# Paranasal sinus opacification in headache sufferers: A population-based imaging study (the HUNT study-MRI)

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**Abstract:**

**Background**: The association between headache and paranasal sinus disease is still unclear. Because of symptom overlap, the two conditions cannot be easily studied on the basis of symptoms alone. The aim of the present study was to investigate if paranasal sinus opacification at magnetic resonance imaging (MRI) was associated with migraine, tension type headache (TTH) or unclassified headache.

**Methods**: This was a cross-sectional study of 844 randomly selected participants (463 women, range 50-65 years, mean 57.7 years). Based on 14 headache questions, participants were allocated to four mutually exclusive groups: migraine, TTH, unclassified headache or headache free. At MRI, opacifications as mucosal thickening, polyps/retention cysts and fluid in the five paired sinuses were measured and recorded if ≥ 1 millimetre. For each participant, opacification thickness was summed for each sinus and in addition, a total sum of all sinuses was calculated.

Opacification in each sinus was compared between headache free participants and the headache groups using non-parametric tests, and the total sum by logistical regression.

**Results**: No significant association was found between paranasal sinus opacification and headache in general, or when headache was differentiated into migraine, TTH and unclassified headache. This was also true in separate analyses of mucosal thickening and fluid, and of opacification from each paranasal sinus.

**Conclusion**: Migraine, TTH and unclassified headache were found not to be associated with an increased degree of paranasal sinus opacification at MRI.

**Keywords**

Paranasal sinuses, headache, migraine, tension headache, sinus headache, magnetic resonance imaging, opacification

## Introduction

Headache is a common complaint in the general population (1) and represents a large socioeconomic burden for society (2). The term “sinus headache” is commonly used when paranasal sinus disease is thought to cause headache (3). Specialists consider this a rare cause of headache, but nevertheless a large proportion of patients diagnose themselves with “sinus headache” (4), and most of these patients suffer from migraine (5).

It has been shown that patients with chronic rhinosinusitis have a significantly higher risk of chronic headache compared to the general population (6). At the same time, headache sufferers without rhinosinusitis (negative computed tomography or nasal endoscopy) have an increased level of symptoms on the 22 item-sino-nasal-outcome test (SNOT 22) compared to controls (7), and some symptoms of sinus disease, such as a stuffy nose, rhinorrhoea and facial pain, can also occur in migraine (8). Thus, because of this symptom overlap it is problematic to study the association between sinonasal disease and headache solely on the basis of symptoms. Acute and chronic rhinosinusitis are accepted as causes of headache in the International Classification of Headache Disorders, 3nd Edition beta (9), if headache follows the clinical course of rhinosinusitis, verified by endoscopy, imaging or clinical examination.

Very few studies have used diagnostic imaging of the paranasal sinuses in large populations to evaluate the association between sinonasal disease and headache. The few that exist have either included a selected group of patients (10, 11), have not included a control group (12), or have not differentiated between migraine and tension-type headache (TTH) (11, 13).

The aim of this cross-sectional study was to investigate the association between paranasal sinus opacification at magnetic resonance imaging (MRI) and headache, including migraine,

tension-type headache and unclassified headache in the general population with participants recruited from a large epidemiological study in Norway (The HUNT study-MRI).

## Material and methods

### *Study sample*

The Nord-Trøndelag health study (the HUNT study) is a large-scale epidemiological study that was conducted in three main waves: HUNT1 (1984 to 1986), HUNT2 (1995 to 1997), and HUNT3 (2006 to 2008) (14). In each wave, the entire population of the Norwegian county of Nord-Trøndelag aged 20 years or older was invited to participate. In total, 77 212 (89%), 65 237 (70%) and 50 807 (54%) individuals participated in HUNT1, HUNT2 and HUNT3, respectively. Detailed information about their health status was collected through questionnaires, biomedical measurements and blood samples (14).

A total of 1560 participants were randomly selected for an MRI of the head as part of the HUNT MRI study. Criteria were age 50-65 years at the time of the HUNT3 screening, domicile less than 45 minutes of travel from the MRI examination centre in Levanger, and participation in all three HUNT studies (n=14,033). Of these, 554 did not respond to the invitation, were excluded owing to general MRI contraindications, stratification or because the examination had to be terminated during the scan, leaving 1006 participants who gave written consent and had the MRI. Details of the HUNT MRI study are described elsewhere (15-17). After the MRI examinations were performed in the period July 2007 to December 2009, 24 participants were excluded from this particular study because of low image quality of the paranasal sinuses. Of the 982 participants where image quality was sufficient (18), 138 participants were excluded due to missing information on headache. Finally, 844 participants were included (54% participation rate): 463 women and 381 men, age range 50 – 66 years, mean age 57.7 years.

### *Headache diagnosis*

The questionnaire in HUNT3 consisted of 14 questions regarding headache. All participants answering yes to the screening question "Have you suffered from headache during the last 12 months?" were asked to fill out 13 subsequent questions, designed to determine whether the person had migraine and tension-type headache (TTH). The questions reflected the International Classification of Headache Disorders, 2nd Edition (ICHD-II) criteria for these disorders (19) with three exceptions: Migraine was also accepted when the attacks lasted less than four hours, as the HUNT Study did not specifically ask about untreated attacks. Sensitivity to light and sound was covered in one question, and only participants experiencing headache on ≥1 day per month were categorised as having TTH, as the specificity was higher in frequent and chronic TTH. The diagnoses were mutually exclusive. Unclassified headache was an exclusion diagnosis defined by a positive answer to the screening question for headache, but without the necessary characteristics to be classified as migraine or TTH. Individuals who answered "no" to the screening question were classified as "headache free" and regarded as the reference group. The validity of these questionnaire-based diagnoses has been reported previously (20): for any headache, Hagen et al found the sensitivity to be 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 69% (kappa value 0.44, 95% CI 0.30-0.58).

### *MRI*

MRI was performed using a 1.5 Tesla HDx scanner (Sigma, GE Healthcare, Waukesha, WI) equipped with an eight channel head coil and software version pre-14.0M4. The scan protocol included axial T2 weighted (w) images, T1w magnetization prepared rapid acquisition gradient echo (MPRAGE) volume, scan axial T2w, T2* and fluid attenuated inversion

recovery (FLAIR) sequences, and a time of flight (TOF) 3D angio sequence. In this study, measurements were performed, using the axial T2w images and coronal, sagittal and axial T1w images. The acquisition parameters of these sequences have been published previously (18).

***MRI readings***

MRI readings were performed in the period April 2012 to July 2013 using DICOM reader (Osirix version 3.2.4, 32 bit; Osirix Foundation, Geneva, Switzerland). Two physicians performed MRI readings independently, one specialised in paranasal sinus radiology (HBE), and one resident in an ear, nose and throat department, with 4 years' experience (AGH). Both were blinded for all participant data. Discrepancy in measurements or interpretation occurred in 21% of the cases. In these cases, the MRIs were re-examined by both examiners and a consensus was reached.

Opacification in the five paired paranasal sinuses (maxillary, anterior and posterior ethmoid, frontal, and sphenoid on the left and right side) were measured at their maximum thickness in millimetres (mm) and recorded if ≥1 mm, as opacification < 1mm was considered normal or insignificant.

The three categories of opacifications were mucosal thickening, polyps/retention cysts, and fluid. Polyps and retention cysts were merged as one category; as they cannot be unambiguously differentiated at MRI (21). Details of how these categories of opacifications were defined have been described previously (18). If more than one category of opacification occurred in the same sinus, each was measured. For each participant, the thickness of each category was measured for each paranasal sinus. These measurements were added, resulting in one sum for mucosal thickening, one sum for polyps/retention cysts, and one sum for fluid for each participant. In addition, these sums were added to a total sum of opacification.

Opacifications in each of the five paired paranasal sinuses (left and right side added) were also calculated.

***Statistical analyses***

With regard to the sum of fluid, the sum of mucosal thickening, the total sum of opacification, and the thickness of opacifications in each paired sinus, the group of headache free participants was compared with each of the headache groups (any headache, migraine, TTH and unclassified headache), using a non-parametric test (Mann-Whitney). This method was also used in sub-analyses for fluid in the maxillary and sphenoid sinuses (right and left side added). Fluid in the other paranasal sinuses was too rare to allow statistical analyses. The outcomes 'any headache', 'migraine', 'TTH' and 'unclassified headache' versus 'headache free' were further investigated using logistic regression analysis, and the odds ratio (OR) with 95% confidence intervals (95%CI) was estimated for the outcome by the total sum of paranasal sinus opacification.

As minor incidental findings are common at MRI of the paranasal sinuses and there is no consensus in the literature on how to define a pathological degree of opacification at MRI, percentiles were used to categorize total sum of opacifications in the logistic regression analysis: Minor degree of opacification (≤ 65th percentile), moderate degree of opacification (66th-85th percentile) and high degree of opacification (>85th percentile). For the total sum of opacification, this corresponded to cut-off values of 8mm for the 66th percentile, and 17mm for the 86th percentile. Among the wide range of health-related information in the HUNT3 study, we have previously identified several important factors associated with headache (22) and paranasal sinus opacification (18). Potential confounders for this study were identified with the use of direct acyclic graphs (DAGs) (23), and in the adjusted

analysis the following variables were included as confounders: sex, age (five-year categories), and smoking (smoker/non-smoker).

The statistical analyses were conducted in PAWS Statistics, version 21 for Macintosh (SPSS Inc., Chicago, Illinois). P-values $\leq 0.05$ were regarded as statistically significant.

The Regional Ethics Committee in central Norway approved the study (2011/2199-1).

**Results**

Of the 844 participants included in this study, 302 (36%) reported having suffered from headache during the past 12 months. The proportion of participants with migraine, TTH and unclassified headache are shown as a flowchart in Figure 1, and alongside information about the confounders in Table 1. The migraine group had a higher proportion of females (73%) and more smokers than the other headache groups.

There was no statistical difference ($p>0.12$) when comparing the sum of fluid, the sum of mucosal thickening, and the total sum in the headache free participants versus the headache groups. This was also true for the sum of opacification in each paired sinus and for the sub-analyses of fluid in the maxillary and sphenoid sinuses. The thickness of the sum of fluid, sum of mucosal thickening, total sum and opacification in the different paranasal sinuses among the headache free and in each headache group are shown in Table 2.

We also found no significant difference when comparing the proportion of participants with and without headache having paranasal sinus opacification (total sum) above the cut off values, both in the unadjusted and adjusted analyses (Table 3).

**Discussion**

To our knowledge, this is the first population-based study to investigate the association between headache, classified according to the ICHD-II criteria, and opacification of the paranasal sinuses at MRI. Neither the opacification of a particular sinus nor a moderate or high degree of the total sum of opacifications were associated with headache in general, or migraine, TTH and unclassified headache. The implication of the study is that those who are headache sufferers in the general population are not more likely to have paranasal sinus opacifications than those without headache. It is important to emphasize that the study has little relevance to the acute situation, e.g. when a patient presents with symptoms of acute sinusitis (24), since there were no data on symptoms, neither headache nor sinonasal on the day of the MRI scan.

The major strengths of this study were its population-based design, the large sample size, and the use of validated headache diagnoses with good sensitivity and high specificity for both migraine and TTH (20). In the multivariate analyses, we were able to adjust for potential confounding factors. Furthermore, the investigated population was not considerably different from the general HUNT population: while the participants were non-selected in terms of health, they had somewhat higher levels of education, and were less likely to be overweight or have hypertension (15). It is also a strength that the MRI readings were performed independently by two readers and blinded for all participant data.

However, some limitations should also be considered: The age range in the investigated groups was relatively restricted, so one should be cautious about generalisation of the results to other age groups; secondly, 138/982 (14%) of the MRI participants did not give information on headache and were excluded from the study. This is a potential source of selection bias, but we believe it is most likely non-differential as headache was only one of several health-related topics in the HUNT questionnaire, which should reduce the likelihood of selective participation based on particular interest in headache.

A further limitation of the present study is that the MRIs were carried out one to two years after the information on headache was collected, thus a change in headache characteristics during this time period could have led to misclassification. However, in another HUNT study (25), good agreement was found for the diagnosis of migraine and the status of being a headache sufferer despite the fact that the questionnaire was filled in 5-9 months prior to interview. Boardman et al (26) found that the prevalence of headache was quite stable over time, but that some headache characteristics changed. Thus, it is likely that most participants with headache would have continued to report headache at the time of the MRI, but could have been classified to other headache groups. As we analysed the whole group of participants with any headache, and subsequently the subgroups of headache, we believe that we have taken this problem into account. We also recognise that some participants could have developed headache in the period between the headache report and the MRI. However, Lyngberg et al (27) found a relatively low incidence of headache in the age group investigated in this study, leading us to believe that this is unlikely to have influenced our results.

There is no general consensus regarding the cut-off values for a pathological degree of opacification at MRI of the paranasal sinuses (28-30). Incidental findings are shown to be quite common in a large proportion of the population (29). In the logistic regression analysis in this study, the cut-off for a moderate degree of opacification was ≥8mm. With this cut-off, we believe we avoid the problem of over-interpreting small findings in the paranasal sinuses. Since the cut-off value could be somewhat arbitrary and present a potential methodological bias, we measured all opacification ≥1mm, as opacification < 1mm is likely normal. In this way we were able to analyse opacification thickness as a continuous variable with the use of non-parametric tests to detect potential differences not captured by using cut-off values in the regression analyses. An alternative way to classify the opacification at MRI would have been to use a scoring system, such as the Lund-Mackay scoring system (31). However, this scoring

system is not validated for MRI, and could have introduced new uncertainties. Other possible ways to evaluate the paranasal sinuses at imaging could have been to use volumetric analyses of opacification, as this has shown a higher correlation to sinonasal symptoms (32), nasal endoscopy and quality of life (33) than Lund-Mackay at CT. This method is novel, and was not available at the time of MRI investigations for this study, but we believe that we have described opacification more precisely than with the use of scoring systems by measurements of opacification in mm. One further limitation was that we did not differentiate between different locations of opacification within the paranasal sinuses, e.g. those in the basis, those close to the upper jaw teeth versus those that could obstruct the sinus ostium. Such differentiation may be of clinical importance, and it should be made in future studies on the relation between paranasal sinus opacifications and headache.

To our knowledge, no population-based study has used paranasal sinus imaging to investigate the association between headache and sinonasal disease. Our results are in concordance with studies in sinusitis patients, showing no association between headache/facial pain and opacification of the paranasal sinuses at CT (10, 13). In these studies, headache was not differentiated into migraine or TTH. In a population-based study, Aaseth et al (6) found that rhinosinusitis diagnosed without CT or nasal endoscopy was significantly associated with headache. This leads us to believe that headache sufferers in the general population may have a higher degree of sinonasal symptoms, but not necessarily fulfil the objective criteria for the diagnosis. A definite diagnosis of rhinosinusitis is based on a combination of sinonasal symptoms and opacification at imaging or mucopurulent discharge or obstruction at nasal endoscopy (24). A future study using all necessary criteria for sinonasal disease in the general population is needed to establish or refute an association between headache and sinonasal disease.

Although evidence for an unambiguous association between headache and opacification of the paranasal sinuses is lacking, primary headache is still frequently misdiagnosed as “sinus headache” (4). The patient’s own desire to attribute the pain to a specific organ might be one reason. Lal et al (34) showed that a large proportion of patients presenting to an otolaryngologist for sinus pressure, pain, or headache had primary headache. Migraine and sinonasal disease have overlapping symptoms: both are often unilateral and with pain in the area of the sinuses. In addition, a migraine attack is accompanied by sensitization of the peripheral neurons of the trigeminal nerves, which may give rise pain from the maxillary division (e.g. nose and midface) of the trigeminal nerve (8). Migraine may also involve unilateral cranial autonomic symptoms like nasal secretion during attacks (35, 36), which may be interpreted as arising from inflammatory sinonasal disease. However, the present study does not indicate that having suffered from migraine should give rise to sinus opacifications over time.

Other sinonasal conditions such as nasal contact points may potentially cause headache (37), although they were not aim of this study. Relevant studies on this topic often lack control groups (38), or have been performed in selected patient groups (39). Based on the lack of association between paranasal sinus opacification and headache in this study, we must underline the importance of having an adequate control group in imaging studies on sinonasal disease, as incidental findings are indeed very prevalent.

In conclusion, migraine, TTH and unclassified headache were found not to be associated with an increased degree of paranasal sinus opacification at MRI.

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## Authorship contribution

AGH contributed in conception and design, acquisition of data, analysis and interpretation of data, writing, drafting the article, and revising it critically for important intellectual content. ASH contributed in conception and design, analysis and interpretation of data, drafting the article and revising it critically. WMT contributed in conception and design, analysis and interpretation of data, drafting the article and revising it critically. SN, VB contributed in conception and design, analysis and interpretation of data, drafting the article and revising it critically. LJS, KH and HBE contributed in conception and design, acquisition of data, analysis and interpretation of data, writing, and drafting the article and revising it critically.

**Clinical implications**

- In a random sample of the general population, any headache, migraine, tension-type headache or unclassified headache according to the ICHD criteria was not associated with increased degree of paranasal sinus opacification at MRI.
- No particular paranasal sinus showed a significantly higher degree of opacification in individuals with any headache, migraine, tension type headache or unclassified headache compared to headache free participants.

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Table 1 Characteristics of the study population (n=844), grouped into migraine, tension type headache (TTH) and unclassified headache according to the International Classification of Headache Disorders, 2nd Edition (ICHD-II).

| | Any headache | | Migraine | | TTH | | Unclassified headache | | Headache free | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % | n | % |
| Participants | 302 | 42 | 90 | 11 | 93 | 11 | 119 | 14 | 542 | 64 |
| Smoking* | 66/296 | 22 | 25/86 | 29 | 21 | 23 | 20/117 | 17 | 99/535 | 19 |
| Women | 187 | 62 | 66 | 73 | 52 | 56 | 69 | 58 | 255 | 47 |
| Mean age | 57.3 | | 57.0 | | 57.3 | | 57.5 | | 58.0 | |

*some participants missing due to missing covariate information

Table 2 Mean thickness for the total sum of all opacification, the sum of mucosal thickening, the sum of fluid and opacification for each paired paranasal sinus (left and right) in millimetres (mean ± SD).

| | n | Sum Fluid | Sum mucosal thickening | Total sum | Maxillary | Anterior ethmoid | Posterior ethmoid | Frontal | Sphenoidal |
|---|---|---|---|---|---|---|---|---|---|
| Headache free | 542 | 0.5±2.3 | 4.0± 7.7 | 8.4±12.3 | 5.6±9.0 | 1.0±2.1 | 1.0±2.2 | 0.4±1.2 | 0.6±2.7 |
| Any headache | 302 | 0.7±3.8 | 3.6±6.2 | 8.4±13.4 | 5.4±9.0 | 1.1±2.2 | 1.0±2.5 | 0.5±1.9 | 0.7±2.8 |
| Migraine | 90 | 0.6±2.5 | 3.2±5.3 | 7.7±13.4 | 5.1±9.2 | 1.0±1.9 | 0.8±1.9 | 0.5±2.2 | 0.7±2.7 |
| TTH | 93 | 0.7±3.6 | 4.3±7.7 | 10.1±14.5 | 6.8±10.2 | 1.0±2.0 | 1.1±2.5 | 0.5±1.5 | 0.8±3.5 |
| Unspecific headache | 119 | 0.7±4.6 | 3.3±5.4 | 7.5±12.6 | 4.4±7.7 | 1.2±2.7 | 1.0±2.8 | 0.5±1.9 | 0.6±2.1 |

[1]Compared to the headache free group, the total sum of all opacification, the sum of mucosal thickening, the sum of fluid and the sum of opacification from each paired paranasal sinus (left and right side) was not significantly different in any of the headache groups ($p>0.12$, Mann-Whitney test).

Table 3 The association between paranasal sinus opacification at MRI and headache (Odds Ratio with 95% CI) in unadjusted and adjusted analyses

| Unadjusted | | n | Any headache | n | Migraine | n | TTH | n | Unclassified |
|---|---|---|---|---|---|---|---|---|---|
| Percentiles | Cut-off in mm | 844 | | 632 | | 635 | | 661 | |
| 0-65 | 8 | 198 | 1.0 (Ref.) | 62 | 1.0 (Ref.) | 53 | 1.0 (Ref.) | 83 | 1.0 (Ref.) |
| 66-85 | 9-17 | 57 | 0.86 (0.60-1.23) | 13 | 0.63 (0.33-1.18) | 24 | 1.35 (0.80-2.29) | 20 | 0.72 (0.42-1.22) |
| 86-100 | > 17 | 47 | 1.09 (0.73-1.63) | 15 | 1.11 (0.60-2.06) | 16 | 1.39 (0.75-2.56) | 16 | 0.89 (0.49-1.60) |
| Adjusted[1] | | n | | n | | n | | n | |
| Percentiles | Cut-off in mm | 831 | | 621 | | 628 | | 652 | |
| 0-65 | 8 | 194 | 1.0 (Ref.) | 60 | 1.0 (Ref.) | 53 | 1.0 (Ref.) | 81 | 1.0 (Ref.) |
| 66-85 | 9-17 | 55 | 0.95 (0.66-1.38) | 11 | 0.74 (0.38-1.42) | 24 | 1.39 (0.81-2.37) | 20 | 0.76 (0.44-1.30) |
| 86-100 | > 17 | 47 | 1.30 (0.85-1.97) | 15 | 1.62 (0.84-3.14) | 16 | 1.53 (0.82-2.89) | 16 | 1.00 (0.54-1.81) |

[1] Adjusted for sex, age and smoking. Some participants missing due to missing covariate information.

Figure 1: Flowchart of participants in this study