LONG TERM OUTCOME OF CHILDHOOD ONSET HEADACHE. A PROSPECTIVE COMMUNITY STUDY

Matti Sillanpää and Maiju M. Saarinen

Departments of Child Neurology and General Practice, University of Turku, Turku, Finland

Corresponding author:

Prof. Matti Sillanpää, MD, PhD

Department of General Practice

20014 University of Turku, Turku

Finland

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Abstract:

Purpose. To examine prevalence, course, and long-term outcome of childhood migraine and other headaches.

Method. Using questionnaires, 1185 children were followed for recurrent headaches (HAs) at ages 7, 14 and 32 years, respectively.

Results. At age 7 years, 4.0% of the 1185 children (girls 3.7%, boys 4.3%) had migraine and 24% (25%/23%) had nonmigrainous HA. In adulthood, 16% (22%/8%) had migraine and 60% (64%/54%) nonmigrainous HA. Childhood migraine persisted into adulthood in 65% of females and 21% of males and nonmigrainous HA in 62% and 59%, respectively. After childhood, 17% of females and 7% of males started to have episodes of migraine. No recurrent HA during the follow-up was reported by 11% (6%/16%). In a multivariate analysis, compared with no childhood HA, childhood migraine increased the risk of adulthood migraine by 3.36-fold (95% CI 1.94–5.82) and that of nonmigrainous HA by 1.72-fold (1.14–2.60).

Discussion and conclusions. Headaches are generally as common in preschool girls as boys. From early school years, HAs steadily increase up to young adulthood, but among boys the prevalence levels off after adolescence. About two thirds of children experienced changes in their headache status during a 25-year follow-up. Any kind of recurrent headache at school entry predicts an increased risk of headache in young adulthood. Special attention should be paid to girls and particularly those girls who have recurrent headache when they start school.

Headache (HA) occurs at any age in childhood, but it is rare in infancy and early childhood[1-5]. At school age, the prevalence of HA and migraine approaches the prevalence rates of adults[6-10]. Several cross-sectional and a few longitudinal studies have shown an equal or higher incidence of HA in boys than girls before pre-puberty, a plateau stage at puberty and a higher rate in girls than in boys at post-puberty and young adulthood[11-13]. Outcome studies show the mean annual remission rate of childhood migraine to be about 6% during the first 3 years of follow-up[14], but 1–2% during a 10 to 50 year follow-up[2,12,13,15-17]. Most outcome studies of childhood HA are cross-sectional or very short-term, retrospective, limited to certain age groups or headache types, based on small, selected samples, or focused only secondarily on HA. There are only a few long-term prospective transitional studies from childhood to adulthood[13,17]. In his population-based study of 9000 schoolchildren, Bille (1997) found 73 children to have "pronounced migraine". No data, however, were given on those children who had nonmigrainous HA or no headache at baseline. Brna et al. (2005) reported data on 60 of 77 children and found headache severity to be predictive of headache outcome in 20 years of follow-up. Improvement in headache was reported by 66%. Tension-type HA was significantly more likely than migraine to remit. In a British birth cohort from 1958 of 17,414 infants[18], 8.2% of the mothers reported HA in their child at age 7 years. At age 33, 14% of the study subjects mentioned headaches, but the source population is not given. It is also unknown how many of them had migraine, because the type and severity of the headaches were not defined.

We report prevalence, course, and outcome of recurrent primary headache and migraine in a cohort of more than 1000 children prospectively followed for 25 years.

Methods

Procedure

The initial study population consisted of a community-based cohort of seven-year-old children born in 1967 and living in the Finnish city of Tampere (total population ca 160,000) and examined for headaches in 1974[19]. The number of children for whom the study design could be applied was 2151. After exclusion of 80 children for failure to obtain data due to school absence on the index day, or intellectual disability or similar reasons, 2071 were eligible and recruited for the study. HA history and status were assessed by the school physician by interviewing the child and his/her parent(s) during routine clinical examination at school entry, using a structured questionnaire. The study design was described previously in detail[12,19,20].

At age 14, the pupils were re-examined while attending the 7th grade in spring 1981 in Tampere, and 1493 (79%) of 1894 eligible participated. HA data were collected in the classroom setting during school hours with a structured one-page questionnaire identical to the form used in the baseline study at age 7 in 1974[12]. In the same year, autumn 1981, a parallel, but separate study was conducted on pupils attending the 8th grade in Tampere, most of whom were born in 1967[20,21]. A total of 1205 participants (84% of 1493) were found to have participated in all three studies performed in 1974, spring 1981 and autumn 1981. The most important reason for a high attrition rate during the school years was a strong population movement to and from Tampere and a subsequent lack of follow-up data from either of the 1974 or 1981 examinations[20]**.** In 1999, at age 32, data were collected by mailed questionnaires. For the present study, relevant data from childhood and adolescence were available on 1185 of the 1205 pupils who were included in the study. Of the 1185, 819 (449 females, 370 males) acceptably completed the questionnaire as adults in 1999 and were included in the longitudinal analyses.

Definitions

Headache was defined as recurrent (two or more) primary episodes of pain in the head area, not secondary to any initial organic disease and, when occurring, experienced as disturbing daily life during the preceding six months. Headache freedom was defined as a condition with no episodes of recurrent primary headache disturbing daily life (but occasional, situational episodes of headache could not be excluded). Migraine was defined according to the Vahlquist criteria[22] both at baseline and follow-up examinations. Nonmigrainous headache was defined as recurrent headache that did not fulfill all the criteria of migraine. The following specifying questions of HA were included in all the questionnaires: frequency of HA per time unit; attack-wise mode of occurrence; unilaterality; concurrent nausea and/or vomiting; visual aura; and family history of migraine in first-degree relatives. Secondary headaches were ruled out by questions concerning problems of eyesight or refractive error; preceding head injury; and concurrent febrile illness, sinusitis, or other known somatic illness. Diagnosis and classification of HA were at all stages made by a physician according to the Vahlquist criteria[22]. Recurrent primary HA was subdivided into migraine, if it fulfilled the Vahlquist criteria, and nonmigrainous HA, if the criteria were not met. During the data collection at age 7 in 1974, the Vahlquist criteria[22] were widely used before the IHS criteria were publicized in 1988[23]. To maintain comparability between the check-ups, the same criteria were used throughout the study. The participants were classified into three subgroups: migraine, nonmigrainous HA, and no recurrent HA[19]. In cases of more than one HA type, the presenting type of HA was considered.

Lost to follow-up

The pattern of attrition of the cohort has been previously reported[24]. Male sex and low school performance (defined by the authors[24] as the lowest quartile, less than 6.9, of the self-reported means of school marks on scale 4–10) were the main predictors for non-responsiveness at 32 years of age. Of the

1185 participants, 366 (31%) were lost to follow-up: 127 (35%) females and 239 (65%) males; $p<0.001$). Within the groups of adulthood migraine, nonmigrainous HA, and no HA, the proportion of female dropouts was 19%, 18%, and 24%, and that of male dropouts 46%, 45%, and 37%, respectively. The proportions of childhood HA status did not significantly differ between the participants and nonparticipants ($p=0.08$ for HA*sex interaction, and $p=0.92$ for sex-adjusted HA main effect). The p-values are from modified Poisson regression models[25].

Statistical analysis

Descriptive data are given as n (%).Risk ratios with 95% confidence intervals (CI) between childhood HA types on adulthood HA were calculated with modified Poisson regression models for binary data[25]. Longitudinal analyses of HA types during follow-up were done with similar models expanded for correlated data[26]. Outcome variables in the Poisson regression models were recurrent HA (combined migraine and nonmigrainous HA); migraine; and HA freedom. Sex and its significant ($p<0.05$) interactions were included in all models as potential confounding factors. In multiple comparisons, the confidence intervals were Bonferroni corrected. The proportions of nonmigrainous HA between sexes in the three age groups were tested with Bonferroni corrected χ^2 tests. Statistical analyses were done using SAS® version 9.4 (SAS Institute, Cary, NC, USA). The study design was approved by the Ethics Committee of the Clinical Institute, University of Turku. Informed consent was obtained from the participants, and the permission for the study in the schools from the parents and the school authorities of the city of Tampere.

Results

Prevalence of recurrent headaches

The prevalence of recurrent headaches, migraine, and nonmigrainous headache at ages 7, 14, and 32 years are presented in Fig. 1. Recurrent HA occurred in 28% of children, 69% of adolescents and 75% of adults. Its prevalence was on the rise from childhood to adulthood in females, but remained actually unchanged after adolescence in males (sex, age, and sex*age interaction: $p<0.001$ for all). The prevalence was virtually the same in girls and boys (28% vs. 27%; $p>0.99$), but significantly higher in females than males in adolescence (73% vs. 66%; $p=0.043$) and in adulthood (86% vs. 62%, $p<0.001$). Prevalence of migraine showed similar trends ($p<0.001$ for sex and age main effects, $p=0.006$ for sex*age interaction). The prevalence was similar in childhood (3.7% vs. 4.2% for girls and boys, respectively; $p=0.58$), while adolescence migraine was significantly more common in girls than in boys (15% vs. 7%; $p<0.001$). In adulthood, the prevalence of migraine (16%) continued to be significantly higher in females than in males (22% vs. 8%; $p<0.001$). Prevalence of nonmigrainous HA did not differ between females and males in childhood (25% vs. 23%; $p>0.99$) or adolescence (58% vs. 60%; $p>0.99$), but was significantly higher in adult females than males (64% vs. 54%; $p=0.010$). (Fig. 1).

Insert Fig. 1 here

Evolution and outcome of childhood recurrent headaches

Fig. 2 illustrates different trajectories between HA types between 7 and 32 years of age. HA status in general was more changing in females than in males. A change of HA status from 7 to 32 years of age occurred in 70% of females and 56% of males. On the other hand, the most stable HA types throughout the study period were female migraine, which remained unchanged in 65%, female nonmigrainous HA (62%), and male nonmigrainous HA (59%). Freedom from HA remained at 20%, and occurred less often in females than males (16% vs. 41%). (Fig. 2).

Insert Fig. 2 here

Of HA free children, five out of six girls and three out of five boys failed to remain HA free into adulthood. Two thirds of the HA free girls and half of the HA free boys experienced adulthood nonmigrainous HA. Almost one fifth of the girls and less than one tenth of the boys developed migraine. Girls with nonmigrainous HA were at high risk of continuous nonmigrainous HA, and almost one third had migraine in adulthood. Eight per cent became, however, HA free. In the majority of boys, nonmigrainous HA continued to occur unchanged but, in contrast to girls, boys were more often HA free in adulthood. Childhood migraine remained unchanged in about two thirds and altered to nonmigrainous HA in three out of ten girls. The risk of continuing migraine in boys was substantially lower than in girls. One fifth still had migraine in adulthood, while two thirds changed to nonmigrainous HA and 14% became HA free. (Fig. 2). Supplementary Fig. 1 shows a flow chart of all transitions between HA types at an individual level from childhood through adolescence to adulthood.

In a 25-year follow-up, headache remission was achieved by 15% of the 819 participants. Of the children with migraine 10% became HA free (females 6% and males 14%). In children with nonmigrainous HA, the proportion was 16% (females 8% and males 29%). The percentage of females was one third of that of males (8% vs. 27%) (Fig. 2). Of the adolescents with HA, 18% remitted and 6% improved from 14 to 32 years of age; a worsening was seen in 27%, and no change in 54%. The tendency to remit was lower in migraine than in nonmigrainous HA (7% vs. 20%) (Supplementary Fig.1).

Predictors of adulthood recurrent headaches

Compared with HA free children, there was a 25% increased risk of any recurrent adulthood HA if the child had migraine and a 14% increased risk in case of childhood nonmigrainous HA. Female vs. male sex increased the risk of any recurrent adulthood HA by a third. (Table 1).

Insert Table 1 here.

Childhood HA and sex predicted migraine in adulthood. Children with nonmigrainous HA vs. no HA had a two-fold risk of adulthood migraine and those with migraine vs. nonmigrainous HA again had a two-fold risk. Therefore, children with migraine vs. no HA were at a four-fold risk for adulthood migraine. The risk was raised to nearly three-fold for females compared to males. (Table 1).

Children with no HA vs. children with nonmigrainous HA had a 1.5-fold chance to be HA-free in adulthood. Childhood migraine as a predictor of no HA in adulthood yielded nonsignificant associations, probably due to sparse data. Males had an over 2.5-fold better chance than females to be HA free in adulthood. (Table 1).

Discussion and conclusions

Prevalence of recurrent headaches in childhood

The present results are from a 25-year follow-up cohort of 7-year-old children in a prospective community study. Our prevalence estimates of recurrent headaches compare well with the reported population data at age 7 years, which usually ranges from 38% to 53%[2,6,19,27,28]. While there was a slight male majority, no real sex difference at age 7 existed, which is consistent with the previous reports[2,18]. However, a large European study[29] reported the prevalence to be "somewhat higher among boys under the age of 10 years". On the other hand, a German study[28] reported non-significantly lower

prevalence for boys than girls of both monthly or weekly headache (12% vs. 13%) and migraine (3% vs. 4%).

Comparison between Vahlquist and IHS 1988 migraine criteria

In comparison with our prevalence rate of migraine (3.7%), the reported rates of migraine by the Vahlquist criteria range from 1.2% to 5.7%[27,30-32]. The Vahlquist criteria yield somewhat higher migraine rates than the IHS criteria[23]; of the 8–9 year old children, 2.96% had migraine according to the Vahlquist criteria vs. 2.33% using the IHS criteria[32]. Mortimer et al. [5] reported the Vahlquist criteria to be in agreement with the IHS criteria in children under the age of 18. In the study of Gherbelli et al.[33], the Vahlquist criteria were less sensitive than the IHS criteria, as they were modified in several ways with terms of duration of the headache episode, and considered single symptoms. Hershey et al.[34] suggested several revisions to the IHS-II criteria to improve the sensitivity of ascertaining pediatric migraine. To date, no satisfactory consensus exists regarding the criteria of pediatric migraine. Given the small differences in estimates and comparisons between the Vahlquist and the first version of the IHS criteria, we considered the first set to adequately reflect prevalence estimates in the present survey.

Prevalence of recurrent headaches in adolescence

The present prevalence of migraine among our 14-year-olds is comparable with previous studies on children of approximately 14-year-olds[3,12,28,35-38], as is the prevalence in adults[29,39,40]. Few papers report sex differences of migraine at puberty. A German study[36] using the IHS 1988 criteria of migraine[23] reported a prevalence of female and male migraine as 13% and 8% at age 12–13 years and 14% and 7% at age 15–16 years, respectively. Their figures are very similar to our female and male prevalence of 15% and 7% at 14 years of age. The female majority as regards migraine was already found in the

years preceding the onset of puberty[36]. Another German study, also using the IHS 1988 criteria, did not find any difference between females (10%) and males (11%)[28].

Our prevalence of adolescence nonmigrainous headache (59%) appears high, but it is of the same order as in comparable studies, e.g., the well-known, large (n=8993) population study (70%) by Bille that included, similar to our study, both frequent and infrequent nonmigrainous headaches at the age of 14 years[2]. Pothmann et al.[36], in their representative sample of 4865 school children, reported 80% to have nonmigrainous HA in 12 to 13 year old children, and 83% in the 15 to 16 year olds. In their unselected sample of school children aged 14 years (n=3863), Sillanpää et al.[3] found nonmigrainous HA in 58% of girls and in 59% of boys. Reports covering monthly, weekly, or "frequent" HAs yield substantially lower percentages.

Evolution of recurrent childhood headaches

An increasing trend in the prevalence of HA in general and migraine in particular up to 13–14 years of age has been reported[41-43]. In our study, a clear increase in female recurrent HA and migraine could be seen from childhood to adolescence and on to adulthood in line with previous literature[43]. Of note is the prevalence of male recurrent HA and migraine, which remained virtually unchanged from adolescence to adulthood. A similar observation was made in a Norwegian study[42] that found the prevalence of frequent (weekly) HA to increase from 12% to 13% among girls aged 12 to 14 years, but was stable across the 13- to 14-year age groups among boys (4.6% and 4.8%, respectively). Virtanen et al[43], found the prevalence of monthly HA to increase in females from 68% to 74% between 14 to 17 years of age, but decrease in males from 62% to 52%, respectively.

Almost two thirds of children at age 7 years may expect changes in their HA status during the following 25 years. Subsequently, our study highlights how common it is for changes in different HA types to occur with increasing age, in either favorable or unfavorable directions. Of our children with recurrent HA, 15% remitted and 6.3% improved during the 25-year follow-up. A worsening was seen in 20%, and no change in 59%. Females entered remission substantially less often than males. An Italian study of 100 HA clinic patients, followed for eight years, is one of the few previous studies on the evolution of childhood HA[44]. They found 79% either remitted (34%) or improved (45%), while 6% deteriorated and 15% remained unchanged. The positive tendency was lower in females than males. The outcome is far more favorable than in our study, but the comparability may be questionable. In their cohort, the baseline age varied from 4 to 18 years, which brings about heterogeneity in the headache evolution patterns. The data were derived from an outpatient clinic, and the mode of data collection was by an interview, which potentially yields answers that are different from those gained in questionnaire studies. Nevertheless, both the Italian and Finnish studies show that the vast majority of children with recurrent HA will have a changing HA profile in the future, and girls will have a less favorable outcome than boys.

Remission of recurrent headaches

In short-term studies on migraine in school children, an annual remission from migraine to HA freedom ranged from 0.9% to 3.9%[11, 12, 16, 45].

Long-term studies of two or more decades follow-up are few. Brna et al.[17] followed 77 children with headache for 20 years. At the end of the follow-up, 27% were in remission. No baseline age for the children was given.

Based on a national birth cohort, Fearon and Hotoph[18] collected headache data in 1991 on 11407 of 17414 cohort members born during one week in Great Britain in 1958. Baseline HA data were received from the mothers who gave an affirmative answer to the question "does your child have frequent headache or migraine". No definition was given to the concepts of "frequent" or "migraine" and the children were not questioned. At the age of 33 years, according to the report, "…14.1% (n=998) mentioned headaches…". The n of the source population is not given, but one may calculate that 998 is 14.1% of 7078 participants. Who they were is unknown. Whatever the source population of young adults is, the prevalence of 14.1% is substantially lower than in the previously reported ones and in the present study. Because of several limitations of the British study, we cannot make comparisons with our study.

The landmark study of Bille[2,13] is by far the longest follow-up study of children; however, it only covers data on migraine. Childhood migraine, defined by the Vahlquist criteria[22], had, in the follow up, remitted in 23% after 25 years[15], in 40% after 30 years[15], and in 43% after 40 years[13]. The corresponding percentage of our migraine free adult participants (55%) is comparable with Bille's figures.

Limitations

One limitation of the present study is the small number of subjects with childhood migraine (n=47, 4% of the total study population) at the age of seven, even though that is the prevalence commonly reported at that age. Consequently, in formal analyses, it was not possible to obtain firm estimates for risk ratios of all HA outcomes. Another limitation is the use of the Vahlquist criteria. The use of the Vahlquist criteria was, however, inevitable to maintain comparability throughout the study. Furthermore, they could be considered to adequately reflect prevalence estimates in the present study. A heightened

dropout rate, unavoidable in very long-term studies, could not be shown to affect the results. Due to limited time set by the school authorities for data collection in classrooms, we had to make choices about potential contributors to the course of HA. We ruled out several aspects of HA including different HA types, somatic comorbidity, and medical and other treatments of HA, and only focused on presenting primary recurrent headache. Finally, while the questionnaire completed by the pupils on follow-up examinations was a photocopy of and then identical with the first questionnaire sheet, the contents of the responses might have been affected, at least to some extent, by the different circumstances at the completion of the questionnaires.

Conclusions and clinical implications

Based on our community-based, 25-year follow-up covering different developmental phases from childhood to adulthood, our study has some important clinical implications. First, headache status at the beginning of school attendance is, in the majority, subject to marked changes with increasing age. Second, girls are at substantially higher risk than boys for adolescence migraine, particularly in the case of any primary headache in childhood. A sizeable increase in migraine obviously starts well before the age of 14. Third, recurrent headache and migraine steadily continue to increase up to young adulthood in girls. Fourth, among boys, changes in the prevalence of migraine and other primary headaches appear to be slight from adolescence up to young adulthood. Inversely, migraine and other headache among young adults are already predictable in adolescence. In conclusion, girls at school age are at high risk of future migraine and other primary recurrent headaches. Special attention should be paid to girls and particularly to those girls who have headaches when they begin school.

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Conflict of Interest Statement

The Authors declare that there is no conflict of interest.

Public Health Relevance

- Every tenth will remain free from recurrent headache from childhood to young adulthood.
- About a half of men, but less than one third of women without headache until mid-puberty have good chances for sustained headache freedom until young adulthood.
- Any kind of recurrent headache at school entry predicts an increased risk of headache in young adulthood.

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Table 1. Risk for any recurrent headache including both migraine and nonmigrainous headache (HA), migraine, and chance of no recurrent headache in one-year cohort of 819 participants followed from childhood to adulthood. Risk ratios (RR) with 95% confidence interval (CI) from multivariable modified Poisson regressions including childhood HA type and sex as predictors.

Recurrent headache at age 32 years	**RR**	**95% CI**
HA at age 7y[a]		
migraine vs. nonmigrainous HA	1.10	(0.93–1.29)
migraine vs. no HA	**1.25**	**(1.07–1.46)**
nonmigrainous HA vs. no HA	**1.14**	**(1.04–1.25)**
Female sex	**1.37**	**(1.25–1.49)**
Migraine at age 32 years	**RR**	**95% CI**
HA at age 7y[a]		
migraine vs. nonmigrainous HA	**2.08**	**(1.23–3.52)**
migraine vs. no HA	**3.67**	**(2.22–6.06)**
nonmigrainous HA vs. no HA	**1.77**	**(1.18–2.65)**
Female sex	**2.69**	**(1.85–3.93)**
No recurrent headache at age 32 years	**RR**	**95% CI**
HA at age 7y[a]		
no HA vs. migraine	2.85	(0.77–10.54)
no HA vs nonmigrainous HA	**1.62**	**(1.08–2.44)**
nonmigrainous HA vs. migraine	1.76	(0.45–6.80)
Male sex	**2.65**	**(2.04–3.45)**

[a] Bonferroni corrected confidence intervals

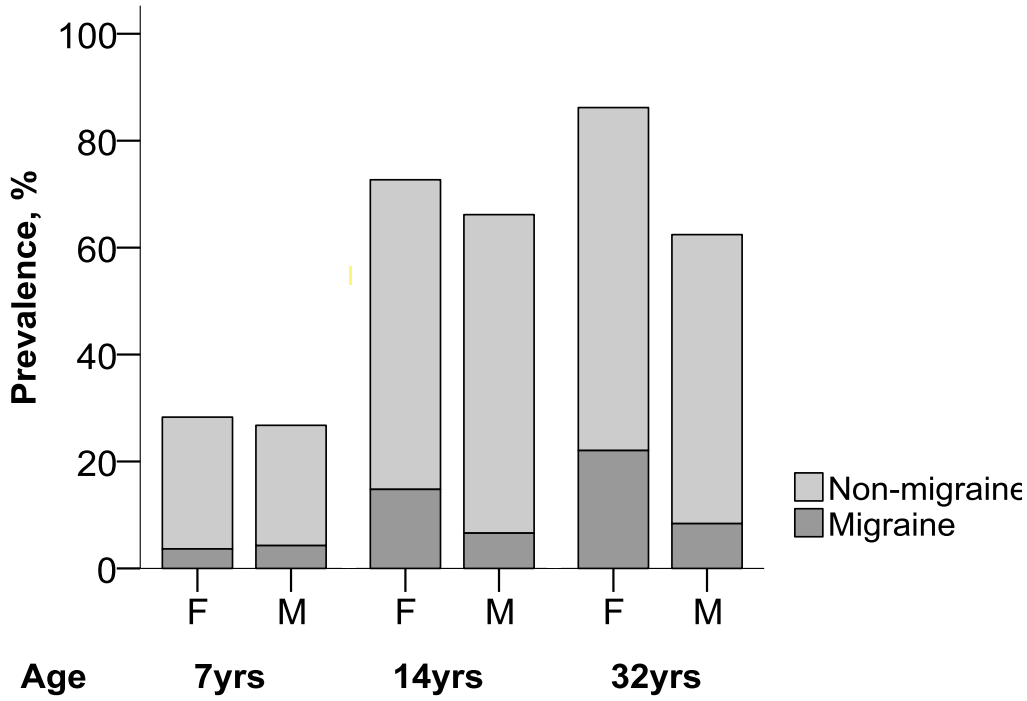
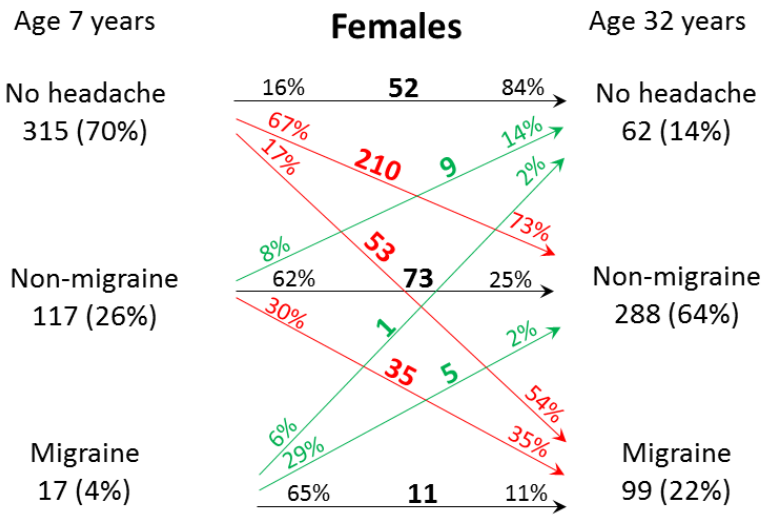


Fig 1. Prevalence of migraine and nonmigrainous headache in a community-based cohort of Finnish schoolchildren followed for 25 years. Number of participants: 1185 (F 576, M 609) at age 7, 1181 (F 575, M 606) at age 14, and 819 (F 449, M 370) at age 32. (F: female; M: male. Migraine: $p<0.001$ for sex and age main effects, $p=0.006$ for sex*age interaction; migraine and nonmigrainous headaches combined: $p<0.001$ for all)



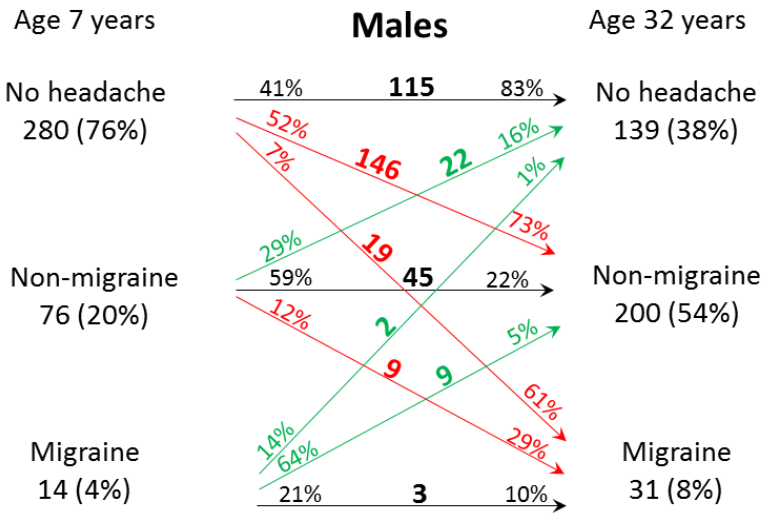


Fig 2. Evolution of headaches from 7 to 32 years of age among the 449 women and 370 men who participated in both 7-year and 32-year studies. The arrows represent alternative trajectories between the three childhood and adulthood headache type groups. Bolded figures in the middle of the arrows give the number of participants on each trajectory. Percentages at the origin of the arrows show the proportions of future headaches within each childhood headache group, percentages on the right ends show the proportions of preceding headaches within each adulthood headache group. ($p<0.001$)