

Does insomnia modify the association between C-reactive protein and migraine?

The Tromsø Study 2015-2016.

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Background The relationship between high sensitivity C-reactive protein (hs-CRP) and migraine is unclear. The aim of this cross-sectional population-based study was to investigate the association between hs-CRP and types of headache, and to evaluate the impact of insomnia on this association.

Methods A total of 20,486 (63%) out of 32,591 invited aged ≥ 40 years or older participated in the seventh wave of the Tromsø study conducted in 2015-2016, and had valid information of headache, insomnia and hs-CRP. The influence of insomnia on the association between questionnaire-based diagnoses of headache and elevated hs-CRP defined as >3.0 mg/L was assessed using multiple logistic regression, estimating prevalence odds ratio (OR) with 95% confidence intervals (CIs).

Results A total of 6290 participants (30.7%) suffered from headache during the last year. Among these, 1736 (8.5%) fulfilled the criteria of migraine, 991 (4.8%) had migraine with aura (MA), 746 (3.6%) migraine without aura (MO) (3.8%), and 4554 (22.2%) had non-migrainous headache. In the final multi-adjusted analysis, elevated hs-CRP was associated with headache (OR 1.10, 95% CI 1.01-1.20), migraine (OR 1.17, 95% CI 1.01-1.35), and MA (OR 1.23, 95% CI 1.01-1.53). No association was found between elevated hs-CRP and MO or non-migrainous headache. The association between hs-CRP and migraine was strongly depended on insomnia status. Among individuals with insomnia, elevated hs-CRP was associated with migraine (OR 1.49, 95% CI 1.02-2.17), and MA (OR 1.59, 95% CI 1.03-2.45), whereas no such relationship was found among those without insomnia.

Conclusions In this cross-sectional study, participants with migraine, in particular MA, were more likely to have elevated hs-CRP, evident only among those with insomnia.

Introduction

Migraine is a chronic disorder with a global prevalence of approximately 15% (1) and ranked as the second leading cause of years lived with disability (2).

Migraine, particularly migraine with aura (MA), is associated with ischemic stroke (3). The precise mechanisms remain unclear, but a neurovascular inflammation as a part of the complex pathophysiological process has been suggested (4). High sensitivity C-reactive protein (hs-CRP), a non-specific marker of inflammation, is associated with risk of cardiovascular events (5). This relationship has most likely been contributing to the increasing focus on CRP and migraine the last decade (6-30).

Most previous studies evaluating the association between CRP and migraine have been case-control studies with small sample sizes reporting inconsistent results. Some have reported significant higher CRP values in migraine patients (8, 12, 13, 19, 23-27), whereas others have not (7, 10, 15, 16, 20, 21). Various results have also been found in population-based studies (9, 11, 14, 29). CRP levels were not increased in migraineurs compared to non-migraineurs in a study from Iceland (11) or in adjusted analyses in a Dutch population-based case-control study (29). In contrast, an association was found between increased CRP and migraine in a large cross-sectional study on women (9). An association between CRP and headache has also been reported in children and adolescents (14). A review of studies published between 2006 and 2014 indicated higher CRP levels in individuals with migraine than in controls (31). However, relatively few previous studies have performed analyses with adjustments for relevant potential confounders.

Insomnia may potentially modify the relationship between hs-CRP and migraine. The relationship between headache and insomnia is well-known (32), and shorter sleep has been

associated with higher level of CRP in a prospective study (33). However, to the best of our knowledge, no previous studies have explored the impact of insomnia on the relationship between CRP and migraine. Such approach may be of value for better understanding the mechanism behind a potential association between CRP and migraine.

The aim of the present large-scale population-based study was to evaluate the cross-sectional association between hs-CRP and types of headache, and to investigate the impact of insomnia on this association. Based on previous knowledge, we hypothesized that migraineurs would be more likely to have elevated hs-CRP.

Methods

The Tromsø study

The Tromsø Study is a population-based cohort study initiated in the municipality of Tromsø, Northern Norway. The study includes seven surveys (Tromsø 1-7) conducted between 1974 and 2016, to which total birth cohorts and representative random samples have been invited. The surveys included questionnaires and interview, biological sampling and clinical examination.

Study population

In Tromsø 7 (2015-2016), all inhabitants aged ≥ 40 years living in Tromsø (n=32,591) were invited, whereof 21,083 (65%) women and men aged 40-99 years participated. Information about headache and insomnia were collected via questionnaires and hs-CRP was analyzed from non-fasting samples. The present analyses are based on data from all 20,486 participants with valid measures of hs-CRP, headache and insomnia (Fig. 1).

C-reactive protein

Hs-CRP was analyzed at the Department of Laboratory Medicine, University Hospital of North Norway, Tromsø, Norway, and was assessed by a particle-enhanced immunoturbidimetric assay on a Modular P autoanalyzer (Roche Diagnostics, Mannheim, Germany) with reagents from the manufacturer with a detection limit of 0.12 mg/L (34). In recent population studies from the US, approximately two-thirds of Americans had serum CRP concentrations less than 3 mg/L, suggesting that 3 mg/L is a reasonable cut point between normal and elevated hs-CRP (35, 36). Thus, in the present study we replicated the strategy used in a previous published study from Tromsø 6 evaluating hs-CRP and cold-pressure tolerance (34), defining normal CRP as 0-3.00 mg/L, and elevated as 3.01-20.00 mg/L. Participants with hs-CRP values >20.00 mg/L, which may indicate acute or chronic disease (38), were excluded (n=116) (Fig.1). The study did not include other exclusion criteria than lack of response on questions about headache and insomnia.

Headache

A questionnaire screening question (“Have you suffered from headache during the last 12 months?”) was used to identify participants with and without headache (reference group).

Participants who answered “yes” to the screening question completed a set of additional questions adapted from the third Nord-Trøndelag Health Study (HUNT3) (39), mainly to diagnose active migraine (i.e. during the last 12 months) according to the second version of the International Classification of Headache Disorders (ICHD- II) (40). Headache sufferers were classified as having active migraine if they fulfilled the following three criteria: 1) Headache attacks lasting 4-72 hours (<4 hours were accepted for those who reported visual disturbance before headache). 2) Headache with at least two of the following characteristics:

pulsating quality, unilateral location, moderate or severe pain intensity, and aggravation of physical activity and 3) During headache, at least one of the following: nausea and/or vomiting, or photophobia and phonophobia. Participants who fulfilled the migraine diagnosis and reported visual disturbance prior to headache were classified as MA, whereas the remaining with migraine had migraine without aura (MO). The remaining participants with headache were classified as having “non-migrainous headache”. The merged group of “any headache” consisted of participants with migraine or non-migrainous headache.

A question about number of headache days per months, with the following options, <1 day, 1-6 days, 7-14 days, and more than 14 days was also available.

The validity of the questionnaire-based headache diagnoses has been evaluated in HUNT3 (39): for any headache, the sensitivity was 88 %, and specificity 86 % (kappa value at 0.70, 95 % CI 0.61-0.79); for migraine the sensitivity was 51 %, and specificity 95 % (kappa value 0.50, 95 % CI 0.32-0.68), and for MA the sensitivity was 50 %, and specificity 95 % (kappa value 0.44, 95 % CI 0.38-0.50) (39).

Insomnia

The sleep-related questions were adapted from the validated Berge Insomnia scale (41) and the questionnaire-based definition of insomnia was given in accordance with DSM-V (Diagnostic and Statistical Manual of Mental Disorders, 5th ed.). Insomnia was defined as 1) Sleep disturbance for at least 3 months during the last year (“If sleep problem, how long time?”); 2) At least 3 times per week with sleep disturbance that reduce performance at school, job and/or social life at least 3 times per week (“How many days per week have you felt so tired that it has affected your work, school or private life?”); 3) Dissatisfied with sleep at least 3 times per week (“How many days per have you been dissatisfied with sleep?”) ; and 4) At

least 3 times per week with duration of minimum 30 minutes having difficulty initiating (“How many nights per week do you usually use more than 30 minutes to fall asleep?”) and/or maintaining (“How many nights per week do you usually wake up for more than 30 minutes in the middle of the night?”) and/or waking up too early (“How many nights per week do you usually wake up 30 minutes earlier than you wished, without being able to go back to sleep again? “).

Covariates

The following variables were examined as potential confounders based on previous literature (35, 37, 42): age (continuous); sex, years of education (≤ 9 , 10-12 and ≥ 13 years); body mass index (BMI) (< 25 , 25.0-29.9, and ≥ 30 kg/m²) (28, 32); smoking (current, previous, and never), physical activity (never, ≤ 1 time per week, ≥ 2 times per week), alcohol consumption (never, < 2 times/week, ≥ 2 times/week), self-reported diabetes (yes/no), self-reported stroke and/or heart infarction (yes/no), and self-reported hypertension (yes/no). Symptoms of anxiety and depression was measured by the 10-item questionnaire of Hopkins symptom checklist (HSCL-10), using mean scores of ≥ 1.85 as cut-off of emotional distress (43).

Ethics

This study was approved by the Regional Committee for Ethics in Medical Research (#2016/1997/Rek sør-øst C and #2014/940/Rek Nord), and the Norwegian Data Protection Authority. The participants have given written informed consent.

Statistical analysis

In the multivariate analyses, using logistic regression, we estimated the prevalence odds ratio (OR) with 95% confidence interval (CI) for the association between two categories of hs-CRP (dependent variable) and types of headache. Participants without headache were used as reference.

We initially adjusted for age and sex (model 1), and subsequently for predefined confounding factors. To determine which factor contributed most to the effect on the adjustment, analyses were carried out with adjustment for each separate factor in addition to age and sex. In model 2, we adjusted for age, sex and BMI. In addition, multiple factors were also tested together. We excluded factors from the model 3 if they did not change OR at all or just changed marginally (≤ 0.01) when evaluating each factor separately or by including several factors grouped together (i.e. self-reported diabetes, stroke/heart infarction, and hypertension). Potential interaction between two variables was evaluated by including the product of the variable in the logistic regression analyses, and the interaction was tested using Wald χ^2 statistics. Subjects with missing data of confounding factors were included in the analysis to reduce the impact of possible bias.

To evaluate insomnia as a modifying factor on the association between CRP and types of headache, we repeated the multi-adjusted analyses in model 3, separating by insomnia status.

Analyses were performed with the IBM SPSS version 25 (SPSS, Chicago, Illinois, USA)

Results

As demonstrated in Table 1, individuals with headache were more likely to be women, younger, and had worse health compared to those without headache.

Prevalence of headache

A total of 6290 (30.7%) participants suffered from headache during the last year, 1736 (8.5%) fulfilled the criteria of migraine, 991 (4.8%) had migraine with aura (MA), 746 (3.6%) migraine without aura (MO) (3.8%), and 4554 (22.2%) had non-migrainous headache.

The association between elevated hs-CRP and headache

In the multivariate analyses, adjusting for age and sex, elevated hs-CRP was associated with headache (OR 1.19, 95% CI 1.09-1.30), migraine (OR 1.24, 95% CI 1.07-1.49), and MA (OR 1.38, 95% CI 1.16-1.64), whereas there were no clear association was found between elevated hs-CRP and MO or non-migrainous headache (Table 2). In the final model 3, adjusting for all confounding factors, elevated hs-CRP was still significant associated with headache (OR 1.10, 95% CI 1.01-1.20), migraine (OR 1.17, 95% CI 1.01-1.35), and MA (OR 1.23, 95% CI 1.01-1.53) (Table 2).

Although no interaction was observed, the impact of headache frequency was evaluated. In age- and sex-adjusted analyses somewhat stronger association with elevated hs-CRP was found for individuals with headache ≥ 7 days/month than for those with headache less than 7 days/month (Table 2). In the final multi-adjusted analyses, elevated hs-CRP was associated with migraine ≥ 7 days/month (OR 1.21, 95% CI 1.01-1.46), but not migraine less than 7 days/month (OR 1.14; 95% CI 0.96-1.35).

The impact of insomnia

A significant interaction between insomnia status and types of headache was found ($p < 0.003$). Table 3 shows fully adjusted analyses separating by insomnia status. A total of 1669 (8.1%) participants fulfilled the DSM-V criteria of insomnia. Among these, elevated hs-CRP was significantly associated with migraine (OR 1.49, 95% CI 1.02-2.17) and MA (OR 1.59, 95% CI 1.03-2.45) (Table 3). No such relationship was found among those without insomnia (Table 3).

Discussion

In this population-based cross-sectional study, participants with migraine, in particular MA, were more likely to have elevated hs-CRP (between >3 -20 mg/L), evident only among those with insomnia.

Comparison with other population-based studies

In accordance with our results, the Women Health study showed that women with migraine were more likely to have CRP 4.2 mg/l or above (OR 1.13, 95% CI 1.05-1.22) than women without migraine (9). Furthermore, among children and adolescents aged 4-19 years, those being in the highest CRP quintile was associated with headache (OR 1.23, 95% CI 1.00-1.51) (14). In the Dutch case-control study (29), greater than median value was defined as elevated hs-CRP. In the unadjusted analyses, MA were more likely to have elevated hs-CRP (1.74, 95% CI 1.09-2.78), and borderline elevated in the multi-adjusted model (OR 1.60, 95% CI 0.97-2.64). In the study from Iceland, CRP levels were not increased in migraineurs compared

to non-migraineurs (11). It should be noted that the Reykjavik study excluded subjects with CRP values above 10 mg/L (11), whereas the exclusion cut-off was above 20 mg/L in the present study.

In accordance with the Dutch study (29), MA was most consistently associated with elevated hs-CRP in the present study. We did not find any association with MO. By reviewing previous studies, a consistent stronger association in MA than MO has not been demonstrated (31). However, in the Dutch study the average number of aura attacks and total number of years of aura were both found to be associated with hs-CRP (29). Correspondingly, in the present study the highest OR for having elevated hs-CRP was found for individuals with migraine at least 7 days/month.

To the best of our knowledge, no previous study has evaluated insomnia as a modifying factor on the association between CRP and migraine or included insomnia as one of the confounding factors. Interestingly, we found that the significant association between elevated hs-CRP and migraine, in particular MA, was only evident among individuals with insomnia.

Interpretation

If there is a causal link between hs-CRP, ischemic cardiovascular disease, and migraine, a stronger relationship between elevated hs-CRP and MA should be expected, because a relationship with ischemic cardiovascular disease is most evident for MA (3). On the other hand, the present results could represent an epiphenomenon, not specific for migraine (31). Based on our results, one may speculate that insomnia may be of major importance on the relationship between CRP and migraine. Possibly, migraine, insomnia and elevated hs-CRP may share a common underlying factor, e.g. related to endothelial function. However, this explanation seems less likely because no consistent relationship has been found between

endothelial function measured by flow-mediated dilatation and insomnia (44) or migraine (45) in population-based studies. In future studies evaluating the association between CRP and migraine, the influence of insomnia should be considered.

Strengths and limitations of the study

The major strengths of this study are the population-based design and the possibility to perform adjustments for important potential confounding factors. However, the possibility of residual confounding by an unrecognized factor cannot be ruled out. The participation rate (65%) was good, but generalization of results should be performed with caution. Finally, the diagnosis of insomnia in this study was in accordance with the current DSM-V criteria of insomnia.

Several study limitations should also be considered. Firstly, the cross-sectional design does not permit any conclusions about causality. Secondly, the diagnoses of headache and insomnia were questionnaire-based, which may have led to misclassification. However, the questionnaire-based diagnosis of migraine has previously shown acceptable agreement with corresponding diagnosis in a clinical interview (39). MA diagnosis was based on one question about visual disturbance before headache, with high specificity, but low sensitivity (39).

Ideally, more details about the aura symptoms had been informative, e.g. the proportion of migraine attacks which were accompanied by aura. The sleep-related questions were adapted from the Bergen Insomnia Scale, which has previously been validated against the DSM-IV criteria for insomnia (41). The DSM-V criteria of insomnia is somewhat different from other recent population-based studies that either have used the older DSM-IV definition of insomnia (46) or studies which have operationalized the ICDS-3 criteria for insomnia considering dissatisfaction with sleep quality or sleep length not mandatory for the diagnosis of insomnia (47). The definition of insomnia used in the present study is stricter, demanding

dissatisfaction with sleep as a mandatory criterion for the definition of insomnia.

Conclusions

In this population-based cross-sectional study, participants with migraine, in particular MA, were more likely to have elevated hs-CRP, evident only among those with insomnia.

Clinical implications

- Participants with migraine, in particular migraine with aura, were more likely to have elevated hs-CRP
- The association between elevated hs-CRP and migraine was only found among participants with insomnia.

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Conflicts of interest: None declared.

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Table 1 Characteristics of participants (n=20,486) in the Tromsø Study 2015-2016 according to types of headache.

	No headache	Any headache	MA	MO	Non-migrainous headache
Participants, n	14,196	6,290	991	745	4554
Women, n (%)	6637 (46.8)	4137 (65.8)	755 (76.2)	589 (79.1)	2793 (61.3)
Mean age, years (SD)	58.8 (11.6)	53.5 (9.9)	52.3 (9.2)	50.5 (7.9)	54.3 (10.2)
Age ≥ 60 years (%)	6656 (46.9)	1643 (26.1)	212 (21.4)	102 (13.7)	1329 (29.2)
Education > 12 years, n (%) (missing=343)	6867 (48.4)	3096 (49.2)	469 (47.3)	433 (58.1)	2194 (48.2)
Current daily smoking, n (%) (missing=179)	1849 (13.0)	971 (15.4)	171 (17.3)	79 (10.6)	721 (15.8)
Mean BMI, kg/m ² (SD) (missing=55)	27.3 (4.4)	27.5 (4.8)	27.6 (5.2)	26.9 (4.8)	27.6 (4.7)
Mean HSCL-10 (SD) (missing=137)	1.2 (0.3)	1.4 (0.5)	1.6 (0.6)	1.4 (0.5)	1.4 (0.4)
Alcohol abstainers, n (%) (missing=121)	1021 (7.2)	571 (9.1)	118 (11.9)	65 (8.7)	388 (8.5)
Physical inactivity, n (%) (missing=70)	581 (4.1)	227 (3.6)	38 (3.8)	22 (3.0)	167 (3.7)
Self-reported hypertension, n (%)	2811 (19.8)	1064 (16.9)	158 (15.9)	82 (11.0)	824 (18.1)
Self-reported stroke and/or heart infarction (%)	932 (6.6%)	237 (3.8%)	34 (3.4)	17 (2.3)	186 (4.1)
Self-reported diabetes mellitus, n (%)	698 (4.9)	254 (4.0)	41 (4.1)	20 (2.7)	193 (4.2)
DSM-V insomnia, n (%)	753 (5.3)	916 (14.6)	205 (20.7)	125 (16.8)	586 (12.9)
Mean hs-CRP (95% CI)	1.7 (1.6-1.7)	1.7 (1.7-1.8)	1.8 (1.7-1.9)	1.6 (1.5-1.8)	1.7 (1.7-1.8)

MA=migraine with aura; MO=Migraine without aura; HSCL= Hopkins Symptom Checklist 10-item version; BMI=body mass index; hs-CRP=high sensitivity C-reactive protein; CI= Confidence intervals; DSM-V=Diagnostic and statistical manual of mental disorders, 5th ed.

Table 2. Odds ratio (OR) with 95% confidence interval (CI) of C-reactive protein (CRP) defined as >3.0-20.0 mg/l according type of headache

		High CRP	Model 1	Model 2	Model 3
	Total	N	OR (95% CI)	OR (95% CI)	OR (95% CI)
No headache	14,196	2044	1.00	1.00	1.00
Any headache	6,290	990	1.19 (1.09-1.30)	1.14 (1.04-1.25)	1.10 (1.01-1.20)
<7 days/month	4936	761	1.17 (1.06-1.28)	1.13 (1.02-1.24)	1.10 (0.99-1.21)
≥ 7 days/month	1354	229	1.28 (1.10-1.24)	1.19 (1.02-1.24)	1.09 (0.93-1.28)
Migraine	1736	277	1.24 (1.07-1.49)	1.12 (1.02-1.40)	1.17 (1.01-1.35)
< 7 days/month	1294	198	1.18 (1.00-1.39)	1.15 (0.97-1.77)	1.14 (0.96-1.35)
≥ 7 days/month	442	79	1.44 (1.12-1.86)	1.40 (1.08-1.87)	1.22 (1.01-1.46)
MA	991	175	1.38 (1.16-1.64)	1.29 (1.08-1.55)	1.23 (1.01-1.53)
< 7 days/month	719	123	1.36 (1.11-1.67)	1.28 (1.04-1.58)	1.31 (0.94-1.81)
≥ 7 days/month	272	52	1.53 (1.13-2.09)	1.45 (1.05-1.99)	1.32 (0.95-1.82)
MO	745	102	1.05 (0.84-1.30)	1.08 (0.86-1.35)	1.08 (0.86-1.36)
< 7 days/month	580	75	1.01 (0.79-1.30)	1.04 (0.80-1.35)	1.05 (0.81-1.37)
≥ 7 days/month	165	27	1.32 (0.74-2.01)	1.35 (0.84-2.07)	1.34 (0.87-2.07)
Other headaches	4554	713	1.17 (1.07-1.29)	1.12 (1.01-1.24)	1.07 (0.97-1.19)
< 7 days/month	3642	563	1.17 (1.06-1.30)	1.13 (1.01-1.26)	1.10 (0.99-1.23)
≥ 7 days/month	912	150	1.23 (1.03-1.98)	1.13 (0.97-1.36)	1.03 (0.85-1.25)

)

MA=migraine with aura; MO=Migraine without aura.

Model 1: Adjusted for age, and sex.

Model 2: Adjusted for age, sex and body mass index.

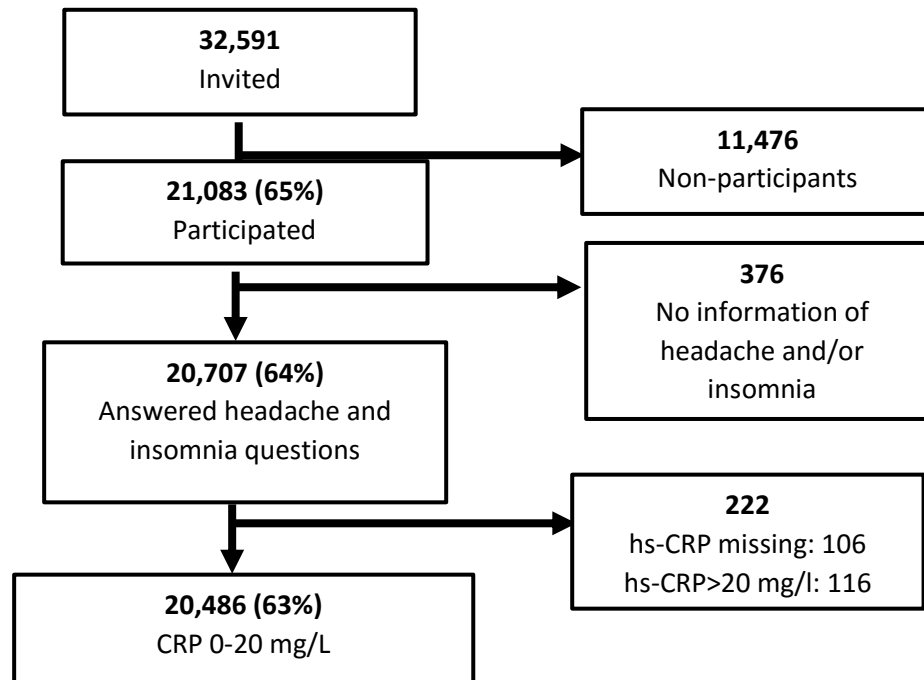
Model 3: Adjusted for age, sex, body mass index, smoking, education level, alcohol use, physical activity and anxiety and depression measured by Hopkins Symptom Checklist

Table 3. Multi-adjusted* odds ratio (OR) with 95% confidence interval (CI) of elevated C-reactive protein (CRP) defined as >3.0-20.0 mg/l according to type of headache separated by insomnia status

	Total	No insomnia		Insomnia	
		N	OR (95% CI)	N	OR (95% CI)
No headache	14,196	13,443	1.00	753	1.00
Any headache	6,290	5,374	1.06 (0.97-1.17)	916	1.32 (0.99-1.76)
Migraine	1736	1,406	1.10 (0.93-1.30)	330	1.49 (1.02-2.17)
MA	991	786	1.15 (0.93-1.41)	205	1.59 (1.03-2.45)
MO	745	620	1.03 (0.80-1.33)	125	1.31 (0.75-2.28)
Other headaches	4554	3,968	1.05 (0.95-1.17)	586	1.25 (0.91-1.70)

* Adjusted for age, sex, body mass index, smoking, education level, alcohol use, physical activity and anxiety and depression measured by Hopkins Symptom Checklist
MA=migraine with aura; MO=Migraine without aura.

Figure 1. Flow chart of participation in Tromsø Study 2015-2016



hs-CRP= high sensitivity C-reactive protein