Lifestyle factors and risk of migraine and tension-type headache. Follow-up data from the Nord-Trøndelag Health Surveys 1995-1997 and 2006-2008.

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Aims The aim of this population-based historical cohort study was to investigate the influence of lifestyle factors on the risk of developing migraine or tension-type headache (TTH).

Methods Data from the Nord-Trøndelag Health Study performed in 1995-1997 and 2006-2008 2006-2008 was used. A total of 15,276 participants without headache at baseline were included. A Poisson regression was used to evaluate the associations between lifestyle factors and risk ratios (RRs) of migraine and TTH 11 years later. Precision of the estimates was assessed by 95% confidence interval (CIs).

Results Increased risk of migraine (RR 1.30, 95% CI 1.11-1.52) was found in smokers (past or current) compared to those who never had smoked. Hard physical exercise 1-2 hours per week reduced the risk of migraine (OR 0.71, 95% CI 0.54-0.94) compared to inactivity, and the risk of migraine was also lower among those who consumed alcohol (RR 0.73, 95% CI 0.57-0.94) compared to abstainers. No association was found between smoking, physical activity, alcohol use and risk of TTH.

Conclusions The main finding was that current and previous smoking was associated with increased risk of migraine, but not of TTH.

Introduction

Physical inactivity, alcohol overuse, smoking and obesity have a well-known negative influence on health (1-4). Few longitudinal population-based studies have evaluated the impact of these modifiable lifestyle factors on the risk of migraine and other headaches.

Many cross-sectional studies have suggested an association between migraine and other headaches and obesity (5), whereas the association with smoking varies between population-based studies (6). Some studies have found a positive association between smoking and headache (7-11), but three other studies have not (12-14). Similarly, the cross-sectional relationship between alcohol use and migraine is unclear (15). No relationship between alcohol consumption and migraine have been found in some cross-sectional studies (e.g. 13, 14), whereas others have reported lower prevalence of migraine among alcohol users (7, 16).

Regarding physical activity several longitudinal population-based studies have been performed. Based on data from the Nord-Trøndelag Health Surveys (HUNT), we have previously reported that physical inactivity increased the risk of headache (17), and that smoking and physical inactivity more than doubled the risk of medication-overuse headache (18).

In the present study, we have analyzed historical data in the HUNT population. Our aim was to evaluate the influence of physical activity, alcohol use, smoking and body mass index (BMI) on the risk of developing migraine or tension-type headache (TTH).

Methods

Study design

This is a population-based historical cohort study. The influence of lifestyle factors at baseline was evaluated on the risk of headache 11 years later**.**

Study Population

The HUNT surveys have been conducted in Nord-Trøndelag County, Norway, in 1984-1986 (HUNT 1), in 1995-1997 (HUNT2), and in 2006-2008 (HUNT3) (19). All surveys incorporate

comprehensive questionnaires regarding health history, and the participants were invited to a clinical examination, involving the measurement of weight, height, blood pressure and of blood sampling (19). In HUNT2 and HUNT3 the entire population of the Nord-Trøndelag County aged 20 years of age or more was invited to answer many health-related items in two different questionnaires (Q1 and Q2), including questions about lifestyle factors and headache.

Headache status in HUNT2

Subjects who answered yes to the Q2 screening question in HUNT2 "Have you suffered from headache during the last 12 months?" were classified as headache sufferers. Those who answered "no" to the screening question were defined as the population at risk being without headache. The validity of the questionnaire-based status of being a headache sufferer has been reported previously with a sensitivity of 83% and specificity of 85% (kappa value 0.57, 95% CI 0.41-0.73) (20).

Lifestyle factors in HUNT2

Body mass index (BMI) was calculated based on measurements of weight and height. The BMI categories were defined in accordance with the World Health Organization (WHO) criteria for the Western population; underweight < 18.50, normal range 18.50-24.99, overweight 25.0-29.99, and obesity ≥30.0 kg/m^2 (5). The Q1 included four questions about past or present daily use of cigarettes, cigars, cigarillos or pipe. Participants were divided into three categories; current daily smoking, previously daily smoking and never daily smoking in accordance with other HUNT studies (e.g. 7, 21). Physical activity was assessed by the following validated question: "How much of your leisure time have you been physically active during the last year? The participants were then asked to specify number of hours per week of light (no sweating or heavy breathing) and hard (sweating and heavy breathing) physical activity with the response options; "none", "less than hour", "1-2 hours", and "three or more hours for both light and hard activity" (17, 22). The question about hard physical activity has found to be a valid measure of vigorous activity (22). Based on the non-validated question in Q1 "How many times per month do you usually drink alcohol", the

participants were divided into four groups; no use, less than 4 times per month, 4-7 times/month, or at least 8 times/month (7).

Headache diagnosis in HUNT3

The HUNT3 Q2 questionnaire included 14 questions regarding headache designed to determine whether the person suffered from headache, and fulfilled the International Classification of Headache Disorders, second edition (ICHD-II) criteria for migraine or TTH (23). The diagnoses were mutually exclusive. "Unclassified headache" emerged as an exclusion diagnosis defined by a positive answer to the screening question, but without fulfilling the diagnosis of migraine or TTH. The composite group of "any headache" consisted of participants with migraine, TTH, or unclassified headache. The validity of these questionnaire-based diagnoses and the prevalence of the various headache disorders have been reported previously (24): for any headache, the sensitivity was 88% and specificity 86% (kappa value 0.70, 95% CI 0.61-0.79); for migraine, the sensitivity was 51% and specificity 95% (Kappa values 0.50, 95% CI 0.32-0.68); and for TTH ≥1 days/month the sensitivity was 96% and specificity was 0.69% (kappa value 0.44, 95% CI 0.30-0.58) (24).

Study population

In HUNT2, 65,257 persons (70%) participated out of 93,898 invited (Figure 1). Among these, 51,856 (55% of all invited) answered whether they suffered from headache or not. A total of 93,860 persons were invited in HUNT3, whereof 39,690 (42%) answered the headache questions. Among the 65,257 persons who participated in HUNT2, 8,545 had died and 4,357 moved out of the county before HUNT3. In total, 40,255 persons participated in both HUNT2 and HUNT3. Among these, 26,197 (65%) had answered headache questions in both HUNT2 and HUNT3. The population at risk of headache in HUNT2 counted 15,276 individuals who did not suffer from headache in that survey (Figure 1). Among these, 7,495 were women and 7,781 were men.

Potential confounders

HUNT2 included a wide range of health-related information, and several factors have previously been identified to be associated with any headache and migraine (25). However, over-adjustment bias is a potential problem in epidemiological studies (26). Thus, in accordance with a pre-planned strategy, it was decided to include the following variables available at HUNT2 as potential confounders because of their well-known impact on headache prevalence (25, 27): age (5-years categories); gender, years of education in HUNT2 (≤9, 10-12 and ≥13 years); and anxiety and depression as measured by the scores of the total Hospital Anxiety and Depression Scale (HADS) (continuous variable).

Ethics

All participants signed a written consent, and the study was approved by the Regional Committee for Ethics in Medical Research. The study was carried out according to the Declaration of Helsinki.

Statistical analysis

A modified Poisson regression with a robust error variance was used to estimate risk ratios (RRs) of migraine, TTH and unclassified headache associated with BMI, smoking, alcohol use and physical activity (28). For the lifestyle exposures, participants who reported easy or hard physical activity were compared with the reference group with physical inactivity. Overweight, obese and underweight participants were compared with the reference group with normal weight (BMI 18.50-24.99 kg/m^2). Current and previous smokers were compared to the reference group of never smokers, and participants who reported use of alcohol were compared to the reference group with no use. Precision of RRs were assessed by 95% confidence intervals (CIs). The confounding effect of each potential confounder was quantified by comparing the adjusted RR with the crude RR. Total HADS score changed the RR less than 0.01, and was therefore not included in the final analyses. All associations were adjusted for the three other confounding factors: age, gender, and education (<10 years, 10-12 years, ≥13 years).

Potential interaction between to variables was evaluated by including the product of the variables in the regression model (e.g. headache and age, and headache and gender), and the

interaction was tested using Wald test. For smoking we performed a sensitivity analysis where age was dichotomized as <50 and ≥ 50 years of age, resulting in two groups of approximately equal size. In the final analyses, participants with incomplete data for education (n=309) were included (as a separate missing category) to reduce the impact of non-response bias.

Data analyses were performed with the IBM SPSS version 22 (SPSS, Chicago, Illinois, USA)

Results

Baseline characteristics of the population at risk in HUNT2 related to headache categories in HUNT3 are given in Table 1. At follow-up, the prevalence of any headache was 16.1%, for migraine 4.2%, TTH 5.6%, and unclassified headache 6.3%. People with headache were younger and more likely to be current smokers than those without headache (Table 1).

Table 2 shows the association between lifestyle factors at baseline and risk of headache at follow-up. No interaction was observed between headache and gender ($P_{interaction}$> 0.50), and thus all results are presented for men and women combined.

Smoking

In the multivariate analyses, previous and current smoking were both associated with increased risk migraine compared to never smoking (Table 2). When merging previous and current smoking into a single category, those who had smoked had an increased risk of migraine (RR 1.30, 95% CI 1.11-1.52), compared to those who had never smoked. No such relationship was found between smoking and TTH.

A statistical significant interaction was found between age and migraine ($P_{interaction}$ <0.001). In the sensitivity analysis, age was dichotomized as <50 and ≥ 50 years of age. Current smokers below 50 years of age had an increased risk of migraine (RR 1.37, 95% CI 1.12-1.68) compared to those who had never smoked, whereas no relationship was found between previous smokers and migraine. In those aged 50 years and above, previous smokers had an increased risk of migraine

(RR 1.71, 95% CI 1.19-2.47) compared to those who never had smoked, whereas no relationship was found between current smokers and migraine.

BMI

No evident association found between BMI categories and migraine or TTH (Table 2).

Physical activity

No clear dose-response relationship between physical activity groups and migraine or TTH was found. However, 1-2 hour's hard physical activity per week was associated with reduced risk of migraine (RR 0.71, 95% CI 0.54-0.94) compared to being inactive (Table 2). Risk of migraine was also reduced (RR 0.78, 95% CI 0.62-0.99) in those with 1-3 hours light activity/week (Table 2).

Use of alcohol

A lower risk of headache (RR 0.78, 95% CI 0.64-0.93) and migraine (RR 0.52, 95% CI 0.32-0.82) was found among those who reported to use alcohol eight times or more per month (n=1099), compared to abstainers (n=1275) (Table 2). Among all individuals who reported using alcohol at least once a month (n=13,952), the RR of migraine was 0.73 (95% CI 0.57-0.94) compared to abstainers. No associations were found between alcohol use and risk of TTH and unclassified headache.

Discussion

In this population-based cohort study the main finding was an increased risk of migraine in current smokers below 50 years of age and in previous smokers aged 50 years or above.

Strengths and limitations of the study

The major strengths of this study are the longitudinal population-based cohort design with many participants, a wide age range, and the use of validated diagnoses of headache (24). In the

multivariate analyses, many potential confounding factors were available. However, to avoid over-adjustment bias (26), we adjusted only for the most established confounding factors in headache epidemiological studies. However, the possibility of residual confounding by an unrecognized factor cannot be ruled out. We adjusted for the same confounding factors in all analyses, making the estimated RRs for the four different lifestyle factors comparable.

Several study limitations should also be considered. Firstly, we have no information about potential risk factors of headache that may have appeared during the follow-up period before HUNT3. Secondly, subjects who answered no to the screening question in HUNT2 "Have you suffered from headache during the last 12 months?" were classified as without headache and comprised the population at risk. However, this group also included those who experienced headache without defining themselves as being headache sufferers. In fact, 74% of participants in the validation study of HUNT3 reported having had headache during the last year, whereas only 31% stated that they had suffered from headache during the same period (29). Thus, in this follow-up study, we evaluated the influence of lifestyle factors on the risk of changing the status from being a non-headache sufferer into being a headache sufferer, subdivided into migraine, TTH or unclassified headache.

Thirdly, generalization of the results to the entire population must be made with some caution, since only 50% of those who answered headache questions in HUNT2 were included in the present study (61% of those eligible for HUNT3), and we cannot be certain that loss to follow-up was random.

Comparison with other studies

Smoking

Conflicting data have been found in previous cross-sectional population-based studies (6). While some studies have found an association between smoking and headache (7-11), others have not (12-14). Analyses stratifying for age are lacking. This was, however, performed in a cross-sectional study based on HUNT2 data (7), demonstrating that headache was associated with current smoking

in individuals <40 years (OR 1.4, 95% CI 1.2-1.5), and in ex-smokers for those ≥40 years (OR 1.1, 95% CI 1.1-1.2). Regarding ex-smokers, a similar tendency was found in a follow-up study of 4472 smokers in USA aged 18-30 years (hazard ratio for migraine of 1.35, 95% CI 1.08-1.68 in current smokers and 1.23, 95% CI 0.93-1.62 in former smokers) (8).

BMI

In contrast to findings in a previous meta-analysis (5) and in cross-sectional studies based on HUNT2 (9, 25), no clear association between BMI and risk of migraine or other headaches was found in the present study

Physical exercise

Most studies evaluating physical exercise and headache have a cross-sectional design. In accordance with the present results, a lower prevalence of migraine has been found among those who exercise regularly (30), and a previous follow-up study based on HUNT1 and HUNT2 showed that physical inactivity increased the risk of headache compared to those who were physical active (17). In addition, recently published cross-sectional data based on HUNT3 indicate an inverse relationship between peak oxygen uptake and headache and migraine for adults below 50 years of age (31).

Use of alcohol

Some cross-sectional studies, including one of HUNT2 (7), have reported lower prevalence of migraine among alcohol users (16). To our knowledge, the current report is the first follow-up study to show that the risk of developing migraine was lower among those who consumed alcohol, when compared to abstainers.

Interpretation

We found an increased risk of any headache and migraine in current smokers below 50 years of age

and in previous smokers aged 50 years or above. The mechanism behind these findings is unclear and likely complex. Tobacco has well-known analgesic properties (6), and one possible explanation is that smoking leads to headache in a similar way that analgesics lead to medication overuse headache (MOH) (7). Supporting of this hypothesis it the finding that smoking more than doubles the risk of MOH, but does not increase the risk of chronic daily headache without MOH (18). However, the increased risk of headache and migraine in older previous smokers need to be explained by other mechanisms. It is possible that being an ex-smoker in this age group is an indicator of behavior that promotes headache or reflects dysfunctional pain coping strategies.

We found that smoking increased the risk of migraine. Interestingly, migraine and smoking are both risk factors for stroke (32). The pathophysiological mechanisms explaining the relationship between migraine and stroke is still unclear (32). Althought adjustment for smoking is performed in analyses evaluating migraine as a risk factor for stroke, we cannot rule out the possibility of residual confounding and that smoking, at least in part, may cause the increased risk of stroke in migraineurs.

The lower risk of migraine among those who consumed alcohol as compared to abstainers, is likely to reflect the fact that alcohol is a common perceived trigger of headache and migraine (reversed causality) (15). Conceivably, individuals who at baseline in HUNT2 already had experienced headache or migraine attacks without defining themselves as headache sufferers may tend to avoid use of alcohol.

We did not find any clear dose-response relation between physical activity groups and headache, but hard physical activity 1-2 hours per week was associated with reduced risk of any headache and migraine. Several factors may explain this finding. Firstly, we cannot rule out the possibility that individuals who already had experienced severe headache or migraine attacks may avoid exercise (reversed causality). Secondly, regular hard activity may be protective against headache through psychological or biological mechanisms, e.g. by enhancing endorphin production.

Conclusions

In this population-based cohort study current and former smokers had increased risk of migraine, but not of TTH.

Clinical implications

- Smoking was associated with increased risk of headache and migraine
- Alcohol use decrease the risk of migraine
- No association was found between body mass index and risk of headache

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Conflicts of interest: None declared.

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References

1. Lee IM, Shiroma EJ, Lobelo F, et al. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. *Lancet* 2012; 380: 219-229

2. Must A, Spadano J, Coakley EH, et al. The disease burden associated with overweight and obesity. *JAMA* 1999; 282: 1523-1529.
3. Rehm J, Gmel G, Sempos CT, et al. Alcohol-related morbidity and mortality. *Alcohol Res Health* 2003; 27: 39-51.
4. Doll R, Peto R. Mortality in relation to smoking: 20 years' observations on male British doctors. *Br Med J* 1976; 2: 1525-1536
5. Ornello R, Ripa P, Pistoia F el al. Migraine and body mass index categories: a systematic review and meta-analysis of observational studies. *J Headache Pain* 2015; 16: 27
6. Taylor FR. Tobacco, Nicotine, and Headache. *Headache* 2015; 55: 1028-1044.
7. Aamodt AH, Hagen K, Bråthen G, et al. Headache prevalence related to smoking and alcohol use. The Head-HUNT study. *Eur J Neurol* 2006; 13: 1233-1238.
8. Hozawa A, Houston T, Steffes MW, et al. The association of cigarette smoking with self-reported disease before middle age: The Coronary Artery Risk Development in Young Adults (CARDIA) study. *Prev Med*. 2006; 42: 193-199.
9. Robberstad L, Dyb G, Hagen K, et al. An unfavorable lifestyle and recurrent headaches among adolescents: the HUNT study. *Neurology* 2010; 75: 712-717.
10. Straube A, Pfaffenrath V, Ladwig KH, et al. Prevalence of chronic migraine and medication overuse headache in Germany – the German DMKG headache study. *Cephalalgia*. 2010; 30: 207-213.
11. Gan WO, Estus S, Smith JH. Association between overall and mentholated cigarette smoking with headache in a nationally representative sample. *Headache* 2016; 56: 511-518.
12. Nikiforow R, Hokkanen E. An epidemiological study of headache in an urban and a rural population in northern Finland. *Headache* 1978; 18: 137–145.
13. Rasmussen BK. Migraine and tension-type headache in a general population: precipitating factors, female hormones, sleep pattern and relation to lifestyle. *Pain* 1993; 53: 65–72.
14. Takeshima T, Ishizaki K, Fukuhara Y, et al. Population-based door-to-door survey of

migraine in Japan: the Daisen study. *Headache* 2004; 44: 8–19.

15. Dueland AN. Headache and Alcohol. *Headache* 2015; 55: 1045-1049.
16. Le H, Tfelt-Hansen P, Skytthe A, et al. Association between migraine, lifestyle and socioeconomic factors: a population-based cross-sectional study. *J Headache Pain* 2011; 12: 157-172.
17. Varkey E, Hagen K, Zwart JA, et al. Physical activity and headache: results from the Nord-Trøndelag Health Study (HUNT). *Cephalalgia* 2008; 28: 1292-1297.
18. Hagen K, Linde M, Steiner TJ, et al. Risk factors of medication-overuse headache: an 11-year follow-up. The Nord-Trøndelag Health Study. *Pain* 2012; 153: 56-61.
19. Krokstad S, Langhammer A, Hveem K, et al. Cohort profile: the HUNT Study, Norway. *Int J Epidemiol* 2013; 42: 968-977.
20. Hagen K, Zwart JA, Vatten L, et al. Head-HUNT: Validity and reliability of a headache questionnaire in a large population-based study in Norway. *Cephalalgia* 2000; 20: 244-251.
21. Lyngbakken MN, Skranes JB, de Lemos JA, et al. Impact of Smoking on Circulating Cardiac Troponin I Concentrations and Cardiovascular Events in the General Population: The HUNT Study (Nord-Trøndelag Health Study*). Circulation* 2016; 134: 1962-1972.
22. Kurtze N, Rangul V, Hustvedt BE, et al. Reliability and validity of self-reported physical activity in the Nord-Trøndelag Health Study (HUNT 2). *Eur J Epidemiol* 2007; 22: 379-87.
23. Headache Classificiation Committee of the International Headache Society (IHS). The International Classification of Headache Disorders 2nd Edition. *Cephalalgia* 2004; 24 Suppl 1: 2-150.
24. Hagen K, Zwart JA, Aamodt AH, et al. The validity of questionnaire-based diagnoses: The third Nord-Trøndelag Health Study 2006-2008. *J Headache Pain* 2010; 11: 67-73.
25. Hagen K, Stovner LJ and Zwart JA. Potentials and pitfalls in analytical headache epidemiological studies. Lessons to be learned from the Head-HUNT Study. *Cephalalgia*

2007; 27: 403-413.

26. Schisterman EF, Cole SR, Platt RW. Overadjustment Bias and Unnecessary Adjustment in Epidemiologic Studies. *Epidemiology* 2009; 20: 488-495.
27. Linde M, Stovner LJ, Zwart JA, et al. Time trends in the prevalence of headache disorders. The Nord-Trondelag Health Studies (HUNT 2 and HUNT 3). *Cephalalgia* 2011; 31: 585-596.
28. Zou G. A modified poisson regression approach to prospective studies with binary data. *Am J Epidemiol* 2004; 159: 702-706.
29. Hagen K, Zwart JA, Aamodt AH, et al. A face-to-face interview of participants in HUNT 3: The impact of the screening question on headache prevalence. *J Headache Pain* 2008; 9: 289-294.
30. Queiroz LP, Peres MF, Piovesan EJ, et al. A nationwide population-based study of migraine in Brazil. *Cephalalgia* 2009; 29: 642-649.
31. Hagen K, Wisloff U, Ellingsen O, et al. Headache and peak oxygen uptake: The HUNT3 study. *Cephalalgia* 2016; 36: 437-444.
32. Hu X, Zhou Y, Zhao H, Peng C. Migraine and the risk of stroke: an updated meta-analysis of prospective cohort studies. *Neurol Sci* 2017; 38: 33-40.