759/ 338 295	1.00 (reference)	
Medium	4060/ 710 865	1.08 (1.02-1.15)	0.01
Low	1044/ 163 946	1.18 (1.08-1.28)	<0.001
All migraine diagnoses (inpatient and outpatient)			
Cardiovascular fitness[1]	Migraine / Total No.	HR (95% CI)[2]	P
High	2655/ 338 295	1.00 (reference)	
Medium	5852/ 710 865	1.05 (1.00-1.12)	0.14
Low	1536/ 163 946	1.05 (0.98-1.12)	0.30

Abbreviations: BMI, body mass index; CI, confidence interval; No., number of events; HR, hazard ratio
[1] High level= reference category
[2]Adjusted for age, conscription calendar year and region and parental education.

DISCUSSION

In this large, prospective cohort of young adult men, cardiovascular fitness was inversely associated with future migraine. Though quite similar, the risks were somewhat larger for filled migraine-specific drug prescriptions than for outpatient migraine diagnosis. The increased relative risk of migraine among those with a low level of cardiovascular fitness was higher than for those with a medium level fitness. However, more new migraine cases detected in this study were attributable to medium cardiovascular fitness rather than to low cardiovascular fitness, given that medium cardiovascular fitness is more common in the population.

Comparisons with other studies

This population-based longitudinal study provides new insights into the effects of cardiovascular fitness on migraine risk. While not directly comparable with cardiovascular fitness, there are two prospective studies evaluating the relationships between physical activity and migraine with inconsistent results.[5 8] However, it is important to distinguish the terms

cardiovascular fitness and physical activity. Cardiovascular fitness is more strongly related to health outcomes than physical activity, and activity not resulting in an increase in fitness level may not provide protective effects against adverse health outcomes.[26] Hence, studies of cardiovascular fitness in addition to physical activity are of great importance. A cross-sectional study found an inverse relationship of peak oxygen uptake and migraine in adults younger than 50,[6] but given its cross-sectional study design, no conclusions can be made regarding the direction of the observed effect.

Effect modification by BMI and blood pressure

The association of cardiovascular fitness and migraine was only apparent in men with normal and high BMI but not in those with low BMI. Prospective studies of BMI and later risk of migraine appear to be lacking, but a meta-analysis of cross-sectional studies concluded that the risk of migraine appears to be moderately increased in both obese and underweight individuals.[14] Our results suggest that there is no additional beneficial effect of having a higher cardiovascular fitness in men with a low BMI at baseline, but it should be noted that the number of men in this category was limited and there may have been reduced power. It is also possible that there might be a common underlying factor influencing both BMI and migraine.

While an association between cardiovascular fitness and migraine was observed in all categories of systolic blood pressure, this was not the case for the group with a diastolic blood pressure of ≥ 80 mmHg. This observation may partly be explained by the previously reported relationship between higher blood pressures and hypoalgesia.[27] It could also reflect an unknown, underlying cause in young men with deviant blood pressures. Further studies are needed to elucidate the effects of BMI and blood pressure on the interrelationship between cardiovascular fitness and migraine.

Possible mechanisms

The increased risk of migraine with lower cardiovascular fitness observed in this study may be explained by a combination of several factors. There might be an unknown, common predisposing factor for both low cardiovascular fitness and migraine given the clear association of migraine with unfavourable cardiovascular risk factor profiles.[28] An association between migraine and cardiovascular risk comorbidities could be explained by a common pathology underlying both conditions and migraine might be a local manifestation of a systemic, rather that neurological, phenomenon.[28] Our research findings expand on previous studies linking migraine to cardiovascular risk factor profiles, highlighting the long-term association between cardiovascular fitness and migraine.

Several areas of the brain are still developing during late adolescence, and it is also possible that cardiovascular fitness during this period has long-term effects on brain health that might reduce susceptibility to migraine. Low cardiovascular fitness increases the risk of several other neurological and psychiatric disorders such as stroke,[3] epilepsy,[4] and depression.[29] It could be that a common mechanism affecting neuroprotection, neurogenesis, synaptic plasticity, neuroinflammation, and neurotrophic factors such as brain-derived neurotrophic factor (BDNF) may be involved.[30] Hence, higher cardiovascular fitness might result in a greater "brain reserve" that may act as a compensatory buffer of brain plasticity and neural resources and better enable the brain to cope with neuropathology, resulting in long-lasting beneficial effects on brain health.[31] Indeed, there is increasing evidence suggesting that behavioural interventions such as physical activity during critical stages of development can have such long-lasting and robust effects on the brain.[31]

Cardiovascular fitness may also influence migraine burden such as pain. Several studies report lower migraine burden with more physical activity[32] and a recent randomized study of exercise in migraine patients showed decreased migraine pain, intensity and frequency after the training intervention.[33] Neuroadaptive changes with pain are well-known[34] and decreased levels of

BDNF have been reported in patients with migraine.[35] Higher fitness level during adolescence could induce long-lasting structural and/or biochemical changes to the brain, generating a higher threshold for migraine pain. Further, although we excluded men with migraine prior to or for two years after conscription, it is possible that some men with undiagnosed migraine were included in the study. Men burdened with undiagnosed migraine at baseline might exercise less, which could result in lower cardiovascular fitness at conscription.

Strengths and limitations

Strengths of this study include the population-based design, its large size and the objective measurements of cardiovascular fitness at baseline. Other strengths are available information on a large number of important covariates, the long follow-up time and the use of national register data to identify conscripts who later developed migraine. Further, this study focuses on men, an understudied population in migraine research.

Several limitations should be considered when interpreting our results. We show that 2% of the men filled a first-time prescription of migraine-specific medication during follow-up. However, the mean prevalence of current migraine among adult men in Europe has been estimated to be 8% in a review combining studies with variable timeframes.[36] Although our figures show first-time prescriptions, which are not equivalent to prevalence, the incidence of migraine in the current study is likely underestimated. Our outcome measurements only capture men who seek health care and we are unable to identify men using over the counter migraine medication only, no medication at all, or preventative medications. Altogether, these definitions likely select for men with more severe migraine episodes, which cannot be handled by the patient himself. Although we excluded men who died or emigrated before the Prescribed Drug Register started in 2005, we may have missed men who enlisted during the earlier years and had migraine that later resolved (or men who did not seek treatment for migraine later). Boys with an early migraine diagnosis that resolved prior to conscription might have been misclassified as having

migraine at baseline and would hence be wrongfully excluded from the analyses. Although we have reduced the risk of possible reverse causation by excluding men with migraine prior to or during the two years after conscription, there is still a possibility that adolescent men had migraine but were not diagnosed and had not received prescribed migraine medication. Such men have been included in the current study and this could influence cardiovascular fitness if they were less active due to their migraine. The hospital register does not include codes from primary care; therefore, men without hospital-based care could only be identified through the Prescribed Drug Register. By removing inpatient diagnoses of migraine from the analyses, we might also introduce a selection bias. In Sweden, migraine or cluster headache are the only indications for triptans and ergotamide (FASS; https://www.fass.se/). We have excluded men with prescribed migraine-specific medication at baseline as well as men diagnosed with cluster headache. However, there is still a small possibility that these medications could be prescribed for other indications and such subjects would be included in our study. The migraine diagnosis based on ICD codes has not been formally validated. However, we have no reason to believe that the generally high positive predictive values observed for other ICD codes in the National Hospital Register would not apply to migraine.

Although we have controlled for confounding by adjusting for information on several covariates, residual and unmeasurable confounding may still be present as our study is observational. In particular, we had no information on smoking and alcohol consumption. Our research goal was to estimate the effect of baseline cardiovascular fitness on long-term risk of migraine. Therefore, we do not include data on cardiovascular fitness or other health-related risk factors at later stages in life. We have no information regarding changes over time. An additional limitation is that, due to the identification method of migraine used, we were not able to stratify subjects according to migraine frequency or severity, episode duration or aura status. Hence, we do not know how cardiovascular fitness influences the risk of different subtypes of

migraine. Our findings should not be interpreted as explanatory regarding the causal chain leading to the onset of migraine. Moreover, the amount of missing values for cardiovascular fitness could have biased the results. However, since proportions with missing values were very similar among men with and without migraine-specific medication, it is unlikely that this would differentially affect the observed associations. The main purpose of the Swedish Conscription Register was for military use and detailed descriptions of causes for missing data are classified. As women have a different body composition, physiology and clinical features of migraine[16], our findings should not be directly extrapolated to women.

CONCLUSION

Lower cardiovascular fitness in adult young men increases the risk of future migraine. Our study calls for targeted research to test whether interventions to improve cardiovascular fitness result in reduced risk of developing migraine among men with low cardiovascular fitness levels. In addition, studies that explore possible mediators of the effect of cardiovascular fitness on the later development of migraine may provide insights into the biological understanding of migraine, informing the development of further preventive strategies.

Authors contribution JN, SG, ML, DÅ, MÅ, MW and GK conceptualized the study. JN, SG, DÅ, MÅ, MW and GK contributed to data acquisition. JN, SG, JLR and TK designed the analyses, and JN and SG performed the analyses. All co-authors contributed to interpretation of as well as drafting and critically revising the manuscript for important intellectual content. JN, SG and GK are the guarantors."

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Competing interests TK has received honoraria from Lilly for providing methodological advice and from Novartis for a lecture on neuroepidemiology. He further has received honoraria from The BMJ for editorial services and serves as a consultant on US National Institutes of Health grants on migraine. The other authors have no conflicts of interest.

Patient consent Not required

Ethics approval: The Ethics Committee of the University of Gothenburg and Confidentiality Clearance at Statistics Sweden approved this study (Dnr 462-14).

Provenance and peer review: Not commissioned; externally peer reviewed.

Data sharing statement: No additional data are available.

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FIGURE LEGENDS

Figure 1 Flowchart of the study populations showing included and excluded subjects and number of outcomes.

Figure 2 Risk ratios of prescribed migraine-specific medication in relation to cardiovascular fitness levels stratified by categories of body mass index, systolic and diastolic blood pressure at baseline.

Footnote Figure 2:

Abbreviations: BMI, body mass index; Cl, confidence interval; DBP, diastolic blood pressure; No., number of events; RR, risk ratio; SBP, systolic blood pressure.

RR adjusted for age, conscription calendar year and region parental education.

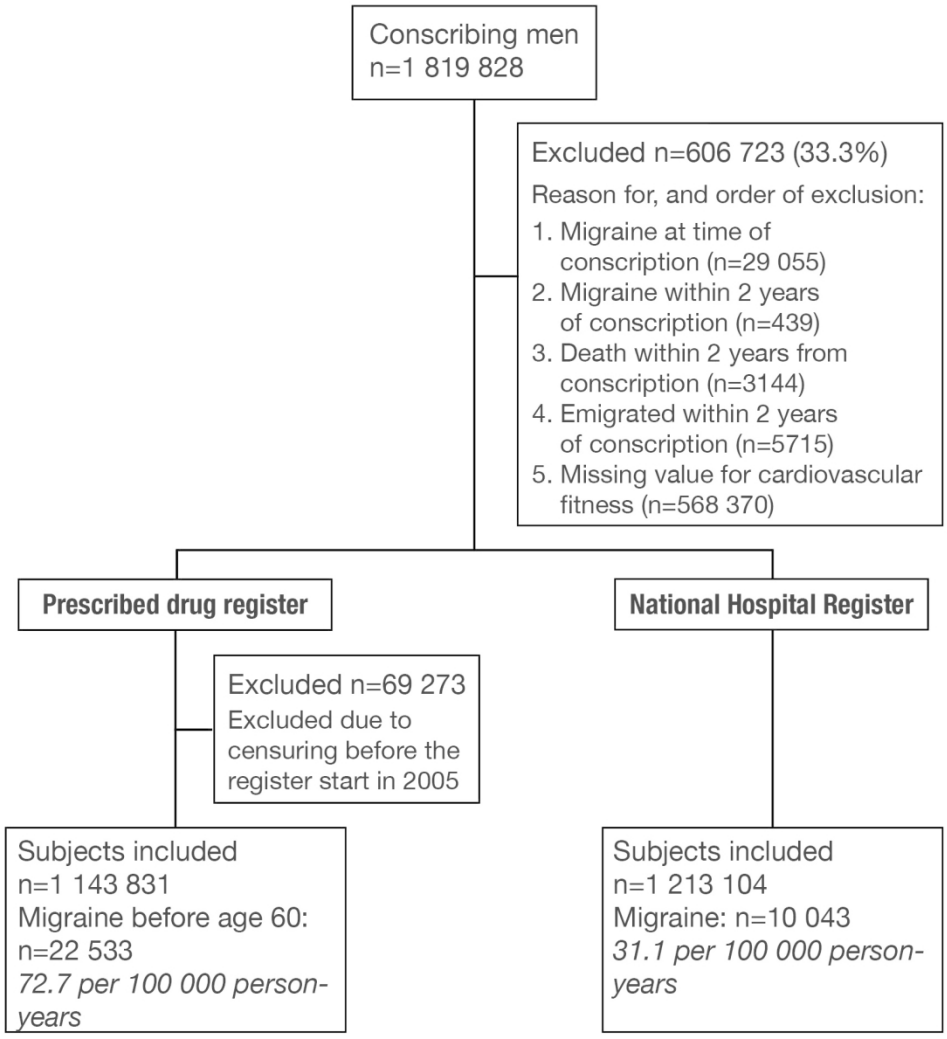

Figure 1 Flowchart of the study populations showing included and excluded subjects and number of outcomes.

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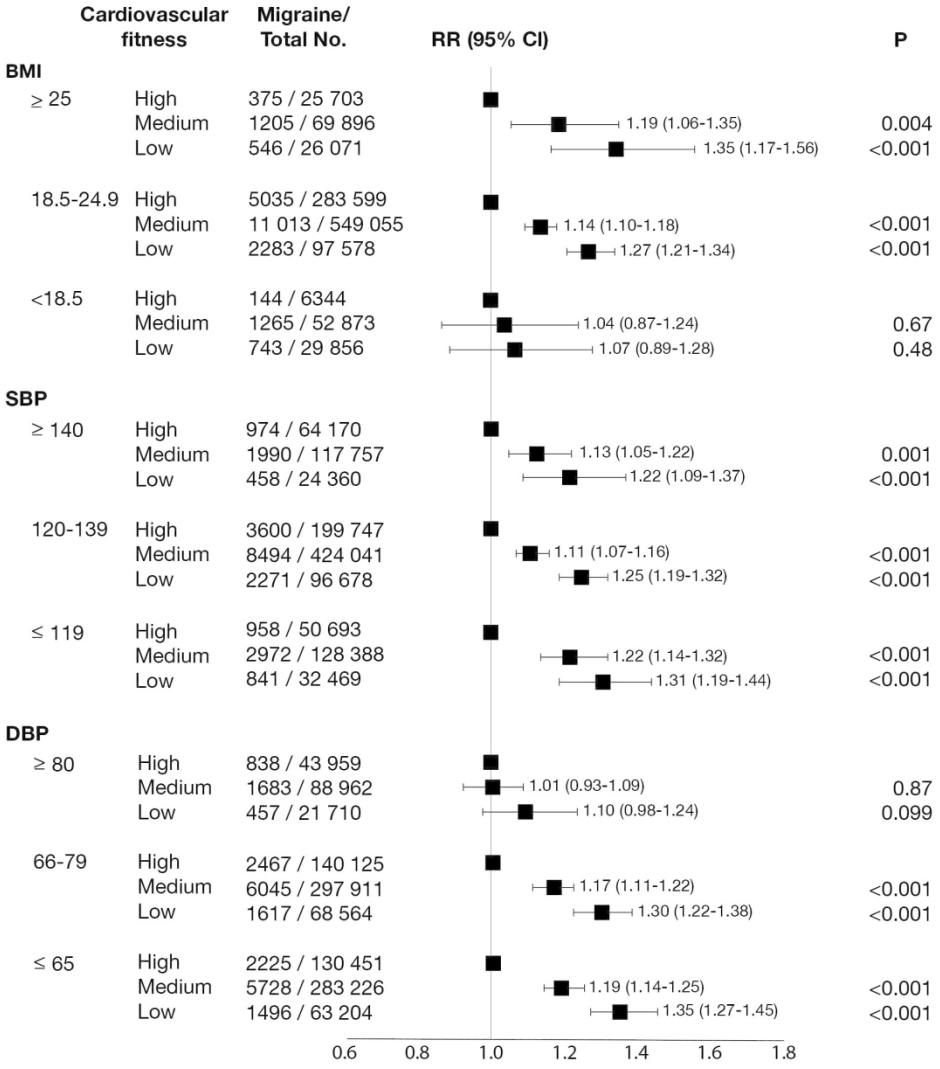

Figure 2 Risk ratios of prescribed migraine-specific medication in relation to cardiovascular fitness levels stratified by categories of body mass index, systolic and diastolic blood pressure at baseline.

170x182mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	*(a)* Indicate the study's design with a commonly used term in the title or the abstract **The title describes the study as a "prospective population-based study".**
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found **The abstract describes Objectives, Design, Setting, Participants, Outcomes, Results and Conclusion.**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **The background and rationale questions are described in the Introduction (p. 4-5).**
Objectives	3	State specific objectives, including any prespecified hypotheses **Objectives/research questions are stated in the Introduction (p. 5).**
Methods		
Study design	4	Present key elements of study design early in the paper **Key elements of the study design are presented in the Introduction (p.5) and Method (p.5) section. The study design is further described throughout the whole Method section.**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **The setting is described in the Method section (p.5-6). Location and dates are described on p. 6, 8-10.**
Participants	6	*(a)* Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **A description of the study population is described in the Method section (p.5-6). Methods of follow-up are described on p. 7-10.**
		(b) For matched studies, give matching criteria and number of exposed and unexposed **n/a**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Outcomes are discussed on p.8, exposure on p. 6, confounders and covariates on p. 7 and effect modifiers on p. 9.** **Exposure is level of cardiovascular fitness at age 18. The outcome of migraine is defined as a recorded dispensing of prescribed migraine-specific medication (between age 20 and 60), identified using the Swedish Prescribed Drug Register. Confounders are conscription test region, year and age as well as parental education and BMI. Effect modifiers are BMI and blood pressure.**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **Measure of the exposure are described in the Method section (p. 6), of covariates (p. 7) and of outcome variables (p. 8).**
Bias	9	Describe any efforts to address potential sources of bias

		Potential sources of bias are discussed under Limitation in the Discussion section (p. 16-17).
Study size	10	Explain how the study size was arrived at **Study size is described in the Method section (p. 5), the Result section (p. 10) and Figure 1.**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **Description of quantitative variables and groupings are described in the Method section (p. 6-7).**
Statistical methods	12	*(a)* Describe all statistical methods, including those used to control for confounding **All statistical methods are described in the Statistical analyses subsection.**
		(b) Describe any methods used to examine subgroups and interactions **Description of subgroup analysis and effect modification are described in the Statistical analyses subsection.**
		(c) Explain how missing data were addressed **Missing data are reported in Table 1 and addressed in the Method section (p. 10) and in the Strengths and limitation subsection (p. 17).**
		(d) If applicable, explain how loss to follow-up was addressed **Loss to follow-up due to deaths and emigrations are described in the Method section (p.6).**
		(e) Describe any sensitivity analyses **A subanalysis is described in the Method section (p. 8-11).**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **The numbers are presented in Figure 1.**
		(b) Give reasons for non-participation at each stage **Reasons are described in Figure 1.**
		(c) Consider use of a flow diagram **Figure 1 is a flow diagram.**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **Baseline characteristics of the population are described in Table 1.**
		(b) Indicate number of participants with missing data for each variable of interest **Missing data are shown in Table 1.**
		(c) Summarise follow-up time (eg, average and total amount) **Follow-up time is shown in Figure 1.**
Outcome data	15*	Report numbers of outcome events or summary measures over time **Number of outcomes are shown in Figure 1, Table 2 and in the Result section (p.10).**
Main results	16	*(a)* Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **Adjusted estimates and 95% confidence intervals are presented for all outcomes. Confounders are described in the Method section (p.7, 9).**
		(b) Report category boundaries when continuous variables were categorized **n/a**

		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **n/a**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **Subanalyses are described in the Statistical analyses subsection (p.8-11).**
Discussion		
Key results	18	Summarise key results with reference to study objectives **Key results are summarised in the Discussion section (p. 13).**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **Limitations are discussed in the Strengths and limitations subsection (p.16-17).**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **Conclusions are included as a final subsection to the Discussion section (p. 17-18).**
Generalisability	21	Discuss the generalisability (external validity) of the study results **This is discussed in the Strengths and limitations subsection (p.16-17).**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **Funding is reported in a separate section (p.18).**

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Cardiovascular fitness and risk of migraine: a large, prospective population-based study of Swedish young adult men

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Cardiovascular fitness and risk of migraine: a large, prospective population-based study of Swedish young adult men

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ABSTRACT

Objectives: To examine the longitudinal relationship between cardiovascular fitness in young adult men and future risk of migraine, and to estimate eventual differential effects among categories of BMI and blood pressure.

Design: National, prospective, population-based cohort study

Setting: Sweden 1968-2014

Participants 18-year-old Swedish men (n= 1 819 828) who underwent mandatory military conscription examinations during the years 1968-2005.

Primary and secondary outcomes: The primary outcome was the first dispensation of prescribed migraine-specific medication, identified using the Swedish Prescribed Drug Register. The secondary outcome was documented migraine diagnosis from the Swedish National Hospital Register.

Results: During follow-up, 22 533 men filled a prescription for migraine-specific medication. After confounding adjustment, compared to high cardiovascular fitness, low and medium fitness increased the risk of migraine-specific medication (RR_{low}: 1.29, 95% Cl 1.24-1.35; population attributable fraction: 3.6% 95% Cl 1.7%-5.3% and RR_{medium}: 1.15, 95% Cl 1.12-1.19; population attributable fraction: 8.0% 95% Cl 4.0%-11.7%). To assess potential effect measure modification, stratified analyses of these association by levels of BMI and blood pressure showed that lower fitness levels increased risk of migraine across all groups except among underweight men or men with high diastolic blood pressure.

Conclusions: Young men with a lower cardiovascular fitness had a higher long-term risk of developing pharmacological prescription-requiring migraine. This study contributes with information regarding risk factors for migraine in men, an understudied population in migraine research.

Key words: migraine, cardiovascular fitness, prospective, risk factor, men, cohort

Strengths and limitations of this study

- This is a large, longitudinal study of a nearly total population sample of young Swedish men undergoing mandatory military conscription examinations between 1969 and 2005 (n=1 819 828), employing objective measurements of cardiovascular fitness at baseline.
- The study has a long follow-up time (range: 2-46 years) and relies on high quality national register data to identify men, an understudied population in migraine research, who later develop prescription-requiring migraine.
- The incidence of migraine in our study is likely conservative since men with undiagnosed migraine or those only using over-the-counter or preventative migraine medication are not captured in the available data.
- Although analyses were adjusted for several important potential confounding variables, some residual confounding may remain in the estimates (such as smoking and alcohol consumption).

INTRODUCTION

Migraine is an intermittent neurological disorder with strong influences on the vascular system.[1] Cardiovascular fitness, a state indicating overall capacity of the cardiovascular and respiratory systems and the ability to carry out prolonged strenuous exercise, has been shown to have beneficial effects on vascular health as well as associated with a reduced incidence of several neurological and cardiovascular disorders.[2-4] However, data on the relationship between cardiovascular fitness and the development of migraine are lacking. Higher levels of *physical activity,* a behavior in which body movement produced by muscle action increases the energy expenditure and enhances or maintains cardiovascular fitness[2], have been prospectively associated with a reduced risk of migraine.[5] Physical activity is strongly correlated but is not interchangeable with cardiovascular fitness, as the latter also depends on other components such as genetic makeup.[2]

Although uninformative regarding direction of causality, cross-sectional studies have shown an inverse association of peak oxygen uptake with migraine[6] whereas findings from cross-sectional studies of migraine and physical activity have been heterogeneous.[7-10] Among individuals with migraine, regular physical activity appears to have alleviating effects on migraine symptoms such as frequency and intensity.[11] However, acute physical exercise may also be a trigger of migraine episodes,[12] and individuals with migraine or severe headaches might therefore be more reluctant to exercise. There is also a high comorbidity between migraine and cardiovascular conditions.[13] While factors affecting cardiovascular health, such as weight and blood pressure, have also been shown to influence migraine prevalence,[14 15] the contribution of cardiovascular fitness to long-term migraine risk may be differential across strata of BMI and blood pressure, though this has yet to be formally assessed.

Migraine is two to three times more prevalent in women, and findings on factors influencing migraine in men are scarce.[16]

The primary aim of this study was to estimate the effect of baseline cardiovascular fitness level on the long-term risk of prescription-requiring migraine in a large, prospective population-based cohort of young Swedish men with objective measures of cardiovascular fitness at baseline and a long follow-up time. The secondary aim was to evaluate whether the relationship between cardiovascular fitness and future risk of migraine is modified by baseline levels of BMI or blood pressure.

METODS

We performed a population-based prospective study of young Swedish men enlisting for military service. Exposure variables were obtained at conscription (baseline) from records in the Swedish Military Service Conscription Register. Data from this register were linked to the Swedish Prescribed Drug Register, the National Hospital Registers, the Longitudinal Integration Database for Health Insurance and Labour Market Studies and the Swedish Cause of Death Register. Linkage of individual data was made possible by the unique personal identification number assigned to each registered person in Sweden. After linkage, all data were anonymized and coded by Statistics Sweden in order to maintain the confidentiality for the included men.

During follow-up, use of migraine-specific medication identified through the Swedish Prescribed Drug Register served as a proxy for migraine. Further, in a secondary analysis, hospital diagnoses of migraine, identified in the National Hospital Register, were recorded as outcomes. The Ethics Committee of the University of Gothenburg and Confidentiality Clearance at Statistics Sweden approved this study (Dnr 462-14).

Study population

The source population of the study comprised all men (n=1 819 828) who enlisted for military service during 1968–2005, were 16-25 years old and had a documented test center location.

Enlistment was mandatory during this period for all Swedish men. Only individuals with severe chronic medical or mental conditions, serious disabilities or incarceration were granted exemption (in all, 2–3% of the male population per year). The vast majority were 18 years old at time of conscription (mean age 18.2, SD=0.7). To reduce the risk of possible reverse causation, men with a prescribed migraine-specific medication or migraine diagnosis prior to or during the two years after conscription (identified through the National Hospital Register and Conscription Register) were excluded from all analyses, as were men who died or emigrated within two years of conscription, as well as individuals with missing data on cardiovascular fitness (Figure 1). For analyses using the Prescribed Drug Register, men who died or emigrated prior to the start of the register (2005) were excluded (Figure 1).

Ascertainment of exposure: cardiovascular fitness

All men underwent a 2-day examination at one of six Swedish conscription centers (Southern, Western, Eastern, Central/Bergslagen, Northern lower and Northern upper). Cardiovascular fitness was evaluated at all centers for all included years. Cardiovascular fitness was objectively measured by a physician using a standardized maximal cycle ergometric test. Following five minutes of warm-up, the work rate was increased continuously by 25 W/min until exhaustion. The final work rate (Wmax) was recorded, divided by body weight, and then converted into a stanine score, which served as a measure of cardiovascular fitness. We have previously observed that the frequency distribution of cardiovascular fitness in the dataset is right-skewed and not normally distributed. Therefore, as in other studies,[17] cardiovascular fitness categories were trichotomised as low (score 1–4), medium (score 5–7) and high (score 8–9). Although the protocol for the ergometer test has changed over the years, average cardiovascular fitness scores have remained stable over time (<1% change). The conscription cardiovascular fitness test has also been shown to have good reliability and validity.[18]

Covariates

Weight, height, and systolic and diastolic blood pressures were measured by a physician following a written standard protocol. Systolic and diastolic blood pressures were measured on the first conscription day after 5-10 minutes rest in the supine position. One measurement was generally performed, although when systolic blood pressure was over 145 mmHg or diastolic blood pressure was outside the range of 50-85 mmHg, a second measurement was made on the following day and included in the register instead. Weight (kg) and height (m) were measured and BMI was calculated as (kg/m^2). BMI values < 10 and > 60 km/m^2 were treated as implausible values and excluded. BMI was categorized as low (< 18.5 kg/m^2), normal (18.5-24.9 kg/m^2) and high (> 25.0 kg/m^2). Systolic and diastolic blood pressures were divided into three groups; systolic blood pressure: ≥ 140, 120-139 and ≤ 119 mmHg and diastolic blood pressure: ≥ 80, 66-79 and ≤ 65 mmHg. Information on conscription test center, conscription year, age at conscription, and parental education level were also taken into account as potential sources of confounding. We anticipated differences in conscription procedures and diagnosis frequencies depending on enlistment year. Socioeconomic status has also been shown to affect level of cardiovascular fitness in the current dataset and has been associated with migraine risk.[19] Therefore, we controlled our analyses for parental education as a proxy for socioeconomic status. Information on parental education (80% coverage), as well as emigration, were collected from the Longitudinal Integration Database for Health Insurance and Labour Market Studies (Swedish acronym LISA; http://www.scb.se/Pages/List____257743.aspx) at Statistics Sweden. The LISA database includes data from all Swedish residents aged 16 years and older and is annually updated. Parental education information (maternal and paternal education treated separately) was graded in 3 levels: pre-high school education (up to 9 years), high school education and university/postgraduate education.

Outcome variables

The outcome of migraine between age 20 and 60 was obtained using first recorded dispensing of prescribed migraine-specific medication, identified using the Swedish Prescribed Drug Register. This national register started in 2005 and includes detailed information on all prescription drugs (from primary care and hospital-based care) dispensed by all pharmacies in Sweden.[20] The Prescribed Drug Register is updated monthly, and the prescriptions are grouped according to the Anatomical Therapeutic Chemical (ATC) classification (WHO). The following migraine-specific medications were included: Sumatriptan (N02CC01), Naratriptan (N02CC02), Zolmitriptan (N02CC03), Rizatriptan (N02CC04), Almotriptan (N02CC05), Eletriptan (N02CC06), Frovatriptan (N02CC07), Dihydroergotamine (N02CA01) and Ergotamine (N02CA02). As these medications are also indicated for cluster headache, men with this diagnosis (ICD-10: G44.0; ICD-9: 346C; ICD-8: 346.01) in the National Hospital Register were excluded from the analyses.

Secondary analyses were additionally performed using ICD-codes for migraine diagnosis from the Swedish National Hospital Register as an outcome (ICD-10: G43; ICD-9: 346A,B,X,W; ICD-8: 346.09). This register contains both inpatient and outpatient diagnoses recorded in a hospital setting including referrals to neurologists/migraine specialists and emergency visits. In Sweden, it is mandatory for all private and publicly funded hospitals to register one principal diagnosis at discharge and up to thirty contributory diagnoses. Register coverage for all inpatient care increased gradually during 1968-1986, and diagnoses from hospital outpatient care were documented starting in 2001. The Swedish National Hospital Register is a national, population-based register with high coverage; it is validated with positive predictive values of (85%–95%) for most ICD diagnoses.[21]

Statistical analyses

In order to address the primary aim i.e. how cardiovascular fitness at baseline affects risk of migraine during follow-up, we calculated risk ratios and 95% confidence intervals (CIs) using

Poisson regressions, with exposure time as an offset to correct for differences in exposure time, and robust standard errors. Using these models, we also calculated the maximum likelihood estimations for the adjusted population attributable fractions (PAF) with corresponding 95% CIs.[22 23] We here interpret PAFs as the estimated percentage of all cases of the outcome during follow-up that could have been prevented if the men of specified cardiovascular fitness group had instead belonged to the group with high cardiovascular fitness. We chose to perform risk ratio analyses due to the aggregation of both new and older records in the Prescribed Drug Register at register initiation. For this reason, it was not possible to establish the exact time of first prescription, rendering Cox proportional hazards models unsuitable.

All analyses were adjusted for age at conscription, conscription region, conscription decade and parental education (Model 1). Given that BMI might affect both cardiovascular fitness and migraine, we also performed an additional model (Model 2) additionally adjusting for BMI,[24] though there is uncertainty about the directionality of this relationship. To address our secondary aim i.e. whether the relationship of cardiovascular fitness and migraine was modified by levels of BMI or blood pressure, we stratified the risk estimates from Model 1 by categories of baseline BMI, as well as systolic and diastolic blood pressure, as previously defined. Missing data on parental education levels was treated as an additional, separate category. High cardiovascular fitness was used as the reference category.

We also performed secondary analyses to evaluate the relationship between cardiovascular fitness and risk of hospital-based migraine diagnosis, which likely includes the most severe migraine cases. Since time of diagnosis information was available in this register, Cox proportional hazards models were used to estimate hazard ratios and 95% CIs. The follow-up period began at conscription (baseline), and person-time was included until time of (1) first record of migraine in the National Hospital Register, (2) death, (3) emigration or (4) at the end of follow-up, i.e. on December 31, 2014, whichever happened first. Observed follow-up ranged

from a minimum of 2 years to a maximum 46 years. All death dates were obtained from the Swedish Cause of Death Register, which has kept record of virtually all deaths in Sweden since 1961. We performed separate analyses for outpatient migraine diagnoses only, as well as outpatient and inpatient diagnoses, together. By removing the inpatient diagnoses, individuals with the highest degree of psychiatric and somatic comorbidities, medication overuse, and highest pain scores were excluded[25] rendering the patient group more homogenous. We also performed a separate set of analyses including only primary diagnoses of migraine.

All analyses were conducted using SAS version 9.4 (SAS Institute, NC).

Patient and public involvement

There was no patient involvement in this register-based study.

RESULTS

Baseline characteristics for the full study population and stratified by levels of cardiovascular fitness in the study population are shown in Table 1. Men with lower cardiovascular fitness levels were more likely to have lower parental education, higher BMI, and higher systolic blood pressure than men with higher fitness. After we applied the exclusion criteria, analyses of dispensed migraine-specific medication were conducted using data from a total of 1 143 831 participants. Secondary analyses of migraine diagnoses documented in the National Hospital Register were conducted with 1 213 104 included participants (Figure 1).

Table 1 Baseline characteristics of the study population, stratified by cardiovascular fitness level in a cohort of 1 142 831 male conscripts included in analyses of migraine-specific medication prescription before age 60.

		Level of cardiovascular fitness[1]		
	All, n (%)	High, n (%)	Medium, n (%)	Low, n (%)
Total	1 143 831 (100.0)	316 113 (100.0)	673 536 (100.0)	154 182 (100.0)
Migraine-specific medication	22 533 (2.0)	5 525 (1.7)	13 448 (2.0)	3 560 (2.3)
Decade of conscription				

1968-1969	9619 (0.8)	2920 (0.9)	5169 (0.8)	1 530 (1.0)
1970s	357 123 (32.8)	123 367 (39.0)	198 357 (29.5)	53 399 (34.6)
1980s	432 857 (37.8)	104 672 (33.1)	252 082 (37.4)	76 103 (49.4)
1990s	247 079 (21.6)	65 057 (20.6)	161 868 (24.0)	20 154 (13.1)
2000s	79 153 (6.9)	20 097 (6.4)	56 060 (8.3)	2 996 (1.9)
Place of conscription				
South	263 865 (23.1)	70 546 (22.3)	158 784 (23.6)	34 535 (22.4)
West	245 545 (21.5)	62 247 (19.7)	145 540 (21.6)	37 758 (24.5)
East	246 449 (21.5)	68 731 (21.7)	140 660 (20.9)	37 058 (24.0)
Bergslagen	225 046 (19.7)	63 472 (20.1)	130 994 (19.4)	30 580 (19.8)
Lower Norrland	105 809 (9.3)	31 230 (9.9)	64 667 (9.6)	9 912 (6.4)
Upper Norrland	57 117 (5.0)	19 887 (6.3)	32 891 (4.9)	4 339 (2.8)
Parental education				
Pre–high school	345 478 (30.2)	83 976 (26.6)	199 592 (29.6)	61 910 (40.2)
High school	478 024 (41.8)	124 718 (39.5)	289 883 (43.0)	63 424 (41.1)
University or higher	290 792 (25.4)	100 633 (31.8)	166 772 (24.8)	23 388 (15.2)
Missing	29 537 (2.6)	6 788 (2.1)	17 289 (2.6)	5 460 (3.5)
BMI				
High (≥ 25.0)	89 073 (7.8)	6344 (2.0)	52 873 (7.9)	29 856 (19.4)
Normal (18.5-24.9)	930 230 (81.3)	283 599 (89.7)	549 055 (81.5)	97 578 (63.3)
Low (<18.5)	121 670 (10.6)	25 703 (8.1)	69 896 (10.4)	26 071 (16.9)
Missing	2 858 (0.2)	469 (0.1)	1 712 (0.3)	677 (0.4)
Systolic blood pressure				
≥ 140 mmHg	211 550 (18.5)	50 693 (16.0)	128 388 (19.1)	32 469 (21.1)
120-139 mmHg	720 456 (63.0)	199 746 (63.2)	424 041 (63.0)	96 678 (62.7)
≤119 mmHg	206 286 (18.0)	64 170 (20.3)	117 757 (17.5)	24 360 (15.8)
Missing	5 530 (0.5)	1 505 (0.5)	3 350 (0.5)	675 (0.4)
Diastolic blood pressure				
≥ 80 mmHg	476 880 (41.7)	130 450 (41.3)	283 226 (42.1)	63 204 (41.0)
66-79 mmHg	506 599 (44.3)	140 125 (44.3)	297 911 (44.2)	68 564 (44.5)
≤ 65 mmHg	154 631 (13.5)	43 959 (13.9)	88 962 (13.2)	21 710 (14.1)
Missing	5721 (0.5)	1580 (0.5)	3437 (0.5)	704 (0.5)

Abbreviations: BMI, body mass index

[1]Performance was trichotomised as low (score 1–4), medium (score 5–7) and high (score 8–9).

Cardiovascular fitness and future dispensing of migraine-specific medication

Prescriptions for migraine-specific medication were filled by 22 533 of the included men (2.0%). Compared to those with a high cardiovascular fitness level at conscription, both low and medium levels of fitness were associated with an increased risk for use of migraine-specific medication during follow-up (adjusted RR 1.29, 95% Cl 1.24-1.35 and 1.15, 95% Cl 1.12-1.19; Table 2). The PAF of medium cardiovascular fitness for migraine-specific medication (8.0%) was higher than that of low fitness (3.6%). Including BMI as an additional potential source of confounding in the multivariable models did not change the RRs or PAFs substantially. The proportion of men with missing values for cardiovascular fitness was 31.6% for men with migraine-specific medication and 32.4% for men without.

Table 2 Risk ratios and population attributable fractions for prescribed migraine-specific medication before age 60 in relation to cardiovascular fitness levels in young adult men.

		Model 1[2], n= 1 143 831	
Cardiovascular fitness[1]	Migraine / Total No.	RR (95% CI)	PAF (95% CI)
High	5 525 / 316 113	1.00 (reference)	
Medium	13 448 / 673 536	1.15 (1.12-1.19)	8.0% (4.0-11.7)
Low	3 550 / 154 182	1.29 (1.24-1.35)	3.6% (1.7- 5.3)
		Model 2[3], n= 1 140 973	
Cardiovascular fitness[1]	Migraine / Total No.	RR (95% CI)	PAF (95% CI)
High	5 517 / 315 644	1.00 (reference)	
Medium	13 411 / 671 824	1.14 (1.11-1.18)	7.5% (3.2-11.4)
Low	3 537 / 153 505	1.27 (1.21-1.32)	3.3% (1.2- 5.2)

Abbreviations: BMI, body mass index; CI, confidence interval; PAF, population attributable fraction; No., number of events; RR, risk ratio

[1] High level= reference category

[2]Adjusted for age, conscription calendar year and region and parental education.

[3]Adjusted for age, conscription calendar year and region, parental education and BMI

Risks stratified by categories of BMI and blood pressure

The association of cardiovascular fitness with future migraine-specific medication was analysed in separate strata of BMI and blood pressure groups to assess potential effect measure modification (Figure 2). Low and medium fitness were associated with an increased risk for migraine medication prescription among men with high and normal BMI, but no increased risk for the outcome was observed among underweight men. Upon stratification for systolic blood pressure levels, low and medium fitness had similar associations with future migraine medication across all three categories. Fitness was not associated with future migraine-specific medication prescription in men with high diastolic blood pressure (≥80 mmHg), but was associated with increased risk of prescription in men with lower diastolic blood pressures (in 66-79 mmHg as well as ≤65 mmHg groups).

Cardiovascular fitness and future migraine diagnosis

Migraine diagnoses were recorded in the National Hospital Register for 10 043 men (0.8% of the entire study population). Most (82%) were primary diagnoses. Approximately one-third of the men with a migraine diagnosis in the National Hospital Register were also observed to have

a migraine medication prescription in the Prescribed Drug Register. Lower cardiovascular fitness was found to increase the risk of a first-time migraine outpatient diagnosis (Table 3). Adding migraine codes for inpatient migraine to the outpatient codes did not result in a substantial change in our findings. Associations were similar when analysing only primary migraine diagnoses. For primary outpatient diagnoses, the HR for low and medium cardiovascular fitness were 1.15, 95% CI 1.05-1.26 and 1.07, 95% CI 1.01-1.14, respectively. For combined primary outpatient and inpatient diagnoses, the HR for low fitness was 0.98, 95% CI 0.91-1.09 and HR for medium fitness was 1.03, 95% CI 0.98-1.09.

Table 3 Hazard ratios of migraine diagnoses, recorded in the National Hospital Register, in relation to cardiovascular fitness levels in young adult men followed for up to 46 years.

Outpatient migraine diagnoses only		
Cardiovascular fitness[1]	Migraine / Total No.	HR (95% CI)[2]
High	1759/ 338 295	1.00 (reference)
Medium	4060/ 710 865	1.08 (1.02-1.15)
Low	1044/ 163 946	1.18 (1.08-1.28)
All migraine diagnoses (inpatient and outpatient)		
Cardiovascular fitness[1]	Migraine / Total No.	HR (95% CI)[2]
High	2655/ 338 295	1.00 (reference)
Medium	5852/ 710 865	1.05 (1.00-1.12)
Low	1536/ 163 946	1.05 (0.98-1.12)

Abbreviations: BMI, body mass index; CI, confidence interval; No., number of events; HR, hazard ratio
[1] High level= reference category
[2]Adjusted for age, conscription calendar year and region and parental education.

DISCUSSION

In this large, prospective cohort of young adult men, cardiovascular fitness was inversely associated with future prescription-requiring migraine. Though quite similar, the risks were somewhat larger for filled migraine-specific drug prescriptions than for outpatient migraine diagnosis. The increased relative risk of migraine among those with a low level of cardiovascular fitness was higher than for those with a medium level fitness. However, more

new migraine cases detected in this study were attributable to medium cardiovascular fitness, which was more common in the study population, rather than to low cardiovascular fitness.

Comparisons with other studies

This longitudinal, population-based study provides new insights into the effects of cardiovascular fitness on migraine risk. While not directly comparable with cardiovascular fitness, two prospective studies have previously evaluated the relationships between physical activity and migraine with inconsistent results.[5 8] We emphasize the importance of distinguishing cardiovascular fitness from physical activity. Cardiovascular fitness is more strongly related to health outcomes than physical activity, and activity not resulting in an increase in fitness level may not provide protective effects against adverse health outcomes.[26] For this reason, studies of cardiovascular fitness in addition to physical activity are of great importance. A cross-sectional study found an inverse relationship of peak oxygen uptake and migraine in adults younger than 50,[6] but given its cross-sectional study design, no conclusions can be made regarding the direction of the observed effect.

Effect measure modification by BMI and blood pressure

The association of cardiovascular fitness and migraine was only observed in men with normal and high BMI but not in those with low BMI. Prospective studies of BMI and later risk of migraine appear to be lacking, but a meta-analysis of cross-sectional studies concluded that the risk of migraine appears to be moderately increased in both obese and underweight individuals.[14] Our results suggest that among men with a low BMI at age 18, there was no additional beneficial effect of having a higher cardiovascular fitness with respect to prescription-requiring migraine risk later in life. It should, however, be noted that the number of men in this category was limited. It is also possible that there might be a common underlying factor influencing both BMI and migraine.

While an association between lower cardiovascular fitness and later migraine was observed across all categories of systolic blood pressure, this was not the case for the group with a diastolic blood pressure of ≥ 80 mmHg. This observation may partly be explained by the previously reported relationship between higher blood pressures and hypoalgesia.[27] It could also reflect an unknown, underlying cause of migraine in young men with extreme blood pressures. Additional studies are needed to further elucidate the modifying effects of BMI and blood pressure on the interrelationship between cardiovascular fitness and migraine.

Possible mechanisms

The increased risk of migraine among men with lower cardiovascular fitness at age 18 observed in this study may be explained by a combination of several factors. There might be an unknown, common predisposing factor for both lower cardiovascular fitness levels and migraine given the known, clear association of migraine with unfavourable cardiovascular risk factor profiles.[28] An association between migraine and cardiovascular risk comorbidities could be explained by a common pathology underlying both conditions and migraine might be a local manifestation of a systemic, rather that neurological, phenomenon.[28] Our research findings expand on previous studies linking migraine to cardiovascular risk factor profiles, highlighting the long-term association between cardiovascular fitness and migraine.

Several areas of the brain are still developing during late adolescence, and it is also possible that cardiovascular fitness during this period has long-term effects on brain health that might reduce susceptibility to migraine. Low cardiovascular fitness has been shown to increase the risk of several other neurological and psychiatric disorders such as stroke,[3] epilepsy,[4] and depression.[29] It could be that a common mechanism affecting neuroprotection, neurogenesis, synaptic plasticity, neuroinflammation, and neurotrophic factors such as brain-derived neurotrophic factor (BDNF) may be involved.[30] Hence, higher cardiovascular fitness might result in a greater "brain reserve" that may act as a compensatory buffer of brain plasticity and

neural resources and better enable the brain to cope with neuropathology, resulting in long-lasting beneficial effects on brain health.[31] Indeed, there is increasing evidence suggesting that behavioural interventions such as physical activity during critical stages of development can have such long-lasting and robust effects on the brain.[31]

Cardiovascular fitness may influence specific aspects of migraine burden contributing to severity. Several studies report lower migraine burden with more physical activity[32] and a recent randomized study of exercise in migraine patients showed decreased migraine pain, intensity, and frequency after the training intervention.[33] Neuroadaptive changes with pain are well-known,[34] and decreased levels of Brain-Derived Neurotrophic Factor (BDNF) have been reported in patients with migraine.[35] Higher fitness levels during adolescence could contribute to long-lasting structural and/or biochemical changes to the brain, generating a higher threshold for migraine pain.

Strengths and limitations

Strengths of this study include the population-based design, its large size and the objective measurements of cardiovascular fitness at baseline. Other strengths are available information on a large number of important covariates, the long available follow-up time, and the linkage of national register data to identify conscripts who later developed migraine. Furthermore, our study focuses on men, an understudied population in migraine research.

Several limitations should, however, be considered when interpreting our results. We show that 2% of the men filled a first-time prescription of migraine-specific medication during follow-up. However, the mean prevalence of current migraine among adult men in Europe has been estimated to be 8% in a review combining studies with variable timeframes.[36] Although our figures show first-time prescriptions, these should not be interpreted as equivalent to prevalence. Since our outcome measurements only capture men who seek healthcare and we are unable to identify men using over the counter migraine medication only, no medication at

all, or preventative medications, incidence of migraine in the current study is likely underestimated. The included men classified as having the outcome likely have more severe migraine episodes, which cannot be managed by the patient himself.

Although we excluded men who died or emigrated before the Prescribed Drug Register started in 2005, we may have missed men who enlisted during the earlier years and had migraine that later resolved (or men who did not seek treatment for migraine later). Boys with an early migraine diagnosis that resolved prior to conscription might have been misclassified as having migraine at baseline and would hence be wrongfully excluded from the analyses. Although we have attempted to reduce the risk of possible reverse causation by excluding men with migraine prior to or during the two years after conscription, there is still a possibility that adolescent men had migraine but were not diagnosed and had not received prescribed migraine medication. Such men have been included in the current study and this could influence cardiovascular fitness if they were less active due to their migraine.

The hospital register does not include codes from primary care; therefore, men suffering from migraine without hospital-based care could only be otherwise identified through the Prescribed Drug Register. In Sweden, migraine or cluster headache are the only indications for triptans and ergotamide (FASS; https://www.fass.se/). We have excluded men with prescribed migraine-specific medication at baseline as well as men diagnosed with cluster headache. However, there is still a small possibility that these medications could be prescribed for other indications and these participants could be misclassified as having the outcome of interest in our analyses using the Prescribed Drug Register data. The migraine diagnosis based on ICD codes has not been formally validated in the Swedish Hospital Hospital Register. However, we have no reason to believe that the generally high positive predictive values observed for other ICD codes in this register would not also apply to migraine.

Although we have controlled for confounding by adjusting for information on several covariates, residual and unmeasurable confounding may still be present. In particular, we had no information on smoking and alcohol consumption.

Our research goal was to estimate the effect of baseline cardiovascular fitness on long-term risk of migraine. Therefore, we do not include data on cardiovascular fitness or other health-related risk factors at later stages in life. We have no information regarding changes in this variable over time. An additional limitation is that, due to the identification method of migraine used, we were not able to stratify subjects according to migraine frequency or severity, episode duration or aura status. Hence, we could not assess how cardiovascular fitness influences the risk of different subtypes of migraine. We emphasize that our findings should not be interpreted as explanatory regarding the causal chain leading to the onset of migraine.

We acknowledge the relatively large number of missing values for cardiovascular fitness exposure variable. However, since proportions with missing values were very similar among men with and without migraine-specific medication, we think it is unlikely this missingness would be differential. Since the main purpose of the Swedish Conscription Register was for military use, detailed descriptions of causes for missing data are classified, and we thus unfortunately cannot explore these reasons further. Lastly, we emphasize that since women have a different body composition, physiology ,and clinical features of migraine[16], our findings should not be directly extrapolated to women.

CONCLUSION

Lower cardiovascular fitness in adult young men was found to be associated with increased risk of future prescription-requiring migraine. Our study calls for future targeted research to assess whether interventions to improve cardiovascular fitness result in a reduced risk of developing migraine among men with low cardiovascular fitness levels. In addition, studies that explore

possible mediators of the effect of cardiovascular fitness on the later development of migraine may provide important insights into the biological understanding of migraine, ultimately informing the development of further preventive strategies.

Authors contribution JN, SG, ML, DÅ, MÅ, MW and GK conceptualized the study. JN, SG, DÅ, MÅ, MW and GK contributed to data acquisition. JN, SG, JLR and TK designed the analyses, and JN and SG performed the analyses. All co-authors contributed to interpretation of as well as drafting and critically revising the manuscript for important intellectual content. JN, SG and GK are the guarantors."

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Competing interests TK reports having contributed to an advisory board of CoLucid and a research project funded by Amgen, for which the Charité – Universitätsmedizin Berlin received an unrestricted compensation. He further reports having received honoraria from Lilly, Newsenselab, and Total for providing methodological advice, from Novartis and from Daiichi Sankyo for providing a lecture on neuroepidemiology and research methods, and from the BMJ for editorial services. The other authors have no conflicts of interest.

Patient consent Not required

Ethics approval: The Ethics Committee of the University of Gothenburg and Confidentiality Clearance at Statistics Sweden approved this study (Dnr 462-14).

Provenance and peer review: Not commissioned; externally peer reviewed.

Data sharing statement: No additional data are available.

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FIGURE LEGENDS

Figure 1 Flowchart of the study populations showing included and excluded subjects and number of outcomes.

Figure 2 Risk ratios of prescribed migraine-specific medication in relation to cardiovascular fitness levels stratified by categories of body mass index, systolic and diastolic blood pressure at baseline.

Footnote Figure 2:

Abbreviations: BMI, body mass index; Cl, confidence interval; DBP, diastolic blood pressure; No., number of events; RR, risk ratio; SBP, systolic blood pressure.

RR adjusted for age, conscription calendar year and region parental education.

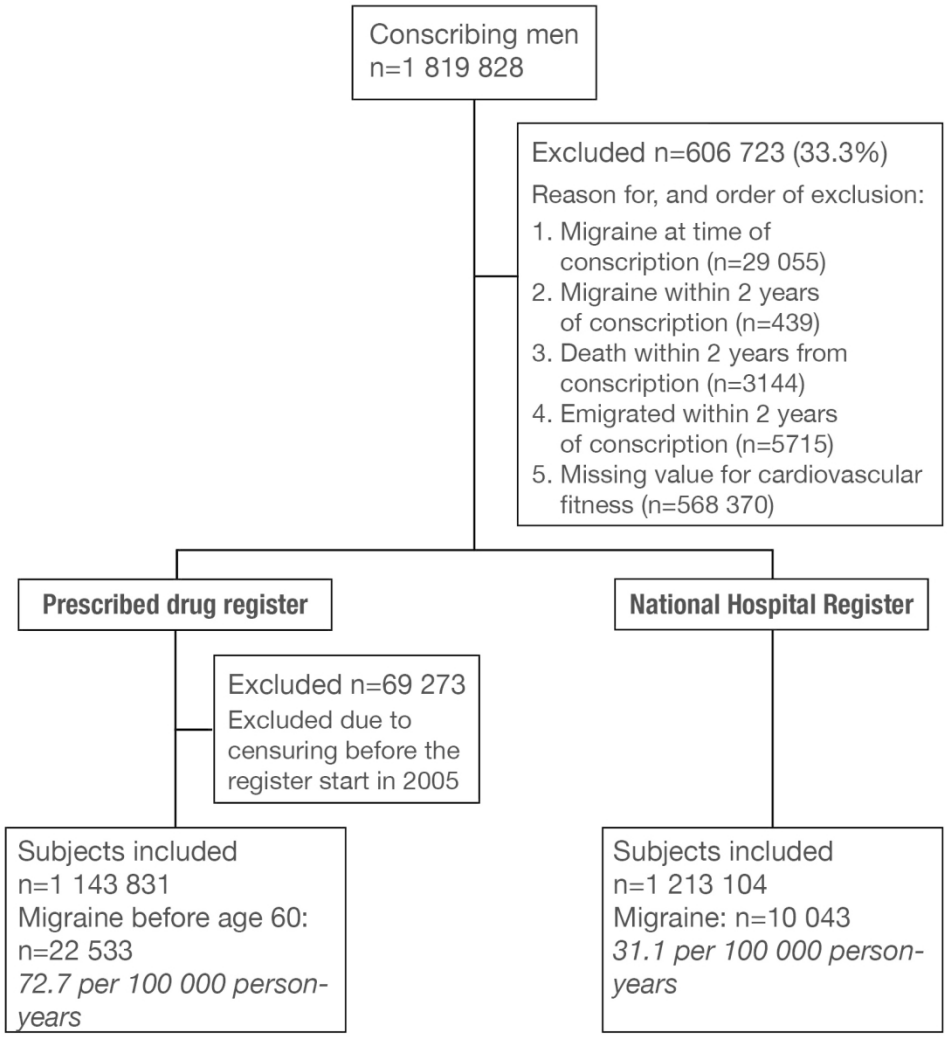

Figure 1 Flowchart of the study populations showing included and excluded subjects and number of outcomes.

153x161mm (300 x 300 DPI)

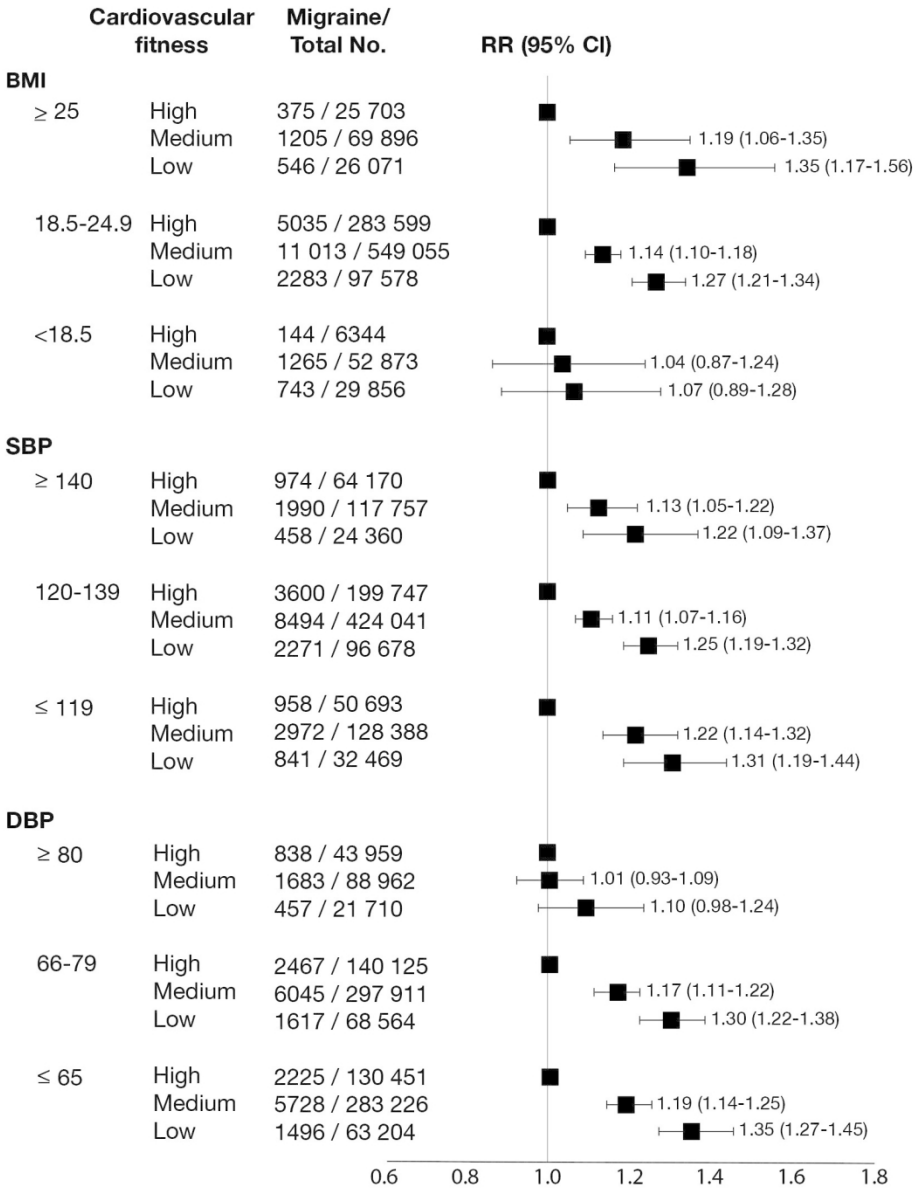

Figure 2 Risk ratios of prescribed migraine-specific medication in relation to cardiovascular fitness levels stratified by categories of body mass index, systolic and diastolic blood pressure at baseline.

Footnote Figure 2:
Abbreviations: BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; No., number of events; RR, risk ratio; SBP, systolic blood pressure.
RR adjusted for age, conscription calendar year and region parental education.

145x182mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	*(a)* Indicate the study's design with a commonly used term in the title or the abstract **The title describes the study as a "prospective population-based study".**
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found **The abstract describes Objectives, Design, Setting, Participants, Outcomes, Results and Conclusion.**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **The background and rationale questions are described in the Introduction (p. 4-5).**
Objectives	3	State specific objectives, including any prespecified hypotheses **Objectives/research questions are stated in the Introduction (p. 5).**
Methods		
Study design	4	Present key elements of study design early in the paper **Key elements of the study design are presented in the Introduction (p.5) and Method (p.5) section. The study design is further described throughout the whole Method section.**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **The setting is described in the Method section (p.5-6). Location and dates are described on p. 6, 8-10.**
Participants	6	*(a)* Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **A description of the study population is described in the Method section (p.5-6). Methods of follow-up are described on p. 7-10.**
		(b) For matched studies, give matching criteria and number of exposed and unexposed **n/a**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Outcomes are discussed on p.8, exposure on p. 6, confounders and covariates on p. 7 and effect modifiers on p. 9.** **Exposure is level of cardiovascular fitness at age 18. The outcome of migraine is defined as a recorded dispensing of prescribed migraine-specific medication (between age 20 and 60), identified using the Swedish Prescribed Drug Register. Confounders are conscription test region, year and age as well as parental education and BMI. Effect modifiers are BMI and blood pressure.**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **Measure of the exposure are described in the Method section (p. 6), of covariates (p. 7) and of outcome variables (p. 8).**
Bias	9	Describe any efforts to address potential sources of bias

		Potential sources of bias are discussed under Limitation in the Discussion section (p. 16-17).
Study size	10	Explain how the study size was arrived at **Study size is described in the Method section (p. 5), the Result section (p. 10) and Figure 1.**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **Description of quantitative variables and groupings are described in the Method section (p. 6-7).**
Statistical methods	12	*(a)* Describe all statistical methods, including those used to control for confounding **All statistical methods are described in the Statistical analyses subsection.**
		(b) Describe any methods used to examine subgroups and interactions **Description of subgroup analysis and effect modification are described in the Statistical analyses subsection.**
		(c) Explain how missing data were addressed **Missing data are reported in Table 1 and addressed in the Method section (p. 10) and in the Strengths and limitation subsection (p. 17).**
		(d) If applicable, explain how loss to follow-up was addressed **Loss to follow-up due to deaths and emigrations are described in the Method section (p.6).**
		(e) Describe any sensitivity analyses **A subanalysis is described in the Method section (p. 8-11).**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **The numbers are presented in Figure 1.**
		(b) Give reasons for non-participation at each stage **Reasons are described in Figure 1.**
		(c) Consider use of a flow diagram **Figure 1 is a flow diagram.**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **Baseline characteristics of the population are described in Table 1.**
		(b) Indicate number of participants with missing data for each variable of interest **Missing data are shown in Table 1.**
		(c) Summarise follow-up time (eg, average and total amount) **Follow-up time is shown in Figure 1.**
Outcome data	15*	Report numbers of outcome events or summary measures over time **Number of outcomes are shown in Figure 1, Table 2 and in the Result section (p.10).**
Main results	16	*(a)* Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **Adjusted estimates and 95% confidence intervals are presented for all outcomes. Confounders are described in the Method section (p.7, 9).**
		(b) Report category boundaries when continuous variables were categorized **n/a**

		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **n/a**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **Subanalyses are described in the Statistical analyses subsection (p.8-11).**
Discussion		
Key results	18	Summarise key results with reference to study objectives **Key results are summarised in the Discussion section (p. 13).**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **Limitations are discussed in the Strengths and limitations subsection (p.16-17).**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **Conclusions are included as a final subsection to the Discussion section (p. 17-18).**
Generalisability	21	Discuss the generalisability (external validity) of the study results **This is discussed in the Strengths and limitations subsection (p.16-17).**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **Funding is reported in a separate section (p.18).**

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.