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EPIDEMIOLOGICAL STUDIES OF CHILDHOOD AND ADOLESCENCE HEADACHE

by

Ruut Virtanen

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From the Departments of Child Neurology and Public Health, University of Turku, Turku, Finland

Supervised by

Professor Matti Sillanpää, *MD, PhD*
Department of Child Neurology
University of Turku
Turku, Finland

Docent Minna Aromaa, *MD, PhD*
Turku City Hospital, Turku
Department of Public Health
University of Turku
Turku, Finland

Reviewed by

Professor Heikki Rantala, *MD, PhD*
Department of Paediatrics
University of Oulu
Oulu, Finland

Med dr Katarina Laurell, *MD, PhD*
Department of Neuroscience
University of Uppsala
Uppsala, Sweden

Opponent:

Professor, Pekka Larivaara, *MD, PhD*
Department of General Practice
University of Oulu
Oulu, Finland

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To my dearest ones: Risto, Sara and Ville

ABSTRACT

Ruut Virtanen

Epidemiological studies of childhood and adolescence headache

Departments of Child Neurology and Public Health, University of Turku, Finland.

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The main purpose of this study was to examine the changes in the prevalence, incidence, and characteristics of headache in childhood and adolescence. In addition, the predictors of the change in the occurrence of childhood headache and the association between adolescent headache and behavior were studied.

The occurrence and characteristics of headache were investigated as part of a prospective follow-up study, where 6-year-old children and their families (n=1132) were followed to the age of 12-years (n=1126). The study design entailed both a cohort and case-control group. The incidence of headache and the association between headache and behavior were studied in another cohort, consisting of 11-year-old twins (n=5393), who were followed to the age of 17 (n=4159).

The prevalence rates of headache increased during the follow-up, especially in boys whose mothers suffered from frequent headache. The incidence rates of frequent headache changed the most in girls between ages of 11 and 14. Early-onset migraine and tension-type headache were equal predictors of migraine at age 12. The age-related changes observed in pain localization, concurrent symptoms and triggers were considerable. Headache frequency was significantly associated with externalizing and internalizing problem behaviors and adaptive behaviors as rated by parents, but only with externalizing problem behaviors as rated by teachers.

Headache both in children and adolescents is characterized by its changing nature. Its prevention and treatment should take familial, environmental and psychosocial aspects into account.

Keywords: Child, adolescent, headache, headache type, prevalence, incidence, change, characteristics, behaviour

TIIVISTELMÄ

Ruut Virtanen

Epidemiologisia tutkimuksia lapsuus- ja nuoruusiän päänsärystä

Lastenneurologian yksikkö ja Kansanterveystieteen osasto, Turun yliopisto, Suomi.

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Tutkimuksen tarkoituksena oli selvittää lapsuudessa ja nuoruudessa ilmenevän päänsäryn esiintyvyyden, ilmaantuvuuden ja päänsäryn erityispiirteiden muutoksia. Lisäksi tutkittiin päänsäryn esiintymisen ennustetekijöitä ja käyttäytymisongelmien yhteyttä nuoruusajan päänsärkyyn.

Päänsäryn esiintymistä ja erityispiirteitä tutkittiin osana väestöpohjaista seurantatutkimusta, jossa 6-vuotiaita lapsia ja heidän perheitään (n=1132) seurattiin 12-vuoden ikään asti (n=1126). Tutkimus toteutettiin osittain kohorttiasetelmana ja osittain tapaus-verrokki-asetelmana. Päänsäryn insidenssiä ja käyttäytymisen yhteyksiä päänsärkyyn tutkittiin kohorttiasetelmassa, jossa 11-vuotiaiden kaksosten (n=5393) otosta seurattiin 17-vuoden ikään asti (n=4159).

Tutkimuksen päätuloksena oli päänsäryn lisääntyminen seurantavuosien aikana erityisesti pojilla, joiden äidillä oli päänsärkyoire. Suurin muutos usein toistuvan päänsäryn ilmaantuvuudessa havaittiin tytöillä 11- ja 14 ikävuoden aikana. Nuorella iällä alkava migreeni ja jännityspäänsärky ennustivat yhtä todennäköisesti migreenin esiintymistä murrosiässä. Päänsärkykivun paikka, liitännäisoireet ja säryn laukaisevat tekijät liittyivät puberteettiin. Päänsäryllä oli selvä yhteys vanhempien ilmoittamiin lapsen externalisoiviin ja internalisoiviin käytösongelmiin ja sopeutumisongelmiin sekä opettajien ilmoittamiin eksternalisoiviin käytösongelmiin.

Lapsuus- ja nuoruusiän päänsärky on luonteeltaan muuttuva. Päänsäryn ehkäisyssä ja hoidossa tulee huomioida perheeseen ja ympäristöön liittyvät sekä psykososiaaliset tekijät.

Avainsanat: lapsi, nuori, päänsärky, päänsäryn tyyppi, esiintyvyys, ilmaantuvuus, muutos, erityispiirteet, käyttäytyminen.

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ABBREVIATIONS

CBCL	Child Behavior Checklist
CI	confidence interval
COR	cumulative odds ratio
CPR	Central Population Registry
DZ	dizygotic
GEE	Generalized Estimation Equations
IHS	International Headache Society
HA	headache
MHA	migraine headache
MWOA	migraine without aura
MPNI	Multidimensional Peer Nomination Inventory
Pr-MPNI	Parent Rating Form
Tr-MPNI	Teacher Rating Form
MZ	monozygotic
OR	odds ratio
P	significance level, p-value
SD	standard deviation
TTH	tension-type headache

LIST OF ORIGINAL PUBLICATIONS

The thesis is based on the following original articles, referred to in the text by their Roman numerals from I to IV.

I **Ruut Virtanen**, Minna Aromaa, Päivi Rautava, Liisa Metsähonkala, Pirjo Anttila, Hans Helenius, Matti Sillanpää. Changes in headache prevalence between pre-school and pre-pubertal ages. Cephalalgia 2002; 22:179-185.

II **Ruut Virtanen**, Minna Aromaa, Markku Koskenvuo, Matti Sillanpää, Richard J Rose, Liisa Metsähonkala, Hans Helenius, Pirjo Anttila, Jaakko Kaprio. Prevalence and incidence of headache: a follow-up study of adolescent Finnish twins. Submitted

III **Ruut Virtanen**, Minna Aromaa, Päivi Rautava, Liisa Metsähonkala, Pirjo Anttila, Hans Helenius, Matti Sillanpää. Changing headache from preschool age to puberty. A controlled study. Cephalalgia 2007; 27:294-303.

IV **Ruut Virtanen**, Minna Aromaa, Markku Koskenvuo, Matti Sillanpää, Lea Pulkkinen, Liisa Metsähonkala, Sakari Suominen, Richard J Rose, Hans Helenius, Jaakko Kaprio. Externalizing problem behaviors and headache: a follow-up study of adolescent Finnish twins. Pediatrics 2004; 114:981-987.

1. INTRODUCTION

Headache is one of the most common somatic complaints in children (Perquin et al 2000) having an impact on the child, his or her family and even society (Leonardi et al 1998, Lipton et al 2003, Stewart and Lipton 1993). However, the reported frequency rates seem to vary according to age as well as the criteria and classifications used. At school age, 75% of children suffer from occasional headache and 10% experience frequent headache (Larsson 1991, Passchier and Orlebeke 1985). From age 11 onwards, the prevalence and incidence of headache gradually increase (Rozen et al 1999, Sillanpää 1983a).

The first systematic description of the different types and clinical characteristics of headache in children was given by Vahlquist (1949). His set of criteria (Vahlquist and Hackzell 1949) was then applied to several prospective studies on childhood headache. These studies showed that headache varied in type according to age and developmental factors (Bille 1973, Burke and Peters 1956, Congdon and Forsythe 1979, Hinrichs and Keith 1965, Sillanpää 1983a, Sillanpää and Anttila 1996). However, the nature and role of these age-related and developmental factors in the differentiation of headaches and identification of prognostic factors are still unknown.

Although the causes of headaches are rarely life-threatening, adults and children often worry about them (Lewis et al 1996). Children with severe headache report low quality of life and of health (Bandell-Hoekstra et al 2002, Langeveld et al 1997). A family history of headache, especially maternal (Elser and Woody 1990, Bener et al 2000) and psychological factors play an important role in the occurrence of headache (Galli et al 2007, Kröner-Herwig et al 2007, Hjern et al 2008).

Childhood headache is a very complex pain symptom. This study focused on the changes in the prevalence and incidence of headache during childhood and adolescence, as well as on the changes in the types and special characteristics of frequent headache. The role of the behavioral factors associated with headache during puberty was also elucidated.

2. REVIEW OF THE LITERATURE

2.1. Definitions and classifications of childhood and adolescence headache

The definitions of headache vary greatly. They are based on either the location of the abnormality and symptom complexes, or on the pathophysiology and are mainly designed for adults. Creating definite criteria for headache disorders is problematic, because headache is a subjective symptom and there are no reliable tests to confirm the occurrence of headache.

The first description of diagnostic criteria for migraine was established by Vahlquist (1955). His criteria were based on combining recurrent, paroxysmal headache attacks, separated by symptom-free intervals, with at least two of the following factors: nausea, unilateral location, scotoma or related phenomena, and family history of headache. In 1962, the Ad Hoc Committee published the descriptions of fifteen different headache types, but no definite criteria for different headache types were given (Ad Hoc Committee 1962). Thereafter different criteria have been established to define migraine (Deubner 1977, Linet et al 1989, Prensky and Sommer 1979, Sparks 1978, Waters 1971). The first edition of the International Classification of Headache Disorders (IHS 1) was published by the International Headache Society in 1988 and the second one in 2004 (IHS 2), maintaining the main principles of classification for primary headaches. All new population-based studies on headache are based on the IHS criteria

IHS 1 consists of classifications and diagnostic criteria for all headache disorders and is divided into 13 major groups, while IHS 2 has 14 major groups. The major groups are then divided into subtypes. Primary headaches (migraine and tension-type headache) are classified according to symptom-based criteria and secondary headaches according to etiological criteria. Table 1 shows the IHS 1 criteria for migraine and tension type headache (TTH) in children and adolescents.

The IHS 1 criteria are similar for adults and children, but in migraine without aura, the duration of headache is four hours for adults and two for children. Proposals to reduce the duration of minimum headache attack to one hour have been made especially for pediatric migraine (Maytal et al 1997, Mortimer et al 1992a, Raieli et al 1996, Seshia and Wolstein 1995, Winner et al 1995, Wöber-Bingöl et al 1996a). Unlike the Vahlquist criteria, the IHS classification (HIS 1 and 2) does not include a family history of headache as a migraine-specific criterion.

The etiology of migraine and tension-type headache is still not fully understood. According to Silberstein (1992), primary headache can be considered a continuum between migraine and tension-type headache and there may be a common mechanism for most headache types (Graff-Radford and Newman 2002). Children and adolescent may have two or three different types of headache, which are difficult to differentiate (Brna et al 2005). IHS 2 describes the current knowledge of pathophysiology of migraine and tension-type headache. Migraine with aura is shown to be associated with decreased blood flow in the cortex, followed by a gradual transition into hyperemia in the same region, while migraine without aura shows no changes suggesting cortical

spreading depression (i.e. EEG changes followed by decreasing blood flow). In migraine without aura blood flow changes in the brainstem may be seen. Peripheral pain mechanisms are playing role in episodic tension-type headache, and central pain mechanisms play role in chronic tension-type headache.

Table 1. Headache classification of the International Headache Society (IHS 1988)

1. Migraine
2. Tension-type headache
3. Cluster headache and chronic paroxysmal hemicrania
4. Miscellaneous headaches unassociated with structural lesion
5. Headache associated with head trauma
6. Headache associated with vascular disorders
7. Headache associated with non-vascular intracranial disorder
8. Headache associated with substances or their withdrawal
9. Headache associated with non-cephalic infection
10. Headache associated with metabolic disorder
11. Headache or facial pain associated with disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cranial structures
12. Cranial neuralgias, nerve trunk pain and deafferentation pain
13. Headache not classifiable

Table 2. Headache classification of the International Headache Society (IHS 1988). Diagnostic criteria for migraine and tension-type headache in children

1 DIAGNOSTIC CRITERIA FOR MIGRAINE

1.1 *Migraine without aura (common migraine)*
- A. at least five attacks fulfilling criteria
- B. headache attacks lasting untreated 2-48 hours in children below age 15
- C. at least two of the following characteristics:
  1. unilateral position
  2. pulsating quality
  3. moderate or severe pain intensity
  4. aggravation by walking stairs or similar routine physical activity
- D. during headache at least one of the following:
  1. nausea or vomiting
  2. photophobia and phonophobia
- E. at least one of the following:
  1. history, physical and neurological examination do not suggest one of the disorders listed in groups 5-11/Table 1
  2. history, physical and/or neurological examinations do suggest such a disorder, but it is ruled out by appropriate investigations
  3. such a disorder is present, but migraine attacks do not occur for the first time in close temporal relation to the disorder

1.2 *Migraine with aura (classic migraine)*
- A. at least two attacks fulfilling criteria

B. at least three of the following four characteristics:
   1. one or more fully reversible aura symptom, indicating focal cerebral cortical and/or brainstem dysfunction
   2. at least one aura symptom develops gradually over more than four minutes, or two or more symptoms occur in succession
   3. no aura symptom lasts more than 60 minutes. If more than one aura symptom is present, accepted duration is proportionally increased
   4. headache follows aura with a free interval of less than 60 minutes. (It may also begin before or simultaneously with the aura)

C. at least one of the following:
   1. history, physical and neurological examination do not suggest one of the disorders listed in groups 5-11/Table 1
   2. history, physical and/or neurological examinations do suggest such disorder, but it is ruled out by appropriate investigations
   3. such a disorder is present, but migraine attacks do not occur for the first time in close temporal relation to the disorder

1.3 *Ophthalmoplegic migraine*
1.4 *Retinal migraine*
1.5 *Childhood periodic syndromes that may be precursors to or associated with migraine*
1.6 *Complications of migraine*
1.7 *Migrainous disorder not fulfilling above criteria*

2. DIAGNOSTIC CRITERIA FOR TENSION-TYPE HEADACHE

2.1. Episodic tension-type headache

A. at least ten previous headache episodes fulfilling criteria
B. headache lasting from 30 minutes to 7 days
C. at least two of the following pain characteristics:
   1. pressing/tightening (non-pulsating) quality
   2. mild or moderate intensity (may inhibit, but does not prohibit activities)
   3. bilateral location
   4. no aggravation by walking stairs or similar routine physical activity
D. both of the following:
   1. no nausea or vomiting (anorexia may occur)
   2. photophobia and phonophobia are absent, or one but not the other is present
E. at least one of the following:
   1. history, physical and neurological examination do not suggest one of the disorders listed in groups 5-11/Table 1
   2. history, physical and/or neurological examinations do suggest such disorder, but it is ruled out by appropriate investigations
   3. such a disorder is present, but tension-type headache does not occur for the first time in close temporal relation to the disorder

2.2. Chronic tension-type headache

A. average headache frequency 15 days/month (180 days/year) for 6 months fulfilling criteria
B. at least two of the following pain characteristics:
   1. pressing/tightening quality

2. mild or moderate intensity (may inhibit, but does not prohibit activities)
3. bilateral location
4. no aggravation by walking stairs or similar routine physical activity

C. both of the following:
1. no vomiting
2. no more than one of the following: nausea, photophobia or phonophobia

D. at least one of the following:
1. history, physical and neurological examination do not suggest one of the disorders listed in groups 5-11/Table 1
2. history, physical and/or neurological examinations do suggest such disorder, but it is ruled out by appropriate investigations
3. such a disorder is present, but tension-type headache does not occur for the first time in close temporal relation to the disorder

2.3 Tension-type headache not fulfilling the above criteria

2.2. Prevalence of headache

Headache is the most common somatic complaint in children (Perquin et al 2000, Haugland et al 2001). The lifetime prevalence of headache is reported to be 38-47% at age of seven and 70-80% at age 13-15 years (Bille 1962, Egermark-Eriksson 1982, Sillanpää 1976, Sillanpää 1983a). The one-year prevalence of recurrent headache varies between 10 % and 29% (Øster 1972, Abu-Arafeh and Russell 1994, Raieli et al 1995, Lee and Olness 1997, Zwart et al 2004) and that of adolescent headache at least once a year between 52% and 92% (Bandell-Hoekstra et al 2001, Karli et al 2006b). Of 7-15-year-olds, 36-53% report headache in the preceding 6 months (Metsähonkala and Sillanpää 1994, Sillanpää and Anttila 1996, Anttila et al 2002, Dooley et al 2005, Kröner-Herwig et al 2007a). According to Carlsson (1996a), 6% of 7-16 years-olds report weekly overall headache, while for 10-19-year-olds the prevalence rates of weekly headaches in the preceding last 6 months vary from 27% to 33% (Barea et al 1996, Fichtel and Larsson 2002, Gordon et al 2004, Roth-Isigkeit et al 2004, Dooley et al 2005). Table 3a summarizes population based prevalence studies in children and 3b in adolescents.

For migraine, the lifetime prevalence in children aged 7-15 years is 3.9% in Sweden (Bille 1962) and 3.8% in Finland (Sillanpää and Peltonen 1977). Both studies used the Vahlquist criteria. The studies applying the IHS criteria (1988 or 2004) report one-year prevalence rates for migraine from 2.6% up to 21.7% in children aged 5-18 years (Abu-Arafeh and Russell 1994, Raieli et al 1995, Barea et al 1996, Lee and Olness 1997, Split and Neuman 1999, Lu et al 2000, Zwart et al 2004, Wang et al 2005a, Karli et al 2006b). Of 7-12-year-old children, 2.7-13% report overall migraine in preceding 6 months (Metsähonkala and Sillanpää 1994, Sillanpää and Anttila 1996, Anttila et al 2002).

As for tension-type headache, there are quite a few population based studies on its prevalence. In the studies using the IHS criteria (1988), the one-year prevalence of tension-type headache varies from 10% to 18% in children and adolescents (Anttila et al 2002, Ayatollahi et al 2002, Laurell et al 2004, Zwart et al 2004). The highest prevalence rate of last year, up to 73%, has been found among 10-18 aged Brazilian adolescents (Barea et al 1996). In Turkey, the prevalence is 20-24% (Özge et al 2003, Key et al 2004). The prevalence of tension-type headache increases with age (Özge et al 2003, Laurell et al 2004) and is more frequent in 15-17 year-old girls (56%) than boys (44%) (Karli et al 2006a).

Epidemiological studies of headache have shown different prevalence estimates, probably due to methodological discrepancies. Studies differ in their methods of data collection, diagnostic criteria, age groups and populations as well as geographical, sociocultural and ethnic factors. Most epidemiological studies of headache have questioned the subjects on headache within a limited time span (3 or 6 months, one year etc) and in general the lifetime prevalence rates are higher than those of 1-year prevalence (Stovner et al 2006). On the other hand, the 3-month and 1-year prevalence rates do not differ much in children and adolescents (Stovner et al 2006).

Table 3a. Prevalence of childhood headache and migraine in population-based studies.

Author (Year) (Country)	Age range (yrs)	Sample size	Data collection	Time period	Headache type (criteria)	Headache prevalence (%) Male	Female	Total
Children								
Bille (1962) (Sweden)	7-9	3432	PQ	Lifetime	HA overall	48.1	46.4	47.2
					MHA (Vahlquist)	2.5	2.4	2.5
	10-12	3441			HA overall	62.8	63.3	63.9
					MHA (Vahlquist)	3.9	5.4	4.6
	7-15	8993			HA frequent	9.2	12.1	10.6
Øster (1972) (Denmark)	6-19	2178	School records	One year	HA recurrent	18.6	22.7	20.6
Sillanpää (1976) (Finland)	7	4235	Interview, PE	Lifetime	HA overall			37.7
					HA recurrent			6.3
				Present	MHA (Vahlquist)			3.2
Sillanpää and Peltonen (1977) (Finland)	7-15	314	SQ	Lifetime	HA overall	46	64	60.8
					HA recurrent			21
				Present	MHA (Vahlquist)		3.8	
Egermark-Eriksson (1982) (Sweden)	7,11,15	402	PQ, SQ, TQ	Lifetime	HA overall			75
					HA recurrent			23

HA = headache, MHA = migraine headache, PE = physical examination, CQ = child's questionnaire, PQ = parent's questionnaire, SQ = self-administered questionnaire, TQ = teacher's questionnaire, Q = questionnaire completed by parents and child

Table 3a. (continues). Prevalence of childhood headache and migraine in population-based studies.

Author (Country)	Age range (yrs)	Sample size	Data collection	Time period	Headache type (criteria)	Headache prevalence (%) Male	Female	Total
Abu-Arafeh et al (1994) (Scotland)	5-15	1754	PQ, interview PE	One year	HA overall HA severe MHA (IHS 1988)			66 22 10.6
Metsähonkala et al (1994) (Finland)	8-9	3580	Q	6 months	HA overall MHA (IHS 1988)	3.0	2.3	36.6 2.7
Sillanpää and Anttila (1996) (Finland)	7	1436	PQ,PE	6 months	HA overall MHA			51.5 5.7
Carlsson (1996a) (Sweden)	7-16	1144	PQ, SQ	> 1/month >1/week	HA overall			26 6
Lee and Olness (1997) (USA)	5-13	2572	SQ	One year	HA recurrent, severe MHA (IHS 1988)			10.1 8.6
Kröner-Herwig et al (2007a) (Germany)	7-8 9-10	5474	PQ, CQ	6 months	HA less than monthly	26 33	26 29	53.2

HA = headache, MHA = migraine headache, PE = physical examination, CQ = child's questionnaire, PQ = parent's questionnaire, SQ = self-administered questionnaire, TQ = teacher's questionnaire, Q = questionnaire completed by parents and child

Table 3b. Prevalence of adolescent headache and migraine in population-based studies.

Author (Year) (Country)	Age range (yrs)	Sample size	Data collection	Time period	Headache type (criteria)	Headache prevalence (%) Male	Female	Total
Adolescents								
Bille (1962) (Sweden)	13-15	2120	PQ	Lifetime	HA overall	65.1	73.3	69.5
					MHA (Vahlquist)	4.0	6.4	5.3
Raieli et al (1995) (Italy)	11-14	1445	Interview, PE	One year	HA recurrent	19.9	28	23.8
					MHA (IHS 1988)	2.3	2.4	2.3
Barea et al (1996) (Brazil)	10-18	538	Q, interview, PE	Lifetime	HA overall	92.3	94.4	93.2
				One year	HA overall	77.9	87.9	82.9
					MHA (IHS 1988)	9.6	10.3	9.9
Split and Neuman (1999) (Poland)	15-19	2352	Q, PE	One year	MHA (IHS 1988)	10	28.4	21.7
Lu et al (2000) (Taiwan)	13-15	4064	Q, interview	Lifetime	HA overall	81.3	87.9	84.6
				One year	MHA (IHS 1988)	5.7	7.8	6.8
Bandell-Hoekstra et al (2001) (Netherlands)	10-17	2358	Q	Lifetime	HA overall			97
				One year	HA >1/year			92
Anttila et al (2002) (Finland)	12	1409	Q	6 months	HA overall			52
					MHA (IHS 1988)			13.6
Fichtel and Larsson (2002) (Sweden)	13-19	793	Q	6 months	HA >1/week	24	42	33

HA = headache, MHA = migraine headache, PE = physical examination, CQ = child's questionnaire, PQ = parent's questionnaire, SQ = self-administered questionnaire, TQ = teacher's questionnaire, Q = questionnaire completed by parents and child

Table 3b (continues). Prevalence of adolescent headache and migraine in population-based studies.

Author (Year) (Country)	Age range (yrs)	Sample size	Data collection	Time period	Headache type (criteria)	Headache prevalence (%) Male	Female	Total
Roth-Isigkeit et al (2004) (Germany)	10-18	735	Q	3 months	HA overall HA >1/week			65.6 33.7
Zwart et al (2004) (Norway)	13-18	8255	Q	One year	HA overall	69.4	84.2	76.8
		5957	Interview, PE	One year	HA recurrent MHA (IHS 1988)	21.0	36.5	29.1 7
Dooley et al (2005) (Canada)	12-13	1694	Q	6 months	HA frequent (>1/week)			26.3
	14-15	1764						31.2
Wang et al (2005) (Taiwan)	13-15	2414	Interview	One year	MHA (IHS 1988)			
	13					3.3	4.1	3.7
	14					3.9	7.8	5.7
	15					6.1	10.9	8.4
Karli et al (2006b) (Turkey)	12-17	2387	Q	One year	HA recurrent (>1/year)	45.1	59.8	52.2
		1063	Interview		MHA (IHS 2004)			14.5
Kröner-Herwig et al (2007a) (Germany)	11-12	5474	PQ, CQ	6 months	HA less than monthly	31	32	53.2
	13-14					32	27	

HA = headache, MHA = migraine headache, PE = physical examination, CQ = child's questionnaire, PQ = parent's questionnaire, SQ = self-administered questionnaire, TQ = teacher's questionnaire, Q questionnaire completed by parents and child

2.3 Incidence of headache

The studies on the incidence of frequent headache and migraine in children and adolescents are few. In Finnish children starting school at age of seven years, the incidence rates of frequent headache increased from 58.1 per 1000 person-years in 1974 to 277.7 per 1000 person-years in 2002. The incidence of overall migraine was 19.7 per 1000 person-years in 1974 and in 2002 133.2 per 1000 person-years (Anttila et al 2006). According to Stang et al (1992), the incidence of migraine is 270 per 100,000 person-years in 10-14-year-olds and 309 per 100,000 person-years in 15-19-year-olds. The highest incidence in males is at the age of 10-14 years and in females at the age of 20-24 years (Stang et al 1992). Rozen et al (1999) reported that the incidence of medically recognized migraine increased significantly in both women and men in Olmstead County, USA, over a period of 11 years from 1979 to 1990 (Rozen et al 1999). However, a 3-year large-scale nation-wide study observing the trends in the prevalence and incidence of migraine in 13-15-year-old Taiwanese adolescents found no increase in the annual incidence rates between 1999 and 2000 and between 2000 and 2001 (Wang et al 2005b).

In a prospective incidence study, the overall annual incidence of frequent headaches (at least once a week) is 65/1000 among 12-14-year-old adolescents (Larsson and Sund 2005). Laurell et al (2006) report an estimated average annual incidence of 81 and 65 per 1000 children, for tension-type headache and migraine, respectively.

2.4. Determinants of headache

2.4.1. Genetics

Migraine appears to be hereditary and many studies have addressed its inheritance. Still, there is no consensus on the mode of inheritance of different migraine types (Merikangas 1996). Several twin studies have suggested a strong genetic component for migraine. Genetic factors and the individual-specific environmental factors have been found to play equally important roles in the etiology of migraine (Honkasalo et al 1995, Mulder et al 2003), especially migraine without aura, not only in adults (Gervil et al 1999) but also in children (Svensson et al 1999). In their family study, Wessman et al (2002) found significant evidence of linkage between migraine with aura and chromosome 4q24. Furthermore an association between certain markers on chromosome 4q24 and the clinical symptoms of migraine with aura has been recently found (Anttila et al 2006). In contrast, Finnish family studies have found no evidence of migraine with aura susceptibility on chromosomes 15 and 19p13 or on gene ESR1 (Kaunisto et al 2005, Kaunisto et al 2006, Oswell et al 2008).

2.4.2. Familial factors

It is common that children suffering from headache have a family history of headache, usually on the mother's side (Congdon and Forsythe 1979, Sillanpää 1983a, Lee and

Olness 1997, Aromaa et al 1998a, Anttila et al 1999, Bener et al 2000). In a study by Messinger et al (1991), the prevalence of lifetime headache is 64% in headache sufferers when neither parent suffers from headache, 85% when one parent suffers from headache and 98% when both parents suffer from headache. Mother's frequent prepregnancy headache is strongly related to the occurrence of headache in the preschool-aged children (Aromaa et al 1998a). Zencir et al (2004) have found a relationship between migraine in adolescence and familial occurrence of headache. Of children with migraine aged 11-18 years, 56.6% report a positive family history. A first-degree and second-degree family history is positive in 42.9% and 23.8% of migraine cases, respectively (Zencir et al 2004). Migraine among first-degree relatives is reported in 66.7% of the 7-17-year-old children with migraine, in 51.4% of those with TTH and in 29.8% of those without headache (Laurell et al 2005).

2.4.3. Psychological factors

Epidemiological studies have revealed a relationship between migraine and psychological factors, especially depression and anxiety (Andrasik et al 1988, Maratos and Wilkinson 1982). The association between headache and depression has usually been attributed to one of three theoretical models (Figure 1). Adolescents suffering from chronic headaches have been found to have an association between the experience of recent loss and depression and the onset of headache (Maratos and Wilkinson 1982). Stressors within the family are commonly associated with increased occurrence of headache (Aro 1987, Larsson 1988, Kaiser and Primavera 1993). Aromaa et al (1998b) report that concentration difficulties, behavioral problems and depressive symptoms at preschool age are associated with headache occurrence at school entry. The prospective epidemiological study of Pine et al (1996), focusing on the association between major depression and headache from late childhood into early adulthood, shows that major depression predicts prospectively the new onset of headaches in young adulthood. Anxiety symptoms in childhood and anxiety disorders during adolescence have been found to predict migraine in adulthood (Waldie and Poulton 2002)

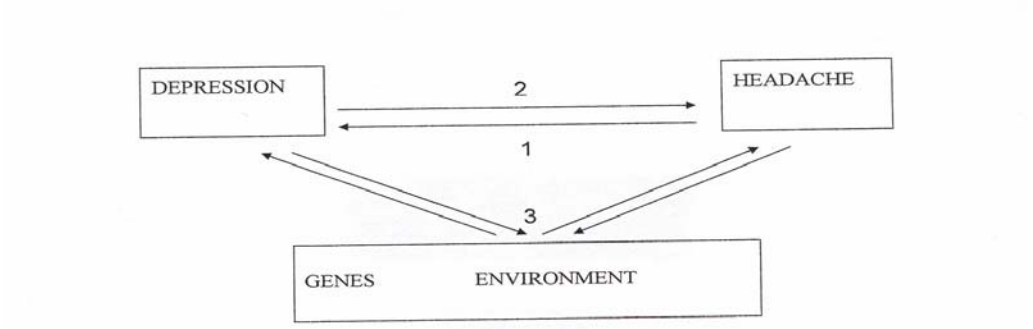


Figure 1. Three hypotheses of the associations between headache and psychosocial factors: 1. Headache causes depression, 2. Depression causes headache and 3. Common genes and/or environmental factors underlie both conditions and account for the association between psychosocial factors and headache

Changes in family life are known to influence children's health and to contribute to childhood disease (Östberg 1996). Discontinuity factors (e.g. divorce) have been used to account for negative changes in the family (Kaltiala-Heino et al 2001). Marital problems, including separation or divorce, have been found to be related to recurrent headache in children (Karwautz et al 1999, Maratos and Wilkinson 1982) and adolescents (Larsson 1988). However, there are also conflicting results (Carlsson et al 1996, Metsähonkala et al 1998, Laurell et al 2005).

Mortimer et al (1992b) reported that a clear migraine precipitant could be identified in 44.4% of the children aged 8-11 years. Stress was found to be a precipitant in 13.9% of their study group (Mortimer et al 1992b). When 2475 migraine and tension-type sufferers were studied, the most common triggers for both migraine and tension-type headache were stress and frequent traveling. Stress was associated with migraine, while physical activity was related to TTH (Zivadinov et al 2003). In contrast to this finding, school stress was more common precipitant in TTH (19.5%) than in migraine (16.5%) among 8-16 year-old schoolchildren, whereas physical exercise triggered more often migraine (26.5%) than in TTH (23.4%) (Özge et al 2003).

The association between headache and depression may result from one or more underlying genes and/or environmental factors (Figure 1). Genes play a role in psychological traits (McGuffin et al 2001). Nearly all behaviors studied show moderate to high heritability (Plomin et al 1994), so both genes and environment play a role in personality and depressive disorders (McGuffin et al 2001). In their prospective cohort study of young adults, Merikangas et al (1990) showed the combination of anxiety disorder and major depression to be strongly associated with migraine. The migraine sufferers reported a significantly earlier onset of anxiety symptoms than those without migraine while the onset of depression tended to occur after the onset of migraine. In

an 8-year-follow-up study (Guidetti et al 1998b) the presence of anxiety at baseline predicted the persistence of migraine 8 years later.

Egger et al (1998) demonstrated a clear gender difference in the association between headaches and psychiatric disorders: frequent headache was associated with depression and anxiety with girls and conduct disorder with boys (Egger et al 1998). Fichtel and Larsson (2002) found also higher levels of depressive symptoms in adolescents with frequent headaches than in adolescents without headache, especially in girls. Depression and low self-esteem were found to precede headache among girls (aged 11-21 years) but not in boys (Rhee 2000).

In a population-based study in Finnish adolescents (Anttila et al 2004) higher levels of internalizing and somatic symptoms as well as social and family problems were reported by children with migraine than those without headache. Children with TTH had higher levels of somatic symptoms and family problems than those without headache. Lanzi et al (2001) found that in 8-18 year-old children and adolescents, particularly depressive and anxiety-linked personality traits tend to be more prevalent in migraine than in TTH. In a recent study (Mazzone et al 2006), internalizing and externalizing symptoms and hyperactivity were higher in the TTH group than in the migraine group, while depression and anxiety scores did not differ between these two headache groups. However, some pediatric studies, anxiety has been associated with TTH (Larsson 1988), but not with migraine (Cooper et al 1987).

Perquin et al (2000) and Egger et al (1999) emphasized that pain comorbidity is a strong factor explaining a sizable proportion of the relationships between frequent headaches and psychological problems. Adolescents with chronic pain reported more psychological vulnerability than those without chronic pain (Merlijn et al 2003). Among Finnish 11-year-old twins, depression, aggression and impulsivity have the strongest relationship to recurrent overall pain (Vaalamo et al 2002). The neurobiology and mechanisms behind the co-occurrence of different pains and psychological symptoms are largely unknown (Besson 1999). There may be malfunction in the descending pain-modulating pathways. Psychological factors may act through modulating pain perception (Loeser and Melzack 1999) or anxiety may play a role as a mediator between stress and pain symptoms (White and Farrell 2006). The serotonergic system may have an effect due to its importance both for anxiety and pain transmission. In addition, genetic factors, pain learning processes (modeling) and parents responses to their child's pain all play a part in the development and maintenance of child and adolescent pain symptoms (Rhee 2003).

2.4.4. Sociodemographic factors

Age and gender. The prevalence of headache is age- and gender-related (Bille 1962, Sillanpää 1983a, Raieli et al 1995, Guidetti and Galli 1998, Haugland et al 2001, Camarda et al 2002). The onset of headache is dependent on gender and in boys migraine starts earlier than in girls (Bille 1962, Sillanpää 1983a), while migraine predominates in postpubertal girls (Raieli et al 1995, Split and Neuman 1999, Lu et al

2000, Zencir et al 2004). On the other hand Zwart et al (2004) report higher prevalence rates in both migraine and TTH for girls aged 12-19 as compared with boys of the same age. The reported prevalence rates of headache have been 3% to 6% at three and four years of age (Zuckerman et al 1987, Borge et al 1994), 20% at five years of age (Sillanpää et al 1991) and 35% to 50% at seven years of age (Bille 1962, Sillanpää and Anttila 1996). Ten to 20 % of children under 10 years of age and 20% to 35% of children aged 11 to 16 have been reported to suffer from recurrent headache (Kristjansdottir and Wahlberg 1993, Carlsson 1996a, Raieli et al 1996). After a 15-year follow-up, the prognosis of overall headache was found to be more favorable for boys than girls in young adulthood (Sillanpää and Aro 2000, Larsson and Sund 2005).

Socioeconomic status of families of headache children. In some studies, the prevalence of headache in childhood and adolescence seems not to be associated with social class (Bille 1962, Passchier and Orlebeke 1985, Mortimer et al 1992b, Kristjansdottir and Wahlberg 1993). A number of studies have, however, reported a relationship between low socioeconomic status and high prevalence of headache and other pain symptoms (Sillanpää et al 1991, Hotopf et al 1998, Anttila et al 2002, Groholt et al 2003, Bigal et al 2007) and high prevalence rates of frequent headache in girls (Kristjansdottir and Wahlberg 1993). In addition, Carlsson (1996a) found that headache in children was more common in districts with high unemployment. In a recent study of Bigal et al (2007), the association between migraine prevalence and socioeconomic status was related to familial occurrence of headache. When one of the parents had migraine, there was no relationship between the prevalence of migraine in 12-19 year-old adolescents and household income, but when neither parent had headache, the relationship between migraine prevalence and low household income was strong.

Residence and housing conditions. No relationship has been found between headache frequency and urban versus rural residence (Kristjansdottir and Wahlberg 1993, Sillanpää et al 1991), while housing conditions may have an effect. Sillanpää et al (1991) showed that a higher number of persons per room and a lower housing standard were associated with a higher frequency of headache among preschool-aged children.

2.4.5. Hormonal factors

Headache prevalence is found to increase in girls in the course of pubertal development, while in boys the rates remain stable throughout puberty (LeResche et al 2005). In their study involving an age cohort of 473 adolescent girls, Sillanpää and Aro (2000) found a higher headache frequency for girls with an earlier age of menarche. The gender difference of headache disorders may be due to female hormones (Rasmussen 1993). Hormonal alterations during adolescence may trigger physical symptoms, especially headache, or even serve as a direct cause of migraine (McGrath 1990). Hormonal changes have also been found to be associated with the increased tendency to physical symptoms, such as headache, in adolescent girls (Perquin et al 2000).

2.5. Characteristics and concurrent symptoms of headache

The classification of the different primary headache types is based on their typical characteristics and associated symptoms. Some features, such as unilaterality, vomiting, nausea, aura, pulsatility, photophobia and phonophobia are considered to be more typical of migraine than of TTH. On the other hand, several studies have found none of these characteristics specific for migraine alone (Seshia 1996, Wöber-Bingöl et al 1996b). Clinically, it is the impression of many pediatric headache specialists that children's migraines are of shorter duration, tend to be bilateral rather than unilateral and that children more often report either photophobia or phonophobia, rather than both (Maytal et al 1997, Winner et al 1997, Winner et al 2003).

In a population-based study of 4000 children aged 4-15 years, Mavromichalis et al (1999) found that all headache attacks in children with migraine lasted from 2 hours to 3 days. Several studies have shown that migraine attacks last less than two hours in children and are shorter than in adults (Wöber-Bingöl et al 1996b, Maytal et al 1997, Hernandez-Latorre and Roig 2000).

Bilateral migraine pain seems to be more common in young children, pain becoming unilateral with increasing age (Prensky and Sommer 1979, Gherpelli et al 1998). In adolescence, most adolescents with migraine report unilateral pain (Winner et al 2003) whereas bilateral location is associated with TTH (Wöber-Bingöl et al 1996b). When studying the agreement between clinical headache diagnoses assigned by pediatric neurologists and symptom-based diagnoses using IHS (1988) criteria Maytal et al (1997) found that unilaterality has a high specificity of 86% when clinical diagnosis used as the reference standard. Whereas bilateral pain is common in childhood, unilaterality has a positive predictive value for migraine of 85% (Maytal et al 1997).

Pulsating headache has not been found to be a specific feature of pediatric migraine (Seshia 1996, Wöber-Bingöl et al 1996b), although its presence may help to exclude other headache types (Winner et al 2003). Pulsating pain is found to be the most sensitive migraine headache characteristic among Turkish children (Özge et al 2003). The pulsation reported by migraine sufferers was significantly related to older children over 10 years of age (Gherpelli et al 1998).

Accompanying symptoms such as photo- and phonophobia, nausea and vomiting are found more often in children with severe headaches than those with less severe headache (Bandell-Hoekstra et al 2001). In young children and adolescents, these symptoms are more often associated with migraine sufferers than with those suffering from TTH (Gallai et al 1995, Wöber-Bingöl et al 2004, Raieli et al 2005). Among 8-16 year-old headache children vomiting and photophobia concurrent with headache were the most specific characteristics for migraine (Özge et al 2003). In their clinical follow-up study, Battistella et al (2006) found that photo- or phonophobia and nausea were more often associated with frequent headache among children at puberty than those at preschool age. When children aged 18 and under were clinically examined by using the IHS 2 criteria, some notable age-dependent differences were found. In children aged 13

or under, nausea was reported more often than in 13-18-year-olds, while photophobia was more common associative symptom in the older group (Hershey et al 2005).

Other neurologic symptoms such as vertigo and dizziness are frequently reported by patients with migraine. According to the IHS classification, the prevalence of migraine was 1.6 times higher in adult dizziness clinic patients as compared with controls from an orthopedic clinic (Neuhauser et al 2001). Benign paroxysmal vertigo in childhood *may be* an early manifestation of migrainous vertigo. In their population-based study, Abu-Arafeh and Russell (1995) found that the prevalence of recurrent vertigo associated with migraine was 2.8% in children aged 6-12 years. Aggravation by physical activity and abdominal symptoms have been found typical of childhood migraine (Wöber-Bingöl et al 1996b, Akyol et al 2007).

2.6. Pain comorbidity of headache

The co-occurrence of headache and different pain symptoms is common (Alfven 1993, Borge et al 1994, Kristjansdottir 1997, Perquin et al 2000, Anttila et al 2001, Fichtel and Larsson 2002, Groholt et al 2003, Ghandour et al 2004, LeResche et al 2005, Østkirchen et al 2006). It is predominant in girls and increases with age (Perquin et al 2000, LeResche et al 2005, Östberg et al 2006, Larsson and Sund 2007). In contrast, Mikkelsson et al (2001) report the prevalence of widespread pain (WSP) to be 10% in both genders in a sample of 11-year-old Finnish twins. Children with headache, especially migraine, are more likely to report other pains and physical symptoms than those without headache (Watson et al 2003, Laurell et al 2005, Brun Sundblad et al 2007). In a representative sample of 1290 Finnish children aged 8-9 years, migraine headache was found to co-occur with neck-shoulder, abdominal and back pain, but not with limb, throat or chest pain or toothache as compared with the children with non-migraine headache (Anttila et al 2001). In addition, pain comorbidity was found in children with frequent non-migraine headache as compared with the children with less frequent non-migraine headache. However, the frequency of migraine headache was not related to comorbid pain (Anttila et al 2001). Children with either migraine or migrainous headache were found to have more clinical signs of temporomandibular disorder than their non-headache controls (Liljeström et al 2005).

Several longitudinal studies have considered the prognostic factors for musculoskeletal pain and headache. In a Swedish study, children aged 8, 11 and 14 with frequent or severe headache reported more multiple pain symptoms than those without headache after a 13-year follow-up (Brattberg 2004). After a 4-year follow-up, the frequency of neck pain was found to correlate with the frequency of headache (Ståhl et al 2004). Finnish 9-11-year-old schoolchildren with once a week or more frequent headache had worse prognosis for musculoskeletal pain after 4-year follow-up than children with less frequent headache (El-Metwally et al 2004). However, in 13-year-old children followed up to age of 16, the presence of comorbid non-headache pain at baseline predicted the persistence of monthly headache (Laimi et al 2005). Frequent headache, sore throat, abdominal pain and asthma at baseline predicted the incidence of low back pain among English and Danish schoolchildren and adolescents (Jones et al 2003,

Hestbaek et al 2006). These studies support the hypothesized cross-sectional association between migraine or non-migraine headache and other pain conditions in childhood and adolescence. The presence of multiple pain symptoms predicts a worse prognosis of headache and the presence of comorbid headache predicted the incidence or worse prognosis for musculoskeletal pain.

2.7. Psychosocial impact of headache

Headache may also result in depression (Figure 1). Andrasik et al (1988) hypothesized that the higher scores of depression, anxiety and somatic complaints seen in adolescents with migraine are a consequence of migraine sufferers having to live with chronic pain. According to Langeveld et al (1996), lowered psychological functioning and internalizing behavior are not typical of patients suffering from migraine or other types of headache, suggesting that internalizing behavior might be related to the experience of chronic pain in general and not specifically to migraine. Stress has also been found to have a clear association with headache. Young adults with a history of childhood headache are significantly more likely to report stress in adolescence than their headache-free controls (Waldie 2001). Also Fearon and Hotopf (2001) report that children with headache are at an increased risk of different psychiatric symptoms in adulthood.

The impact of headache on children has been studied as absenteeism from school and medical consumption (Stang and Osterhaus 1993, Metsähonkala et al 1996). When studying the impact of headache, quality of life has been recognized as a major outcome (Lipton 1995, Solomon 1997). In a recent study involving 2-18-year-olds, quality of life was lower for migraine sufferers than for healthy children and was the lowest for children with chronic daily headache. The impact on quality of life of children with migraine was similar to that of children with arthritis and cancer (Powers et al 2003).

2.8. Outcome of headache

Little is known about the long-term outcome of headache. Table 4 presents population-based follow-up studies of headache in childhood and adolescence. These studies show that both the type and frequency of headache change during childhood and adolescence (Sillanpää 1983b, Bille 1997, Metsähonkala et al 1997, Aromaa et al 2000, Fearon and Hotopf 2001, Camarda et al 2002, Laimi et al 2005, Wang et al 2005a, Larsson and Sund 2005, Laurell et al 2006, Monastero et al 2006). Most studies have focused on migraine or on overall headache (Sillanpää 1983b, Bille 1997, Aromaa et al 2000, Rhee 2000, Fearon and Hotopf 2001, Camarda et al 2002, Larsson and Sund 2005, Wang et al 2005a, Monastero et al 2006) and only two studies have followed both children with TTH and children with migraine (Laurell et al 2006, Laimi et al 2006).

After age 13 the frequency of headache tends to decline especially in boys (Guidetti and Galli 1998, Larsson and Sund 2005, Kienbacher et al 2006). After 40-year follow-up, Bille (1997) found 51% improvement in the frequency of pronounced migraine.

When 13-year-old Taiwanese migraineurs were followed for two years, a remission of 16% was found (Wang et al 2005a). Monastero et al (2006) reported that 38% of adolescents with migraine had remitted after a 10-year follow-up. However, in Finnish 8-9-year-old boys with migraine, remission rates of only 5% were seen after a 3-year follow-up (Metsähonkala et al 1997). Of 12-14-year-old children with weekly headache, 62% improved in one year. At age 14 headache was more persistent than at age 12 (Larsson and Sund 2005).

Changes in the headache types

Childhood headache seems to have a changing pattern (Camarda et al 2002, Wang et al 2005a, Laurell et al 2006). Bille (1997) followed 73 children with pronounced migraine in childhood for 40 years. More than half of children with pronounced migraine still suffered from migraine attacks at the age of 50 years (Bille 1997). When 7-year-old Finnish schoolchildren were followed for seven years, migraine, defined according to Vahlquist criteria, remained migraine in 83% of the girls and in 74% of the boys (Sillanpää 1983b). According to the studies using the IHS criteria, 42-70% of children and adolescents with migraine have still migraine after 2-10 years' follow-up (Metsähonkala et al 1997, Camarda et al 2002, Wang et al 2005a, Laurell et al 2006, Monastero et al 2006). Of Swedish 7-15-year-old children with TTH, the diagnosis persisted in 49% and changed to migraine in 26% (Laurell et al 2006).

The changing character of childhood headache may be explained with the continuum model of headache, considering primary headache a continuum between TTH and migraine (Silberstein 1992). When diagnosing different headache types, there may also be considerable overlap (Zebenholzer et al 2000). Significant change from migraine to TTH is, however, found among adolescents (Laurell et al 2006).

Predictors of the outcome of headache

Different factors have been considered to be predictors of the outcome of adult headache. Most adults with chronic headache report that their headache already started in adolescence (Spierings et al 1998). Various factors seem to turn episodic attacks into a more chronic form of headache and that is why no single etiological and pathophysiological mechanism can be expected (Scher et al 2002) The aggravating role of overused analgesics, peripheral and central sensitization of nociceptors, muscle tenderness, psychological stress and genetic factors have been associated with chronic headache in adults (Benedettis and Lorenzetti 1992, Davidoff 1998, Russell et al 1999, Burstein and Woolf 2000, Lu et al 2001, Zwart et al 2003, Cady et al 2005). However, it is possible that these factors are not predictors of childhood and adolescence headache (McGrath 2001).

In previous population-based studies, frequent and intensive headache and gender have been associated with the outcome of headache and migraine (Larsson and Sund 2005, Wang et al 2005a, Laurell et al 2006). Early onset (before age of 7 years) of headache or migraine predicted frequent headache and migraine at adulthood (Aromaa et al 2000) and also the persistence of migraine after 7-year-follow-up (Sillanpää 1983b).

Other factors associated with the outcome of headache include reduction of leisure time activities, depressive symptoms, anxiety and low self-esteem (Rhee 2000, Fearon and Hotopf 2001, Waldie 2001, Waldie and Poulton 2002, Larsson and Sund 2005). Depression in childhood had an 1.4 odds ratio for frequent headache in adulthood (Fearon and Hotopf 2001). Compared with their unstressed controls, children who reported high stress at age 15 were 2.6 times more likely to be diagnosed with migraine at age 26 and twice as likely to be diagnosed with combined headache (Waldie 2001). In clinical studies factors that have been associated with the outcome of childhood and adolescence headache include the frequency, type, severity and early onset of headache, gender, psychiatric disorders and the time between the onset of headache and a visit to a headache clinic (Guidetti and Galli 1998, Hernandez-Latorre and Roig 2000, Galli et al 2004, Brna et al 2005, Kienbacher et al 2006).

Table 4. Outcome of childhood and adolescence headache and migraine in population-based studies.

Author (Year) (Country)	Age range (yrs)	Sample size	Data collection	Time period	Changes in headache type during follow-up	Changes in headache frequency during follow-up
Bille (1962, 1997) (Sweden)	7-15	6-y F: 254 40-y F:73	B: Q F: I	1 year	6-y F: 66% migraine 40-y F: 51% migraine	6-y F: 34% remission 51% improvement
Sillanpää (1983b) (Finland)	7	2921	Q	1 year	7-y F: Migraine persists: 83% girls, 74% boys	7-y F: 22% remission 37% improvement
Metsähonkala et al (1997) (Finland)	8-9	3-y F: 218 8-y F: 53	B: Q F: I+ diary	6 months	3-y F: 63% migraine, 8% TTH 8-y F: 70% migraine	3-y F: 5% remission
Aromaa et al (2000) (Finland)	7	1205	B: I+Q+CE F: Q	6 months		15-y F: 27% remission
Fearon and Hoptopf (2001) (UK)	7	9841	I	lifetime		26-y F: 21% HA persists, 24% recurrent HA, 12% no HA
Camarda et al (2002) (Italy)	11-14	64	B: I F: Q	?	5-y F: 56% MWOA persists, 13% turns into TTH	5-y F: 30% remission 18% MWOA

Author (Year) (Country)	Age range (yrs)	Sample size	Data collection	Time period	Changes in headache type during follow-up	Changes in headache frequency during follow-up
Wang et al (2005a) (Taiwan)	13	2414	B: Q F: Q	1 year	1-y F: 43% migraine persists 2-y F: 48% migraine persists	1-y F: 8% remission 2-y F: 16% remission
Larsson and Sund (2005) (Sweden)	12-14	2355	Q	?		1-y F. 38% weekly HA persists, 62% improvement
Laimi et al (2006) (Finland)	13	228	I+CE	6 months		3-y F: 51% monthly HA persists, 49% improvment
Laurell et al (2006) (Sweden)	7-15	122	B: Q+I F:Q	One year	3-y F: 61% migraine persists, 18% turn into TTH. 49% TTH persists, 26% turn into migraine	3-y F: 21% migraine remission, 23% TTH remission
Monastero et al (2006) (Italy)	11-14	55	I+CE	?	10-y F: migraine persisted 42%, 20% turned to TTH	10-y F: 38% remission

B = baseline, F = follow-up, Q = questionnaire, I = interview, CE = clinical examination, TTH = tension-type headache, MWOA = migraine without aura, HA = headache

3. AIMS OF THE STUDY

The aims of the study were to investigate:

1. Factors predicting change in headache prevalence between preschool age and pre-puberty (I).
2. Changes in the prevalence and incidence of adolescents frequent headache (II).
3. Changes in the characteristics of headache from preschool age to puberty (III).
4. Association between psychological factors and frequent headache in adolescence (IV).

4. STUDY POPULATIONS AND METHODS

4.1 Study populations

The present study is based on two population-based cohorts: the Finnish Family Competence Study cohort (papers I and III) and the FinnTwin12-study cohort (papers II and IV).

The Finnish Family Competence Study was started in January 1985. The study focuses on ways of life of and health behavior in young Finnish families, with a view to developing public health services in the areas of health education and socio-emotional support. It covered the Province of Turku and Pori, situated in southwestern Finland, with a total population of 713 356.

Subject collection (1/1/1986-31/12/1986) was based on stratified randomized cluster sampling. Stratification involved division of the study area into two parts, the southern area (the catchment area of the Turku University Central Hospital) and the northern area (the catchment area of Satakunta Central Hospital). Each cluster consisted of the population resident in a health-authority area, the smallest administrative unit in the Finnish public health-care system. Eleven of the total of 35 health authority areas were selected by lot, with weighting according to stratum. The mean degree of urbanization of the municipalities in the sample areas did not differ statistically significantly ($p=0.112$) from that of all municipalities in the Province (Rautava and Sillanpää 1989). All 67 maternity health clinics and 72 well-baby clinics in the 11 health-authority areas participated in the study.

The study population consisted of nulliparous women and their spouses starting to expect their first baby and paying their first visit to maternity health clinic in 1986. Invitations to participate in the study were originally presented to 1582 families. Of the women, 1443 (91%) gave informed consent and 139 women refused to participate. The occupational distribution of the refusers was similar to that of the participants ($p=0.271$)(Rautava and Sillanpää 1989).

The mothers gave birth to 1294 first children. Three children died during birth. Eight children died in infancy, and five moved abroad. One hundred and forty-six could not be traced. The remaining 1132 mothers and children were followed from the beginning of pregnancy until the children concerned reached 12 years of age. In the drop-out analysis, the youngest mothers (<20 years old at the beginning of the study), ($p=0.002$) and fathers ($p=0.002$) dropped out of the study more often than other participants. The distributions of basic educational levels, occupational training, socio-economic status, degree of urbanization or the prevalence of frequent headache of the drop-outs did not differ significantly from those of the participants. The study participation chart shows the participation rates at different stages of the study (Figure 2).

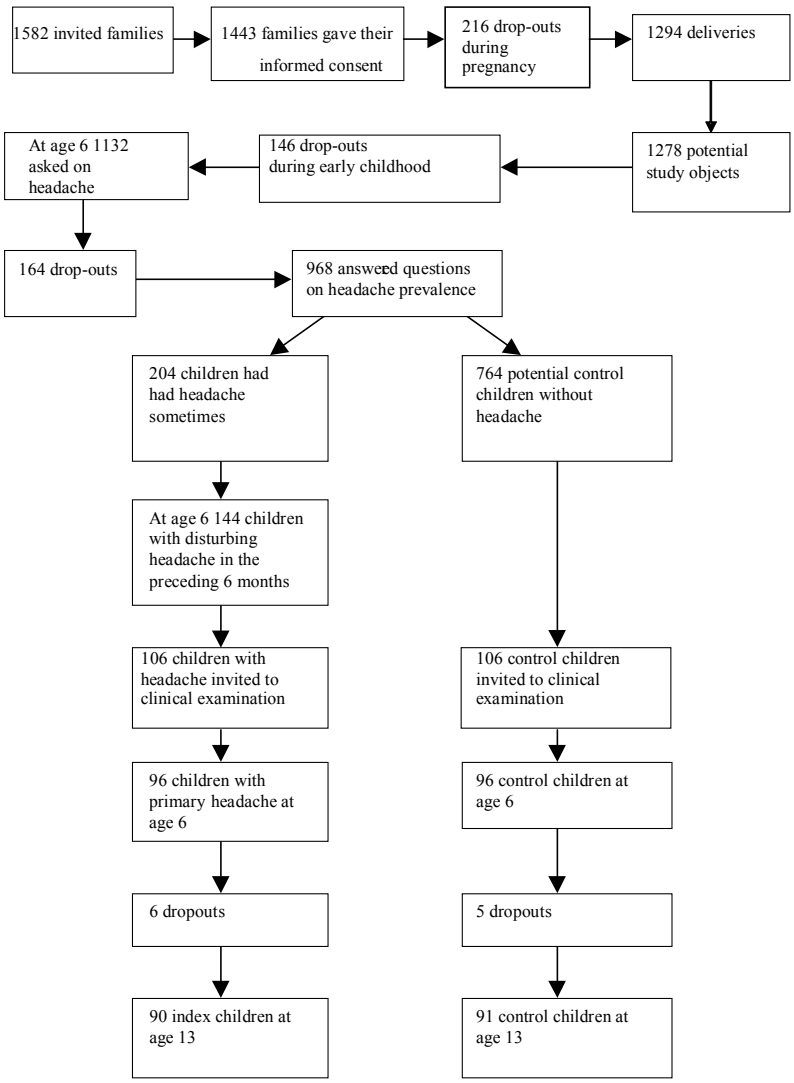


Figure 2. Flow chart from the Finnish Family Competence Study

The FinnTwin12 study is a longitudinal study of Finnish twin children, with its main focus on genetic and environmental determinants of the predictors of health-related behaviors. The study was launched in September 1994, when all twins born 1983-1987 were identified from the Central Population Registry of Finland (CPR) as part of the Finnish Twin Cohort studies. At birth, Finnish citizens are assigned a personal identifying number that incorporates their date of birth. That information, together with links to the maternal and paternal personal identifying numbers, deaths, and other vital statistics as well as the current residential address for each individual, is contained in the CPR. Multiple births were identified through the use of family member links existing for all persons in the CPR. Thus persons born on the same day to the same mother were considered multiples. Excluded were families in which one or both co-twins were living outside Finland, co-twins living apart from both biological parents, families in which the Central Population Registry contained no residential address for a twin, and families in which either twin had died. Eighty-seven percent of the twin families (n=2724) gave informed consent to participate in the study. Permission to contact the school was obtained from 93% of these families. Among non-responders was found no evidence for selection for family type (both versus single parents), parental age, area of residence, type or gender of twin.

4.2 Data collection

The Finnish Family Competence Study. Structured questionnaires were pre-tested in 1985 and then given separately to mothers and fathers, to be returned in sealed envelopes to the investigators. Questionnaires were issued by nurses during visits to well-baby clinics. During the follow-up from pregnancy to child's age of 12, the data was collected in 11 steps. When the children were six and 12 years of age, the questionnaires were mailed to the children's homes. Parents, and nurses at well-baby clinics completed questionnaires about the health and health-related factors of the parents and their children. When the children were 12 years of age they also completed their own questionnaire.

At the child's age of six and 12 years, the parents were asked questions about the occurrence of headache of their child. At age six, completed questionnaires were returned by 968 parents (86% of 1132), at 12 years of age by 906 parents (80% of 1126) and by 900 12-year-old children (79% of 1126). The question about the child's headache during the previous six months before completion of the questionnaire (”present headache”) was answered by 798 families (79% of 968, 84% of 906) at both study phases of 6 and 12 years.

Of the 968 six-year-old children, 204 (22%) had had previous headache disturbing daily activities. Of these children, 144 (71%) had suffered from disturbing headache during the preceding six months (=present headache) (Aromaa et al 1998a)(Figure 2). The children with present headache and matched (age, gender and domicile) control children were invited to participate in the clinical paediatric and neurological examinations at the Departments of Child Neurology and Public Health, Turku University Central Hospital.

Clinical examination of the children. When the children were six years of age 106 (74%) of 144 children with present headache and 106 matched control children, accompanied by their mother or father or both, participated in the study. Children with secondary headaches were excluded from the study. Finally, 96 index children and 96 controls participated in the clinical examination. Appendix 2 shows the questions used in the study in detail.

When the 96 children with headache and 96 control children were 13 years old, they were again invited to participate in a clinical examination. Six (6%) of the index children and 5 (5%) of the control children could not be traced. Another six (6%) families of the index children and three (3%) families of the control children refused to participate in the clinical examination. The reasons for refusals were living far away from the university hospital (n=3), lack of time (n=4), the child's refusal (n=2) or recent death of a family member (n=1). In all these cases, questions on the quality of the child's headache could still be asked on the telephone. At age 13, the final number of index children was 90 and that of control children 91 (Figure 2.). The mean age of the children was 13.0 years (range 12.6-13.6 years) and 90% of them came to the clinical examination with their mother and 10% with their father or with grandparents. In addition to answering the opening questions, the children underwent a careful somatic and clinical examination.

The differences between participants (n=90) and nonparticipants (n=144-90=54) were nonsignificant in terms of mothers's age (p=0.538), educational level (<9 years, 9 years, >9 years; p=0.356), degree of urbanization of the domicile (p=0.131), having siblings (p=1.000), family composition (parents married, p=0.078; parents divorced, p=0.605; one-parent family, p=0.660) The index children had significantly more often a long-term disease (excluding headache) than the controls (p=0.027).

At age 6, the children were clinically examined by one of the researchers and at age 13 by another. For this reason, the interexaminer reliability test was done in seven children, who were separately examined by the two examiners. Of the 173 questionnaire items, four showed differences in the recordings of the examiners. The interexaminer kappa coefficient of these four variables showed satisfactory agreement (0.70-0.76) between examiners.

The FinnTwin12 Study. The study has a three-stage sampling design (Figure 3). The baseline family questionnaires were first mailed to each twin family in the autumn of the year before the twins reached the age of 12. At baseline five separate questionnaires were used: a family questionnaire on the birth, early childhood and development of the twins, followed by separate questionnaires to both parents and both twins in the late autumn. At baseline, headache questions were directed only to four birth cohorts (born 1984-1987, n=3966). In the following spring, the year in which the twin children turned 12, several months after the baseline questionnaires had been returned, the ratings from parents and class teachers of all twins were collected, using a Multidimensional Peer Nomination Inventory (MPNI), developed for this research

(Kaprio et al 2002, Pulkkinen 1995, Pulkkinen et al 1999). Ratings on twins were completed by 93% of teachers and 92% of parents of the entire twin sample.

The first follow-up, performed at age 14, involved mailing the questionnaires to all five birth cohorts in the month of the twins' 14th birthday. At this point, most questions asked at age 11 were repeated and teacher MPNI ratings were obtained. The participation rate for all five birth cohorts was 88% (n=4710).

The second follow-up involved a questionnaire mailed to the twins in the month of the twins' 17th birthday. A total of 77% (n=4159) of twins participated in this follow-up.

At baseline the mean age of the participants was 11.4 (range 10.8 to 12.3) years. Of the 3966 participants, 52% were girls and 48% were boys. At the first follow-up, the mean age was 14.1 (range 13.9 to 14.9) and the gender distribution was 50% (2336 of 4710) for girls and 50% (2374 of 4710) for boys. At the second follow-up, the mean age was 17.7 (range 17.2-19.5) and gender distribution 52% (2149 of 4159) for girls and 48% (2010 of 4159) for boys.

The zygosity of 3731 twin individuals at age 11 (four birth cohorts born 1984-87) and 4396 at age of 14 (all five birth cohorts) was determined from a validated questionnaire method (Kaprio et al 2002). The data consisted of 1251 monozygotic (MZ) and 2480 dizygotic (DZ) twins at age of 11 and of 1438 MZ and 2958 DZ twins at age of 14 and 1309 MZ and 2610 DZ twins at age of 17.

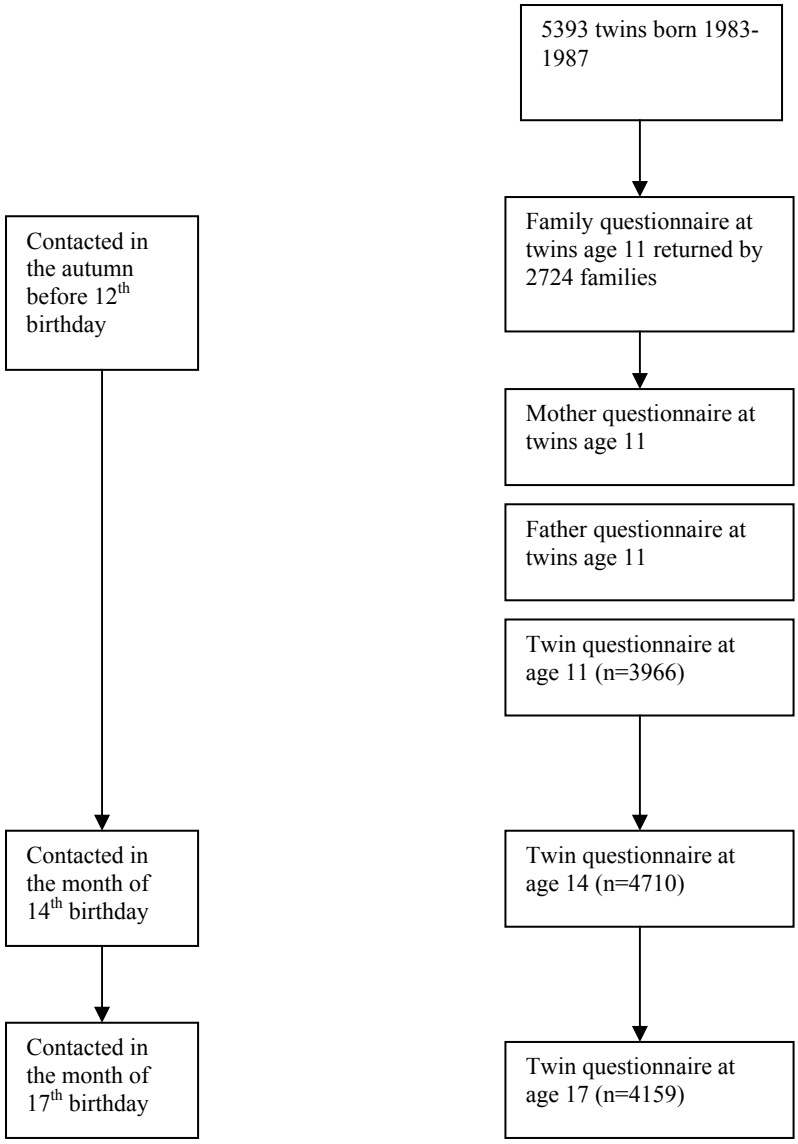


Figure 3. Data collection of FinnTwin12 Study

4.3 Outcome and its determinants

The Finnish Family Competence Study. In the studies on the changes in the prevalence and characteristics in childhood headache (I, III) the parents answered two questions about the child's headache (at the ages of 6 and 12) :

1) "Has your child had headache disturbing his/her daily activities in the preceding six months?" ("present headache")

2) "Has your child had headache disturbing his/her daily activities at some period in his/her life prior to the past six months?" ("previous headache").

At 12 years of age, also the children themselves answered the following questions:

1) "Have you had headache disturbing your daily activities in the preceding six months?"

2) "Have you had headache disturbing your daily activities at some period in your life prior to the past six months?".

To assess their relationship to childhood headache, the following variables were also studied in order: familial occurrence of frequent headache; sociodemographic and psychosocial factors relating to the family; and each child's state of health.

Familial occurrence of headache **(I)** was studied by asking both parents about their headache prior to the mother's pregnancy ("prepregnancy headache"). The same headache questions were asked again 13 years later. If a parent reported at least one episode of headache or migraine attack per month, he or she was regarded as suffering from frequent headache. When the study children were 12 years of age, the parents were asked about headache in the siblings.

The four sociodemographic variables **(I)** were maternal age on becoming pregnant (< 25, 25 to 29 or > 29 years), gender of child, parental occupation (professional, service-sector employee, worker in industry, or other e.g. primary production employees), and nature of residential location of the family (urban, suburban or rural).

Psychosocial variables **(I)** referred to changes in family structure (including divorce or separation of the parents).

The child-health variable **(I)** included longterm illness lasting for more than six months (excluding headache), e.g. diabetes mellitus, asthma or allergy.

Present headache **(III)**

After the clinical examination at both time points, the child's headache was classified using the Classification of the International Headache Society (IHS 1988).

Changes in the characteristics of concurrent symptoms of present headache and different headache types **(III)**

The characteristics of headache were studied from several perspectives: frequency, intensity of pain, triggers, predominant time of onset, aura symptoms, location of pain, duration of untreated attacks (sleep period included), characterization of pain, concurrent symptoms, alleviating and worsening factors, and use of medication. A careful somatic examination (including neurological examination) was also carried out at both ages.

Changes in factors associated with the occurrence of headache **(III)**

To assess the role of any associative factors, open questions were asked: about the child's general health status, including long-term disease (active illness that had lasted for more than six months, excluding headache), e.g. diabetes mellitus, bronchial asthma or allergy and question about travel sickness, syncope and head trauma.

The FinnTwin12 Study. In the studies of psychological factors and incidence of headache (**II, IV**), headache at age of 11 was assessed with following questions: "If you think of the period from today to last summer, how often have you had headache after the last summer?" 1.Every day or almost every day (daily headache, category 1), 2.More often than once a week, but not every day (more than weekly, less than daily headache, category 2), 3.Approximately once a week (weekly headache, category 3), 4.Once a month (monthly headache, category 4), 5.Less than once a month (category 5). Headache frequency was again assessed at ages of 14 and 17 with the question: "How often have you had headache during the last few months?" The response scale was the same as at baseline. If the twin reported at least one episode of headache per month, she/he was regarded as having monthly headache.

Psychological variables **(IV)**. The role of psychological and behavioral factors in adolescent headache was assessed using a multidimensional inventory of child's social behavior developed for peer nomination (MPNI) (Pulkkinen 1982, Pulkkinen et al 1999). The 37-item Teacher Rating Form (Tr-MPNI) and Parent Rating Form (Pr-MPNI) used in the present study, were developed from MPNI (Pulkkinen et al 1999). In both the Tr-MPNI and the Pr-MPNI items are presented in the form of statements (e.g."cannot concentrate in anything"). The teachers and the parents were asked to rate each twin on every item on a four-point scale as follows: 0= does not apply, 1= applies sometimes, but not consistently, 2= certainly applies, but not in a pronounced way, 3= applies in a pronounced way. The ratings yield scores on three major psychological scales called: *Externalizing Problem Behaviors*, consisting of subscales of Aggression, Impulsivity and Inattention, *Adaptive Behaviors*, consisting of subscales of Constructiveness, Compliance and Social Activity and *Internalizing Problem Behaviors*, consisting of subscales of Depression and Anxiety as in the previous analysis by Pulkkinen et al (Pulkkinen et al 1999).

Table 5 summarizes the study designs used in the different original papers.

Table 5. Summary of study designs

PAPER	I	II	III	IV
QUESTION-NAIRES	child 6 and 12 of age	adolescent 11, 14 and 17 of age	child 6 and 12 of age	adolescent 11 and 14 of age
CLINICAL EXAMINATION		child 7[1] and 13 of age		
STUDY DESIGN	prospective follow-up	prospective follow-up + nested case-control	prospective follow-up	cross-sectional prospective follow-up
STUDY MATERIAL	whole child cohorts	whole child cohorts	cases and matched controls	whole child cohorts
OUTCOME VARIABLES	occurrence of headache at 6 and 13 of age	headache frequency at 11, 14 and 17 of age	occurrence of headache at 6 and 13 of age	headache frequency at 11 and 14 of age
OTHER VARIABLES	familial occurrence of frequent headache, sociodemo-graphic, psychosocial variables, child's state of health	incidence of frequent headache	characteristics of headache	psychological variables

[1] published earlier (Aromaa et al 1998a)

4.4 Statistical methods

The Finnish Family Competence Study. The data were first described using percentages and mean values with standard deviations (SD). Associations between categorical variables were studied using cross tabulation and Pearson chi-square test. For change in dichotomic variables, McNemar's test and for change in polytochomous variables, Bowker's test (generalization of McNemar's test) were used in the statistical analyses. For frequency tables with small frequencies, exact p-values were calculated. Associations between variables and occurrence of headache were analyzed by means of univariate and stepwise multivariate logistic regression analysis. Conditional logistic

models were used when the data was based on matched case-control design (Agresti 1990). Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Statistical calculations were performed using the Generalized Estimation Equations (GEE) method for logistic regression analysis of correlated binary responses available in the MULTILOG procedure of the SUDAAN statistical program package (Agresti 1990, Shah et al 1997). Statistical calculations were based on the SAS System for Windows, release 8.1/2001.

The FinnTwin12 Study. Associations among individuals, between variables and frequency of headache were analyzed using cumulative logistic regression models (Hoshmer and Lemeshow 2000). Because frequency of headache was associated with gender, and because the means of psychological variables showed differences between boys and girls (Pulkkinen et al 2003), analyses of associations between headache and psychological factors were made using gender adjustment**.** The strength of associations between headache frequency and psychological variables between genders were analyzed by testing interactions of gender and psychological factors in the logistic models. The data consisted of observations from twins, and observations from twin pairs are expected to correlate. The correlations were taken into account by using the GEE method in the estimation of standard errors of the parameters. Cumulative odds ratios (CORs) and 95% confidence intervals (CIs) were calculated from the logistic regression models corresponding to the standard deviations.

Associations between psychosocial variables and headache were analyzed within discordant twin pairs, where the definition of discordance was applied when one twin had headache at least monthly but the co-twin less often or not at all. Statistical analysis was then carried out using conditional logistic regression analysis. A separate analysis was performed for MZ and DZ twins. Among DZ twins the confounding effect of gender was taken into account by limiting the analysis to same-sexed pairs. The differences of MZ and DZ twins in the strength of the associations of headache frequency and psychological factors were analyzed by testing interaction terms of twin type with psychological factors in the conditional logistic models. ORs and 95%CIs were calculated from the conditional logistic regression models corresponding to the standard deviation. Statistical computing was performed with the SAS System for Windows, release 8.2/2001 and SUDAAN program (Shah et al 1997).

5. RESULTS

5.1. Prevalence of and factors associated with childhood and adolescence headache

5.1.1. Change in the prevalence of preschool and prepuberty headache (I)

When the 6-year-old children with present headache (i.e. headache during the preceding 6 months) were followed to the age of 12 years, the prevalence of present headache increased from 16% to 19% ($p = 0.07$). Only 6% of the children had present headache at both 6 and 12 years of age. Between 6 and 12 years of age, more children began to suffer from headache than remitted (12% versus 9%) (Table 1/I). The prevalence of previous headache (i.e. headache before the preceding 6 months) increased from 19% at 6 years of age to 31% at 12 years of age ($p < 0.001$). The difference in the increase between boys and girls was not statistically significant.

The increase in the prevalence of present headache between 6 and 12 years of age was significantly greater in children whose mothers reported frequent headache (OR 1.7) than in children whose mothers were headache-free. The difference was significant for boys (OR 2.5) but not for girls (Table 2/I). There were no significant differences for boys or girls whose fathers reported frequent headache at the child's age of 12.

A change in the prevalence of headache in children was not significantly associated with the mother's or father's frequent prepregnancy headache, siblings' frequent headache in the 12-years questionnaire, maternal age, parental occupation, nature of residential location, change in family structure or the child's chronic illness.

Table 3/I shows that the strongest associative factor with present headache in children was the occurrence of headache in the mother when the child was at 12 years old. Frequent headache in the father and siblings and any long-term illness in the child at 6 or 12 years of age, or both, were also significantly associated with present headache in the children.

At age 12, no significant association was found between gender of the child, father's frequent headache before pregnancy, place of residence, parental occupation, maternal age or change in family structure and present headache.

5.1.2. Change in the prevalence of pubertal headache (II)

The changes in the prevalence rates can be seen in the figure 2/II. From age 11 to 14, the prevalence of monthly headache (the categories were 1: every day or almost every day, 2: more often than once a week, but not every day, 3: approximately once a week, category 4: once a month) increased from 59% (2263/3966) to 65% (3015/4710) (COR 1.4, 95%CI 1.3-1.5), whereas from age 14 to 17 it decreased to 63% (2649/4159) (COR 0.9, 95%CI 0.8-1.0) (Figure 2/II).

In boys, the prevalence rate increased from 59% to 62% (COR 1.2, 95%CI 1.1-1.4) from age 11 to 14 and after that it decreased to 52% (COR 0.6, 95%CI 0.5-0.7). In girls, the prevalence increased from 60% at age 11 to 68% at age 14 (COR 1.6, 95%CI 1.4-1.8). This increase was slightly higher than that observed between 14 and 17 years of age (from 68% to 74%) (COR 1.2, 95%CI 1.1-1.4) (Figure 2/II).

In girls, the prevalence rate of monthly headache (category 4) at age of 11 decreased from 35% to 32% at age of 14, increasing again to 37% at age of 17. The rate of weekly headache (category 3) in girls was 16% at age of 11, 25% at age of 14 and 25% at age of 17. Such changes were not found in boys (at least once a month headache rates 39%, 38%, 36% and weekly headache 13%, 18%, 13% respectively) (Figure 3/II).

5.2. Incidence of frequent headache in adolescent twins

Incidence of frequent headache between 11 and 14 years of age and between 14 and 17 years of age (II)

At age of 11, 680 of 1919 girls and 747 of 2068 boys had no or only infrequent (i.e. less than once a month or not at all) headache. At age of 14, after a 3-years follow-up, a total of 47% (320/680) of girls and 44% (328/747) of boys reported monthly headache. A total of 327 out of 1919 girls and 360 out of 2068 boys reported that they had no or only infrequent headache at ages of 11 and 14. At age of 17, 44% (143/327) of the girls and 30% (108/360) of the boys suffered from monthly headache.

Among the girls, the incidence rates of at least once a month headache increased from 26% at age of 14 to 28% at age of 17, while among the boys these rates decreased from 32% at age 14 to 22% at age of 17. Such changes were found neither among the girls nor the boys in the other headache frequency categories (Table 1/II).

No significant differences were found between two twin groups (Table 2/II).

The psychological factors associated with the incidence of frequent headache between the ages of 11 and 14 (IV)

At age 11, a total of 1417 children had no or infrequent headache (less than once a month). At follow-up, 646 of them reported at least monthly headache, i.e. represent incident cases. In the parental ratings the following factors assessed at age 11 predicted the incidence of monthly headache at age 14: externalizing problem behaviors, constructiveness and poor compliance. In teacher's ratings at age 11, the only significant predictor for headache was externalizing problem behaviors (Table 2/IV).

When the interaction between gender and psychological factors in association with incidence of monthly headache was analyzed, the association with adaptive behaviors among the girls was statistically significantly higher than among the boys. For girls, the association was statistically significant (OR=1.21), but for boys no significant association was found.

5.3. Headache types in childhood (III)

5.3.1 Change in headache types

When the same children were followed from 6 years of age to age of 13 in a nested case control setting, the headache type remained unchanged in 28 children (53%) whose headache had been classified as migraine at age of six. In 17/53 children (32%) migraine had turned into tension-type. Of the 53 children, 5 (15%) had become totally headache-free. Of the children with TTH (n=37) at age 6, thirteen (35%) still had it, 14 (38%) the headache type had changed into migraine, and 10 (27%) were headache-free at age 13. In the control group 5 (5%) children had begun to suffer from migraine and 7 (8%) from TTH. (Table 1/III).

At the age of 13, 47 children (56%) had migraine and 37 (44%) TTH. Migraine occurred in 26 children (31%) without aura and in 6 (7%) with aura, and 16 (19%) had migrainous disorder not completely fulfilling the IHS criteria. Episodes of TTH occurred in 21 children (25%) and 15 children (18%) had TTH not completely fulfilling the IHS criteria.

5.3.2 Characteristics of headache

Present headache was reported by 72 index children at ages of 6 and 13 years. Figure 2/III shows the changes in the location of the child's headache pain. Among 6-year-old children the most common location of headache was the forehead bilaterally above the eyes (Aromaa et al 1998a), whereas among 13-year-olds it was bilaterally on the temples. Figure 3/III shows the courses of headache episodes with increasing and decreasing intensity of pain at the ages of 6 and 13 years.

The changes in the characteristics of headache are shown in table 2/III. Headache characterized as "occasionally aggravating" at the age of 6 was reported more often as "gnawing" at age 13 years. At age 13 symptoms concurrent with headache (Figure 4) such as odorphobia, dizziness and balance disturbances were more common than at age 6, whereas restlessness, flush and abdominal symptoms reported more often at the age 6. Feeling of hunger and sensation of cold air as headache triggers (Figure 5) were more typical, whereas worries, fears, and anxiety were significantly less important among 13-year-old children than 6-year olds. Coughing increased the headache pain intensity significantly more often and physical exercise less often at the age of 13 than at the age of 6 years (Table 2/III). Headache frequency, intensity or duration did not change significantly during follow-up. No statistically significant differences were seen in aura symptoms or the predominant time of headache onset between the ages of 6 and 13 years.

During the follow-up the number of children using headache medication did not show any statistically significantly change. The most commonly used medication at the age of 13 years was ibuprofen (61%). The other medications used were paratacetamol (30%), salisylic acid (2%), naproxen (2%), ketoprofen (2%) and dexibuprofen (2%).

One percent of the 6-year-old children did not use any headache medication at the age of 13 years.

Figure 4. Change in the concurrent symptoms of headache in children

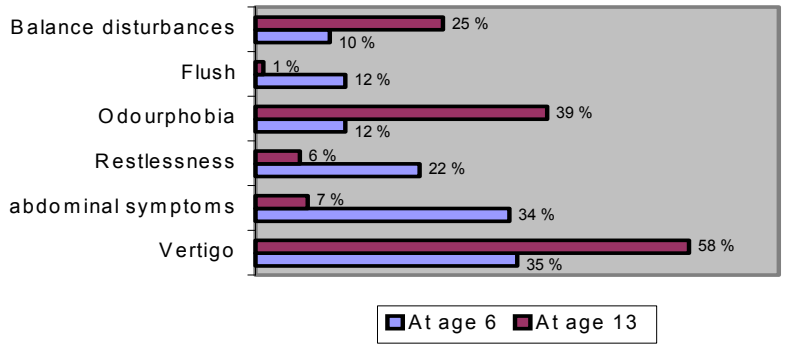
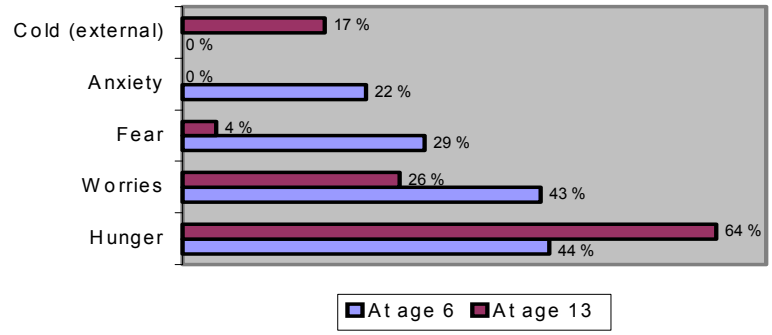


Figure 5. Change in triggers of headache in children



Changes in the characteristics of migraine and tension-type headache

After classification into different headache types, 28 children had migraine and 13 children had TTH at both ages of 6 and 13 years. Both in the migraine and TTH groups, headache pain in the temples was reported more often at the age of 13 than at the age of 6 years (Table 3/III). Odorphobia was the only concurrent symptom more typical at the age of 13 than at the age of 6 in both migraine and TTH. During follow-up, the feeling of hunger and external cold stimuli became more important as triggers of migraine, whereas fears and anxiety became less important. Other concurrent pain, flushing and abdominal symptoms were less typical among children with migraine at puberty than at preschool age. In the TTH group, no such changes were found.

Coughing and nose blowing were typical pain worsening factors in migraine sufferers at age 13, whereas no changes were found in the pain aggravators of the TTH group.

Changes in determinants of the occurrence of headache

Children suffering from headache at age 13 years had statistically significantly more often some other co-occurring long-term disease, especially allergy (p=0.028, OR 2.6, 95%CI=1.0-7.2). They also had severe head injuries (i.e. commotio or contusio cerebri) (p=0.018, OR 3.5, 95%CI=1.1-14.6) more often than children with headache at age 6. The control children showed no such changes (p=0.317, OR 0.7, 95%CI=0.3-1.6 and p=0.818, OR 0.9, 95% CI=0.3-2.5, respectively).

5.4. Emotional and behavioral factors associated with adolescent headache

5.4.1. Factors associated with frequent headache (IV)

In the parental ratings of MPNI at the children's age of 11, the scores from all three psychological main scales (Externalizing and Internalizing Problem Behaviors, Adaptive Behaviors) and from the subscales of Inattention, Constructiveness, Social Activity and Depression were significantly associated with the child's headache frequency. In the teacher ratings of MPNI, the scores for externalizing problem behaviors, especially inattention were found to be associated with headache frequency (Table 6). At age of 14, only the teacher ratings of MPNI were obtained. The results were similar as those obtained three years earlier with a significant association between child's headache frequency and externalizing problem behaviors and inattention.

Differences between boys and girls in the associations of psychological factors with headache frequency at the age of 14 were analyzed by testing interaction terms of gender and psychological factors in the logistic models. The only significant interactions found were with aggression (p=0.043) and depression (p=0.048). However, in a separate analysis for the genders, the association of aggression and the headache frequency was insignificant for both girls and boys. Among boys, the association of depression and the headache frequency was significant (COR=1.15, 95% CI 1.00.-1.32), but not in girls.

5.4.2 Psychological factors in headache discordant twin pairs (IV)

Twin pairs discordant for headache (pairs being either MZ or same-sexed DZ) were defined as pairs in which one twin suffered from headache at least once a month and the co-twin suffered less often, or not at all (668 pairs i.e.. 34% of total sample at age of 11 and 778 pairs i.e. 33% of total sample at age of 14). In parental ratings, headache-discordant pairs showed associations between externalizing and internalizing problem behaviors, adaptive behaviors, inattention, constructiveness and social activity at the age of 11 and monthly headache at age of 14. In teacher ratings, however, no statistically significant associations were found at either age group (Table 3/IV).

The number of headache-discordant MZ twin pairs was 168 at age 11 and 194 at age 14. Among headache-discordant MZ pairs at age 11, only parent-rated externalizing problem behaviors scores were associated with monthly headache (OR= 1.77, 95% CI 1.03-3.02). According to parental MPNI, aggression at age 11 was associated with monthly headache at age 14 (OR=1.75, 95%CI 1.04-2.95). Comparison of gender-matched discordant DZ twin pairs (220 pairs at age of 11, 258 pairs at age of 14) revealed no statistically significant associations.

The differences of MZ and DZ twins in the strength of the associations of headache frequency and psychological factors were analyzed by testing interaction terms of twin type with psychological factors into the conditional logistic models. With aggression the interaction was statistically significant at age 14 ($p=0.02$). Significant interactions were found also in the associations of teacher-rated depression and social anxiety at age 11 and monthly headache at age 14 ($p=0.039$ and $p=0.019$). When MZ and DZ twin pairs were analyzed separately, none of the associations between these variables was statistically significant.

Table 6. The associations between psychological factors at age 11 and headache frequency at ages 11 and 14 in gender-adjusted multivariate cumulative logistic regression analysis (n= 3513).

Psychological factor	Headache at age 11				Headache at age 14	
	Parental Rating at age 11		Teacher Rating at age 11		Teacher Rating at age 14	
	COR	95%CI	COR	95%CI	COR	95%CI
Externalizing problem behaviors	1.19	1.10-1.28**	1.22	1.12-1.32**	1.22	1.12-1.33**
Inattention	1.13	1.03-1.23*	1.15	1.03-1.29**	1.29	1.14-1.45**
Adaptive behaviors	1.09	1.01-1.17*				
Constructiveness	1.10	1.01-1.20*				
Social Activity	1.08	1.00-1.17*				
Internalizing problem behaviors	1.08	1.01-1.15*				
Depression	1.15	1.06-1.24**				

*p<0.05, **p<0.001

6. DISCUSSION

6.1 Study design

Study population

The present results are based on two prospectively followed child populations: firstly a stratified cluster sample of young Finnish families with 6-year-old children and secondly a cohort of Finnish 11-year-old twins.

The original study population of the Finnish Family Competence Study (FFC) was highly representative of the population of the region overall, with no significant selection bias in distribution (Rautava and Sillanpää 1989). The participation rate was good throughout the study cohort. The drop-outs reported more health problems than participants. This may have lead to underestimation of later headache prevalence (Merlijn et 2003).

Twins are found to be representative of singleton populations. In the FinnTwin12 data, the twins have been shown not to differ from their circa 25000 classmates in means or variances on the behavioral scales of the MPNI (Pulkkinen et al 2003). Other studies (Kendler et al 1993; Kendler et al 1995) show that for instance level and variability of psychiatric symptoms reported by twins are similar to those found among non-twin populations. This is in line with our study. In contrast, when behavioral problems were compared between twins and children from general population in Norway, the levels of attention problems and externalizing behavior were similar, whereas an increase in the variance of externalizing behavior was found for twins (Gjone and Novik 1995).

Methods

Three original publications of this thesis focused on the determinants of change in the prevalence and incidence of headache in a prospective follow-up study design. Many previous studies have evaluated the factors associated with childhood and adolescence headache mainly by cross-sectional study methods.

In the clinical part of the headache study of FFC (Finnish Family Competence Study), headache sufferers i.e. the cases were carefully interviewed and clinically examined to obtain information on the characteristics of headache. Their headache was then classified according to the criteria used. Therefore, the researchers were not blinded to the case/control status, which may have limited the generalizability of the results. To maintain comparability, the same version (1988) of the IHS classification was used at both ages of 6 and 13 years. This may have caused some underestimation of migraine diagnoses (Winner et al 1995).

Because the children were clinically examined by two different doctors, the interexaminer reliability test was done in seven children, who were examined by both doctors. The variables used in the present study were derived from the specific characteristics of headache and the clinical examination. They were modified as categorical questions with the options “yes” or “no” in an attempt to minimize

differences in the interpretations of the two examiners. Because standardized questions were used in the questionnaire, interexaminer reliability can be considered very good.

One of the aims of this work was to investigate associations between psychological factors and headache occurrence in childhood and that is why the FinnTwin12 study frame with its validated behavioural scales of MPNI for both parents and teachers was used to provide more information compared with Achenbach's Child Behavior Checklist (CBCL) (Achenbach 1991). The CBCL has been widely used instrument in studies examining the associations between headache and its psychopathology (Andrasik et al 1988, Just et al 2003). As compared with the CBCL, the MPNI has some strengths. It covers not only the behavioral and emotional problems included in the CBCL, but also both active and passive adjusted behavior. Pulkkinen et al (1999) show the reliability and both concurrent and discriminative validity of the multidimensional inventory developed for peer nomination, as well as for teacher and parental assessment.

6.2 Results

The prevalence of monthly headache increased from age 11 up to age 14, especially among girls. Frequent headache in the mother was significantly associated with the increase in the prevalence of headache in boys during the first six school years. The incidence rates of monthly headache were more stable among girls than among boys. The incidence of headache increased in the girls suffering from at least once a month headache between ages of 14 and 17. The likelihood of migraine at puberty was practically equal among children presenting with tension-type headache or migraine at 6 years of age. Age was also linked to considerable changes in pain localization, concurrent symptoms and triggers. Headache frequency among 11- and 14-year-old twins was associated with psychological problem behaviors and adaptive behaviors.

Prevalence of headache in childhood and adolescence

Frequent headache was more common during prepuberty than after that. Other studies have found equal results; headache prevalence increases throughout childhood with female predominance after age of 13 years (Bille 1997, Aromaa et al 2000, Bandell-Hoekstra et al 2001, Fearon and Hoptopf 2001, Fichtel and Larsson 2002, Boardman et al 2003, Russell et al 2006) conforming our results.

Variation in the occurrence of headache was high during childhood years. Six per cent of the children had permanent headache. Some began to suffer from headache and others remitted. Childhood headache is characterized by periods of remission and improvement (Bille 1997, Larsson and Sund 2005, Wang et al 2005, Laurell et al 2006). According to a clinical study in 12-26-year-old adolescents (Guidetti et al 1998), headache was relieved in 45% of the children while 35% were headache-free. After an 8-year follow-up, the situation remained unchanged in 15%. In a three year follow-up of 13-16-year-old adolescents, Laimi et al (2006) found that half of the adolescents with monthly headache improved or remitted. These results are in agreement with the results of the present study. The change in the prevalence of

present headache was small. This may be due to the strictness of the definition used ("headache disturbing daily activities"), originating from our aim to find the cases in which headache affects quality of life.

The prevalence of headache was higher among the boys whose mothers suffered from frequent headache than among those whose mothers were headache-free. Many population-based studies have investigated whether children are at an increased risk of having pain if their parents have pain. A family history of migraine has been found to be strongly associated with an increased risk of migraine in both genders and in all age groups (Stang et al 1996). Multiple pains in the first-degree relatives and migraine in 7-17-year-old children have also been found (Laurell et al 2005). Saunders et al (2007) found that the presence of multiple pains in the mother predicted the presence of multiple pains in children aged 11 to 17 years. There are several explanations why pain in parents might be associated with pain in children: genetics (Honkasalo et al 1995, Larsson et al 1995, Gervil et al 1999), model learning (Turkat et al 1984, Osborne et al 1989) and environmental factors, such as marital conflict (Troxel and Matthews 2004) or low socioeconomic status (Hotopf et al 1998, Sillanpää and Aro 2000, Anttila et al 2002, Groholt et al 2003).

The incidence of headache in adolescence

The changing nature of childhood headache induces problems in calculating and estimating its incidence, as childhood headache may remit for several years and then reoccur. In the present study, some adolescents may have had frequent headache before the baseline stage of the study, which is of importance in interpreting the results. If those adolescents with infrequent (i.e. no or less than once a month) headache had not been included, the incidence values would have been underestimated.

The results of this study showed higher incidence rates of headache (at least once a month) for 11- 14-year-olds as compared with the results of Larsson and Sund (2005) on the incidence of troublesome and frequent headache (a least once a week) in 12-14-year-olds. The lower incidence rates reported for children aged 12-14 years may be due to the inclusion of severe cases only. The study of Larsson and Sund (2005) is prospective and shows a 2-fold incidence of headache for adolescent girls as compared with boys, with an increasing trend with age. Their finding is in accordance with increasing incidence rates of frequent headache from age 11 to 14 years in girls found in this study. This gender difference is likely to be associated with pubertal development and sex hormones.

The previous studies (Stang et al 1992, Rozen et al 1999, Anttila et al 2006) focusing on the incidence of headache, mainly migraine differ methodologically from the present study. These studies have examined the changes in the prevalence and incidence of childhood headache among different child-populations. Stang et al (1992) reported the highest incidences of migraine for 10-14-year-old boys and for 20-24-year-old women. Rozen et al (1999) found that the incidence of migraine increased in both girls and boys over 11 years. The increased incidence rates of childhood headache

shown in these studies may have underlying etiological factors different from those found in this thesis.

Change in outcome and headache types

In the present study, migraine seemed to have poorer outcome than other types of headache. In a population-based study focusing on migraine (Sillanpää 1983b), migraine ceased in 22% of the children between ages 7 and 14 and remained unchanged or became worse in 41% of children. These results are in agreement with the results of present study. In contrast, when Swedish children aged from 7 to 15 were followed for three years, migraine and TTH remitted almost equally; migraine 21% and TTH 23% (Laurell et al 2006) and according to a Finnish study in children aged 13 to 16 TTH remitted in 47% and migraine in 52% of the headache children during puberty (Laimi et al 2006). One possible explanation for this changing pattern of childhood headache is the ”continuum severity theory”, which considers primary headache a continuum between tension-type headache and migraine. In this model, mild headache is labeled as tension-type, severe headache as common migraine, and headache associated with neurological symptoms as classic migraine (Silberstein 1992). Another explanation may be that many children may suffer from two or three different types of headache, and different types may be mixed. Although many studies have been carried out, there is still doubt about whether the criteria used for the diagnosis of the different types of childhood headache are appropriate (Metsähonkala 1999).

Change in the characteristics of headache

Headache pain, which was most commonly located in the forehead above the eyes at preschool age, migrated to the temples at the age of 13, and this change was typical of both migraine and TTH. The unilaterality of headache pain is considered to be one of the features that differentiates migrainous from non migrainous headache in adolescents (Zambrino et al 2000). Some studies (Wöber-Bingöl et al 1995, Maytal et al 1997, Gherpelli et al 1998, Winner et al 2003;) on the sensitivity and specificity of the diagnostic criteria of the International Headache Society for childhood headache (1988) only address criteria such as uni- or bilaterality, without analyzing the specific location of headache pain. Turkogan et al (2006) found that in adolescents aged 10 to 17 years, bilateral frontal-temporal pain was the most common location for both migraine and TTH, whereas unilateral frontal/retro-orbital pain was more common in migraine than in TTH. These results are not in line with our findings, probably due to older age groups studied.

Flushing and abdominal symptoms were more common at preschool age, especially among children suffering from migraine, whereas headache with concurrent neurological symptoms, such as dizziness and balance disturbances, was more typical of adolescents. Neurological symptoms co-occurring with migraine are common in adults (Neuhauser et al 2001) and in children (Abu-Arafeh and Russell 1995) supporting the present thesis. Over a half of the children aged 6-12 years with migraine reported vertigo during a migraine attack (Abu-Arafeh and Russell 1995). Parker

(1997) suggested that migraine in children can be associated with neurological disturbances like vertigo, seizures and movement disorders as part of the so-called "migraine variant". Flushing and abdominal pains are associated with the autonomic nervous system, which role in the pathophysiology of migraine has been investigated in several previous studies (Havanka-Kanniainen et al 1986, Appel et al 1992, Shechter et al 2002). Migraine may be associated with a neurotransmitter imbalance in the brain stem nuclei, whereas dysfunction of the peripheral autonomic nervous system with a decrease of sympathetic activity may be attributed to chronic tension-type headache (Sliwka et al 2001).

Emotional and behavioral factors associated with adolescents headache

Psychological factors such as stress, pressures and fear were found to be common triggers of headache in children (Lewis et al 1996) and in adults (Nadaoka et al 1997). Similarily in this study migraine was triggered by strong emotions such as stress and fear less often in puberty than in preschool age.

Externalizing problem behaviors are not only associated with frequent headache in adolescents, but also seem to have a significant role in the incidence of frequent headache among adolescents. Quite a few studies have shown associations between childhood headache and externalizing problem behaviors. Sillanpää et al (1991) found that behavioral problems were significantly more common in 5-year-old children with headache than in others. In addition, concentration difficulties have been shown to be associated with the occurrence of headache in preschool age (Aromaa et al 1998a). In a Norwegian follow-up study (Borge et al 1994), a significant association was found between behavioral problems at the age of four and complaints of headache and abdominal pain at the age of ten. Crawford et al (1994) found that symptoms of attention deficit hyperactivity disorder were associated with migraine headache. These results, althought obtained in younger children, are in consonance with our results.

Somatic complaints, such as frequent headache, may be used by children as a way to express negative emotions when depression or another emotional disorder occurs (Masi et al 2000). In the present study, frequent headache was significantly associated with internalizing problem behaviors, including depression. The same scale has not been applied in other studies, but studies on anxiety have shown an associated with frequent headache (Smith et al 1999), but not with migraine (Cooper et al 1987).

The results of this thesis suggest that social activity, constructiveness and lack of compliance are associated with frequent headache in adolescents. This is in agreement with previous studies. It appears that children with both headache and adjustment problems have difficulties with their social behavior; which manifest as poor concentration, problems in social relationships and everyday stress (Carlsson 1996a, Carlsson et al 1996b). In accord with this Metsähonkala et al (1998) found that children both with migraine and with non-migrainous headache reported more problems in getting along with other children than children without headache.

In children with frequent headache, the behavioral problems were rated differently by the teachers and the parents. In the teachers-ratings, headache was associated with only externalizing problem behaviors, and in the parental-ratings, also with internalizing problem behaviors. One explanation may be that teachers do not recognize covert symptoms such as anxiety and depression, as they spend only a part of the day with the children. Perhaps these emotions are not expressed to the same extent in the class setting as at home. According to Molins and Clopton (2002) teachers generally identify externalizing problems and boys with problems more easily than internalizing problems and girls with problems.

There are no twin studies addressing the nature of the intermediating effects of frequent headache and psychological factors. Because both headache and personality characteristics have a substantial genetic component and individual genes associated with both phenotypes have been identified, common genes could underlie in both conditions. Nonetheless, we found that externalizing problem behaviors were associated with headache even within headache-discordant MZ co-twins, with a weaker, nonsignificant association within discordant DZ pairs. However, our results indicate that relationships between frequent headache and behavioral problems are not fully explained by genes.

6.3 Recommendations for future studies

The course of headache has a changing pattern during childhood and adolescence. In the future, more attention should be paid to studying familial and psychological factors as determinants and risk factors of the changes in the prevalence and incidence of headache. This would contribute to a better understanding of the etiological factors of childhood and adolescence headache

Few longitudinal studies focus on the prognosis of childhood headache. Prospective twin follow-up studies may be helpful in establishing the associations between behavioral problems and headache, as well as the role of genetical or environmental factors as predictors of adulthood headache.

7. CONCLUSIONS

In the studies included in this dissertation, the following conclusions were demonstrated:

1. Considerable changes occur in the prevalence of headache during childhood and adolescence. It is important to pay attention also to parental headache, especially in boys suffering from frequent headache.
2. Headache at least once a month is more common in girls than boys during puberty. The incidence rates of headache are lower in boys than in girls during puberty. The incidence rates of frequent headache increase in girls between ages of 14 and 17.
3. Migraine at puberty appears to be predicted by prepubertal headache, irrespective of whether it is migraine or tension-type headache. Puberty brings along many important changes in concurrent symptoms, pain localization and triggers of headache.
4. The frequency of adolescents' headache is associated with psychological factors, especially externalizing problem behaviors. This seems to be independent of genetic or familial effects on behavior and headache.

Whether the relationship between frequent maternal headache and childhood headache is genetic or environmental, remains still unclear. In a child with frequent headache externalizing problem behaviors may be a sign of worsening of headache or vice versa; behavioral problems may aggravate headache via the implication of outside stressors.

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APPENDICES

Appendix 1

Mother's and father's questionnaires at pregnancy and at age of 12
Familial occurrence of headache:

How often did you have the following symptoms before pregnancy?

	At least 1/week	At least 1/month	Less often	Hardly ever
Migraine	1	2	3	4
Headache	1	2	3	4
Aching joints	1	2	3	4
Pain in wrists, elbows or shoulder joints	1	2	3	4
Back pain, back ache	1	2	3	4
Swelling in legs or feet	1	2	3	4
Skin disorders	1	2	3	4
Constipation	1	2	3	4
Sleeplessness	1	2	3	4
Distress	1	2	3	4
Depression	1	2	3	4
Nervousness	1	2	3	4
Abdominal pain	1	2	3	4

Siblings' headache occurrence (questionnaire at age of 12)

Have any of the siblings of your child ever had headache disturbing his/her daily activities?
1 no
2 yes
3 no siblings

			Headache	
	girl	boy	last 6 months	previous
sibling is born 19__	1	2	1	2
sibling is born 19__	1	2	1	2
sibling is born 19__	1	2	1	2

Mother's and father's questionnaires at ages of 3, 7 and 12
Sociodemographic variables:

Do you live in?
- A city or town 1
- A rural population center 2
- The countryside 3

Your occupation is: (field and duties)_____

Psychosocial variables:

Adults living with the child now are his/her

- child's biological parents	1
- biologic mother	2
- biologic mother and step-father	3
- biological father	4
- biologic father and step-mother	5
- adoptive parents	6
- fosterparents	7
-other,who_____	8

How many times has your family moved since your child's birth?

_____

Child health variable

Has your child had any long-term illness (lasting over 6 months)?

No	1
Yes, what_____	2

Clinical interview and examination of the children at age of 13 Appendix 2

Child's name:_____ ID:_____
Basic illness of the child:_____

Questions about headache

1. Onset age of headache____years

2. Frequency of headache

Headache has occurred during the last 6 months
-Daily 1
-At least once a week 2
- At least once a month 3
- Less than the above 4

3. Occurrence of headache among relatives

	No	Yes
- Siblings	1	2
- Mother	1	2
- Father	1	2
- Mother's parents	1	2
- Father's parents	1	2
- Mother's siblings	1	2
- Father's siblings	1	2

4. Time of the day

Headache usually occurs in
- Mornings 1
- Afternoons 2
- Evenings 3
- Nights 4

5. Pain localization

Headache is localized	No	Yes
- Unilaterally	1	2
- Bilaterally	1	2
- Occipitally	1	2
- Frontally	1	2
- Above eyes	1	2
- In the temples	1	2
- All over the head	1	2

6. Onset of the attack

How does the attack begin?

	No	Yes
- Unexpectedly	1	2
- Steadily worsening	1	2

7. Preceding symptoms

	No	Yes
- Visual disturbances	1	2
- Nausea	1	2
- Vomiting	1	2
- Restlessness	1	2
- Others, which_____	1	2

Duration_____min

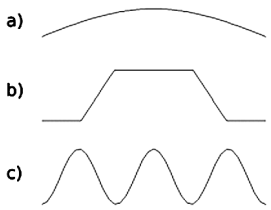
8. Headache duration

The attack lasts_____
(minutes, hours, days)

9. Pain characteristics

How does the child describe the pain?	No	Yes
- Constant	1	2
- Occasionally aggravating	1	2
- Gnawing	1	2
- Pulsating	1	2
- Beating	1	2
- Tearing	1	2
- Drilling	1	2
- Pressing	1	2

10. The course of pain



11. Other symptoms concurrent with headache

	No	Yes
- Photophobia	1	2
- Phonophobia	1	2
- Odorphobia	1	2
- Nausea	1	2
- Vomiting	1	2
- Visual disturbances	1	2
- Shivering	1	2
- Sweating	1	2
- Numbness	1	2
- Dizziness	1	2
- Tiredness, yawning	1	2
- Other current pain	1	2
- Fainting	1	2
- Staring/absence	1	2
- Confusion	1	2
- Restlessness	1	2
- Tinnitus	1	2
- Hemiparesis	1	2
- Balance disturbances	1	2
- Speech disturbances	1	2
- Flush, flushing	1	2
- Fever	1	2
- Nasal congestion	1	2
- Abdominal symptoms	1	2
- Pallor	1	2

12. Headache aggravating factors

	No	Yes
- Coughing	1	2
- Nose blowing	1	2
- Physical exercise	1	2

13. Headache relieving factors

	No	Yes
- Resting, sleeping	1	2
- Dimming of lights	1	2
- Vomiting	1	2
- Eating	1	2
- Medication	1	2

14. Headache triggers

Does any of the following factors trigger the child's headache?	No	Yes
- Tension	1	2
- Worries	1	2
- Fear	1	2
- Anxiety	1	2
- Tiredness	1	2
- Hunger	1	2
- Concurrent illness	1	2
- Chocolate	1	2
- Citrus fruits	1	2
- Cheese	1	2
- Excessive sunlight	1	2
- Heat of the sauna	1	2
- Carbonated drinks	1	2
- Watching TV	1	2
- Cold (external)	1	2
- Cold (internal)	1	2
- Others, what	1	2

_____

15. Clinic appointments

	No	Yes
Has a physician ever examined your child because of headache?	1	2
If so, how many times?____		
Has your child been diagnosed with migraine by a doctor?	1	2
If not, what was the diagnosis? _____		

16. Medication

	No	Yes
Does the child get any medication for headache?	1	2
If yes, what medication(s): _____		
Amount (mg):_____		
Times/day:_____		
How often:_____		

17. The impact of headache

	No	Slightly	Moderately	Markedly
Does the pain disturb your child's normal life?	0	1	2	3
Has your child been absent from school because of headache?	0	1	2	3
Does the headache disturb your family's normal life?	0	1	2	3
Does your child get more attention from the family because of his/her symptoms?	0	1	2	3
Does your child's headache make you:				
- Anguished	0	1	2	3
- Afraid	0	1	2	3
- Tense	0	1	2	3
- Sleepless	0	1	2	3
- Nervous	0	1	2	3
- Excessively worried	0	1	2	3

18. How many days a year does your child have headache?

_____

19. How many times in the last 6 months has your child had headache?

_____

20. Other symptoms

Does your child suffer from:	No	Yes
- Travel sickness	1	2
- Temper tantrums	1	2
- Fainting	1	2

21.

	No	Yes
Has your child ever had severe head injury?	1	2

If the answer is yes, please specify_____

22. Headache diagnosis: _____

Criteria for the diagnosis: _____

Pain related questions	No	Slightly	Moderately	Markedly
In the parents' opinion, is the child sensitive to pain?	0	1	2	3
Is the child afraid of going to the doctor's?	0	1	2	3
Is the child tense while being examined by a doctor?	0	1	2	3
Does the child cry when a blood sample is taken from him/her, or while being vaccinated?	0	1	2	3
Does the mother think that she is sensitive to pain?	0	1	2	3
Does the mother have menstrual pain?	0	1	2	3
Is the father sensitive to pain?	0	1	2	3
Are the child's siblings sensitive to pain?	0	1	2	3

	No	Yes
Does the fear of being hurt prevent the child from participating in physical games?	1	2
In the parents' opinion, do they prevent the child from playing physical games because they fear that the child might be hurt?	1	2
Does the child fear his/her headache attacks?	1	2

So far, has your child had:	At least once/week	At least once/month	Rarely	Hardly ever
- Abdominal pain	0	1	2	3
- Growing pains	0	1	2	3
- Other than growing limb pains	0	1	2	3
- Toothache	0	1	2	3
- Back pain	0	1	2	3
- Other pains_____	0	1	2	3

Does your child's pain make you:

	No	Slightly	Moderately	Markedly
- Anguished	0	1	2	3
- Afraid	0	1	2	3
- Tense	0	1	2	3
- Sleepless	0	1	2	3
- Nervous	0	1	2	3
- Excessively worried	0	1	2	3

Intensity of pain (VAS, 10 cm)

Headache: No pain Unbearable pain
|_____|

Abdominal pain: |_____|

Other pain: |_____|

Which_____

Your child's reaction in stressful situations:	No	Yes
- Turn to another person for support (e.g. parents)	1	2
- Aggressive behavior	1	2
- Helplessness, crying	1	2
- Somatic symptoms (pain)	1	2
- Disturbed bowel functions (diarrhea/constipation)	1	2
- Eating problems	1	2
- Other what _____	1	2

Child's social life

Does your child have:	No	Yes
- Friends	1	2
- A very close friend	1	2
- Close people outside the family	1	2
- Ordinary hobbies	1	2
- Any club activity	1	2

How many h/day____ How many times/week_____

Child at school

How many times has your child changed school during his/her lifetime?

_____

	No	Yes
Is your child's headache more frequent during schooldays than holidays?	1	2
Is your child's teacher aware of your child's headache symptoms?	1	2
Is the school-nurse aware of your child's headache symptoms?	1	2
If yes, has she/he been informed by the child___ or By the parents____?	1	2
Do they react at school to your child's headache symptoms?	1	2
How_____		
Are there any kind of problems because of headache symptoms?	1	2
What kind of problems?_____		
If there are problems, are they addressed in any way?	1	2
How_____		

Does your child's headache disturb his/her schoolwork?

Not at all |_____| Very much

Does your child's headache disturb:

his/her concentration

Not at all |_____| Very much

homework

Not at all |_____| Very much

meeting friends

Not at all |_____| Very much

Upbringing	No	Nearly always	Always
Do the parents mainly agree on the child's upbringing?	0	1	2
How does the respondent parent behave when the child has a temper tantrum?	Almost never	Occasion-ally	Nearly always
She/he:			
- Talks to the child	0	1	2
- Raises his/her voice	0	1	2
- Punishes the child physically	0	1	2
- Lets the child calm down by himself/herself	0	1	2
- Does something else, what	0	1	2

In the family	Almost Never	Now and then	Nearly always
Conflicts in the family are solved by			
- Open arguments	0	1	2
- Sulking	0	1	2
- Denying problems	0	1	2
Between siblings, are there any			
- Quarrels	0	1	2
- Jealousness	0	1	2
- Indifference	0	1	2

	No	Yes
Is the family in financial difficulties?	1	2
Is any family member currently unemployed?	1	2

The family is	Happy	1	2	3	4	5	Unhappy
The relationships between parents are	Close	1	2	3	4	5	Distant

Child's eating habits

	No	Yes
Does your child have regular eating hours?	1	2
Is a hot meal cooked during working days?	1	2

Sleeping

	No	Yes
Does your child have regular sleeping hours?	1	2
When sleeping, does the child		
- Talk	1	2
- Grind his/her teeth	1	2
- Snore	1	2

How many hours does she/he sleep daily?_____

Outdoor activities

How many hours, on average, does she/he spend outdoors during the day?

_____

SOMATIC EXAMINATION

		Normal	Abnormal
1	Weight/height____kg/____cm	1	2
2	Cardiac auscultation	1	2
3	Arterial auscultation	1	2
4	Pulmonary auscultation	1	2
5	Blood pressure_____/_____mmHg	1	2
6	Palpation of abdomen	1	2
7	Skin	1	2
8	Maxillary and frontal sinuses	1	2
9	Mouth and throat	1	2
10	Teeth	1	2
	Malocclusion_____		
11	Temporomandibular joint at palpation	1	2
12	Reflexes		
	- biceps	1	2
	- brachioradialis	1	2
	- achilles	1	2
	- patellae	1	2
	- babinski	1	2
13	Coordination		
	- fingertip to nose	1	2
	- diadochokinesia	1	2
	- ball throwing test	1	2
14	Equilibrium		
	- Romberg	1	2
	- walking the line	1	2
	- one foot jump	1	2
15	Motor coordination		
	- toe-heel walk	1	2
	- squatting	1	2
	- fist clenching	1	2
	- finger opposition	1	2
16	Mimics	1	2
17	Brain nerve status	1	2
18	Eye movements	1	2
19	Pupillae	1	2
20	Papillae	1	2
21	Eyesight	1	2
	E-table: left___ right____		
22	Hearing	1	2
23	Tympanic membrane	1	2
24	Sensory		
	- face	1	2
	- extremities	1	2
25	Occipital insertions	1	2

26	Memory		
	- recent	1	2
	- longitudinal	1	2
27	Speech		
	- missing letters	1	2
	- other abnormalities	1	2
28	Ability to co-operate	1	2
	- if abnormal, how_____		
29	Understanding instructions	1	2
30	Child leaning on parents during examination	1	2
31	Auscultation of skull	1	2
32	Child's way of react in clinical examination:		
	concentrated |_____| not concentrated		
	quiet |_____| talkative		

Appendix 3

Parent's and Teacher's Rating Form (MPNI) for the questionnaires used at ages of 11 and 14.

DESCRIPTIONS OF BEHAVIOR
First, we ask to consider Child A and then Child B

1. Is a good leader and would be suitable to lead a class outing.
2. Is friendly to others.
3. Is sad and depressed.
4. Is restless and cannot stay put during class.
5. Is patient and calm.
6. Is easily hurt if others are mean to him/her.
7. Tries to act reasonably even in difficult situations.
8. Is unable to concentrate on anything.
9. Excludes people from the group by saying, for example, "We don't want to be with her/him."
10. Is shy in front of other students.
11. Acts before thinking.
12. Sorts things out through discussion
13. Teases other people and becomes violent for no reason.
14. Is lonely and has no friends.
15. Talks all the time.
16. Defends those weaker and smaller.
17. Does not listen to instructions.
18. Spreads rumors about other people's personal matters when he/she is mad at them.
19. Is scared by and nervous about new things and situations.
20. Is a student everyone can trust.
21. If he/she gets angry at someone, he/she might hit, push, kick, or throw something at him/her.
22. Is always together with people during breaks and after school.
23. Avoids difficult situations by doing something else.
24. Is often worried.
25. Teases smaller and weaker students.
26. Helps students who need it.
27. Scolds at people he/she is upset with.
28. Does not argues with other people.
29. Is too impatient to wait for his/her turn.
30. Is popular among his/her friends at school.
31. Runs about and climbs everywhere in spite of warnings.
32. Clings to adults or is too dependent.

33. Is disobedient at school.
34. Is conscientious with homework.
35. Gets teased and taunted a lot.
36. Is forgetful.
37. Is hyperactive.

Answer alternatives:
3 the characteristic in question fits the child very well, i.e. it is clearly observable in the child
2 the characteristic in question is definitely displayed in the child, but is not as prominent as above
1 the characteristic in question is sometimes displayed in the child, but is not consistent or strong
0 I have not observed the characteristic in question displayed at all in the child