Genetic and Environmental Influences on Expression of Recurrent Headache as a Function of the Reporting Age in Twins

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To explore age-related mechanisms in the expression of recurrent headache, we evaluated whether genetic and environmental influences are a function of the reporting age using questionnaire information that was gathered in 1973 for 15- to 47-year-old Swedish twins (n = 12,606 twin pairs). Liability to mixed headache (mild migraine and tension-type headache) was explained by non-additive genetic influences (49%) in men aged from 15 to 30 years and additive genetic plus shared environmental influences (28%) in men aged from 31 to 47 years. In women, the explained proportion of variance, which was mainly due to additive genetic effects, ranged from 61% in adolescent twins to 12% in twins aged from 41 to 47 years, whereas individual specific environmental variance was significantly lower in twins aged from 15 to 20 years than in twins aged from 21 to 30 years. Liability to migrainous headache (more severe migraine) was explained by non-additive genetic influences in men, 32% in young men and 45% in old men, while total phenotypic variance was significantly lower in young men than in old men. In women, the explained proportion of variance ranged from 91% in the youngest age group to 37% in the oldest age group, with major contributions from non-additive effects in young and old women (15–20 years and 41–47 years, respectively) and additive genetic effects in intermediate age groups (21–40 years). While total variance showed a positive age trend, genetic variance tended to be stable across age groups, whereas individual specific environmental variance was significantly lower in adolescent women as compared to older women.

Headache is a very common ailment in the general population (Rasmussen, 1995). Between 25% and 50% of the population suffers from recurrent primary headache with migraine and tension-type headache as two major disease entities (Rasmussen & Olesen, 1994). Migraine appears to be a more severe pain condition than tension-type headache (Rasmussen, 1995).

Results from twin studies suggest that genetic factors are of significant importance for recurrent headaches (Gervil et al., 1999a; Honkasalo et al., 1995; Larsson et al., 1995; Svensson et al., 1999; Ulrich et al., 1999a; Ziegler et al., 1998), and probably explain most twin resemblance (Albakri et al., 1995; Gervil et al., 1999b; Merikangas et al., 1994; Ulrich et al., 1999b) and clustering in other sets of relatives (Russell, 1997), whereas environmental influences mainly are attributed to individual specific experiences. The proportion of liability in migraine due to genetic factors (i.e., the heritability) has been found to be 50% in large-scale twin studies conducted in Finland and Sweden (Honkasalo et al., 1995; Larsson et al., 1995). A similar figure was obtained in a sample of volunteer ascertained twins reared apart and reared together (Ziegler et al., 1998), but higher heritability estimates (60%–65%) were obtained in a sample of pairwise ascertained Danish twins (Gervil et al., 1999a; Ulrich et al., 1999a). In a sample of prepubescent twins, the heritability for recurrent headaches was estimated at 70% and significant genetic effects were found for tension-type headache (Svensson et al., 1999). While several methodological differences exist between these twin studies such as time-period and reporting age under consideration, in all of the studies genetic and environmental influences were evaluated regardless of any age effects and reported estimates should be considered the average contribution of genes and environments across age groups. Thus, the extent by which genetic and environmental factors are necessary for the expression of recurrent headaches at different ages is unknown.

Age effects seem to play an important role in primary recurrent headache (Rasmussen & Olesen, 1994; Stewart et al., 1995). The one-year prevalence of migraine, especially in women, shows a conspicuous increase from puberty to mid-life (Stewart et al., 1992). In women above 45 years of age, the one-year prevalence fits a model of exponential decline (Mattsson, 2000). The one-year prevalence of tension-type headache is rather stable across adulthood but declines at older ages (Schwartz et al., 1998). Onset of migraine and tension-type headache varies from childhood to 45 years of age (Rasmussen, 1993), with the second decade of life as the most common onset ages. The outcome of childhood migraine ranges from permanently migraine-free in early adulthood, to migraine with

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migraine-free years, and migraine annually during a 40-year follow-up period (Bille, 1997).

When looking at age effects in twin data it may be of greater relevance to consider the absolute variance of genetic and environmental influences rather than the relative importance. The absolute level of genetic variance may be equal across age groups despite differences in the relative importance, or conversely, the absolute level of genetic variance may differ between age groups despite stability in the relative importance. In this paper, we reanalyze data on recently experienced ("during the past few years") recurrent headaches obtained from a large sample of 15- to 47-year-old Swedish twins and address the question whether genetic and environmental influences differ between age groups.

Participants and Methods

Study Population

The sample for this study was obtained from the Swedish Twin Registry, which is a nationwide register of twin births ascertained from official records of the population (Pedersen & Lichtenstein, 2000). The study population consisted of like-sexed twin pairs born from 1926 to 1958 (The Middle cohort), unbroken by death and traceable in 1970, and contacted by mailed health questionnaires in 1973 (n = 18,282 pairs). The individual response frequency was 83%. Zygosity was determined with a minimum of 95% accuracy using the questionnaire method of similarity as children (Pedersen & Lichtenstein, 2000).

A total of 29,967 twins answered the questions about headaches in the 1973 questionnaire. After exclusion of pairs where only one of the twins answered these questions or zygosity was unclassified, 4939 monozygotic (MZ) pairs and 7667 dizygotic (DZ) pairs were eligible for quantitative genetic analysis. The sample was divided into four age groups as summarized in Table 1.

The data were collected with permission of the Swedish Data Inspection authority and the Ethics Committee of Karolinska Institutet.

Table 1

A Quantitative Genetic Analysis of Expression of Severe Disabling Recurrent Headaches as a Function of Age: The Number of MZ and DZ Twin Pairs

	MZ	DZ	MZ+DZ
Men			
15–20 yrs	495	821	1316
21–30 yrs	831	1270	2101
31–40 yrs	579	969	1548
41–47 yrs	350	552	902
All	2255	3612	5867
Women			
15–20 yrs	572	799	1371
21–30 yrs	997	1434	2431
31–40 yrs	695	1098	1793
41–47 yrs	420	724	1144
All	2684	4055	6739
Total	4939	7667	12606

Note: The sample was drawn from the Middle cohort of the Swedish Twin Registry (i.e., twins born from 1926 to 1958).

Assessment of Headaches

Expression of headache was addressed in two questions of the 1973 questionnaire: "During the latest years have you had recurring headaches, so severe that you have found it difficult to work?" and if positively endorsed, "Is the headache usually accompanied by visual disturbances or vomiting?". Twins answering positively to the first question but not to the second one were classified as cases of *mixed headache*. Twins answering in the affirmative to both questions were classified as cases of *migrainous headache*. These two mutually exclusive diagnoses were used in a previous study of the same twin cohort (Larsson et al., 1995). The operational diagnostic criteria for headache disorders, which were published in 1988, include a more elaborate set of headache symptoms than those used in the present study (Headache Classification Committee of the International Headache Society, 1988). Ever since the introduction of the International Headache Society classification system, terms such as "mixed headache" have become more or less discouraged (Olesen & Lipton, 1994). In the past, this term was used to classify subjects with coexistence of migraine and tension-type headache. In the present study, the term "mixed headache" rather reflects our assumption that assessment of severe disabling recurrent headaches from the general population includes various headaches of predominantly the migraine type but also severe tension-type headaches and to a less extent symptomatic (or secondary) headaches (Rasmussen, 1995). The term "migrainous headache" reflects our assumption that visual disturbance and vomiting are features of migraine rather than tension-type headache (Rasmussen, 1995). To account for a headache diagnosis not in line with the operational consensus criteria, we prefer to use the term migrainous headache rather than "migraine".

Predictive Validity

Follow-up studies may be used for validation of headache diagnoses (Merikangas et al., 1994). For that purpose we evaluated mixed headache and migrainous headache as predictors for lifetime migraine and tension-type headache 26 or 27 years later. Assessment of recurrent headaches at follow-up, embedded in the Screening Across Lifetime Twin (SALT) study, was based on structured telephone interviews by trained lay persons and the International Headache Society criteria were applied to those data. The SALT study focuses on common health problem among twins in the Swedish Twin Registry. The validation study included a sample of 9101 twins born from 1935 to 1944, which answered the questionnaire at base line in 1973. By the time of follow-up, 8462 of these twins were alive, 558 dead, and 81 non-traceable by other reasons. Among eligible twins, 6653 twins (79%) fulfilled headache assessment at follow-up. As a measure of predictive validity, the log odds-ratio of migraine and tension-type headache at follow-up by headache status in 1973 was computed (Hosmer & Lemeshow, 2000). As shown in Table 2 the headache classification used in the present study was essentially valid.

Table 2

Predictive Validity for Expression of Severe Disabling Recurrent Headaches in 1973: Odds-ratio (OR) with 95 Per cent Confidence Interval (95% CI) for Recurrent Headaches Diagnosed at Follow-up 26 or 27 Years Later by Headache Status at Base-line

	Recurrent headaches at follow-up			
	Migraine		Tension-type headache	
	OR	95% CI	OR	95% CI
1973 questionnaire:				
No headaches	1.0	Reference	1.0	Reference
Mixed headache	4.5	3.6, 5.8	2.9	2.3, 3.8
Migrainous headache	10.4	8.3, 13.1	2.6	2.0, 3.5

Note: A sub-sample of twins participating in the 1973 questionnaire (n = 6,653 twins) were followed for lifetime recurrent headaches via structured interviews on the telephone conducted by trained lay personnel 26 or 27 years later. Headaches were classified into migraine and tension-type headache in line with the International Headache Society criteria.

Analyses

We used path models applied to the classical twin study (Heath et al., 1989; Neale & Cardon, 1992) and the Mx program (Neale, 1999) to analyze variance components for liability in recently experienced headaches. Headache data in twin pairs were summarized into two-way contingency tables by zygosity and the four age groups for men and women separately. Under the assumption of a bivariate normal distribution of liability (Falconer, 1965), structural equation models of twin similarity were fitted to cell frequencies, and maximum-likelihood estimates of model parameters and model fit statistics were computed. The tetrachoric correlation coefficient (Everitt, 1992) was used to estimate degree of similarity in twin pairs for liability to headaches.

Phenotypic variation, V(P), can be portioned into main genetic and environmental components of variance (Falconer & Mackay, 1996). Additive genetic variance, V(A), reflects segregating alleles that independently combine to phenotypic variation and each with a small effect. Non-additive genetic variance, V(D), is a construct for interaction between alleles at the same locus or between alleles at different loci. Non-shared environmental variance, V(C), refers to environmental factors that make family members similar to each other. The explained proportion of total phenotypic variance is the sum of V(A), V(D), and V(C). Individual specific environmental variance, V(E), represents residual variance and make family members to differ from each other. Thus, the relative importance of genetic and environmental influences is calculated from expressions such as V(A)/V(P).

To analyze the relative importance of variance components in the present study, the threshold value was estimated from the data and allowed to differ between age groups, whereas the total variance was constrained to be unity in each age group. Standardized threshold values were analyzed using the constraint statement in the Mx program (Neale, 1999). For every non-linear equality constraint, Mx increases the degrees of freedom by the number of non-linear constraints because it is assumed that each constraint identifies a parameter.

To extract raw variances, V(A), V(D), and so forth., we used the same approach as Koopmans and her colleagues, studying genetic and environmental effects on alcohol use initiation as a function of religious upbringing (Koopmans et al., 1999). To assess raw variances across age groups, the threshold value was set to be equal across age strata, whereas the total variance was allowed to differ between the age strata (i.e., unstandardized threshold values were analyzed) (Neale, 1999). In this way, it was possible to examine models that predict non-scalar differences in the level of genetic and environmental variance between strata, while allowing for differences in the prevalence. To obtain a standard normal scale of liability when analyzing the absolute variance, the total variance was constrained to be unity for the oldest age group.

Finally, to test the significance of age heterogeneity in raw variances, the fit of a set of nested sub-models was compared to the fit of the full model. To obtain a sub-model, the value of a certain structural equation parameter was fixed to be equal across age groups. A significance level of 0.01 rather then 0.05 was used because the maximum number of sub-models was five.

Results

Prevalence

The overall prevalence of severe disabling recurrent headaches during the latest years in 15- to 47-year-old Swedish twins was 10.7%. In comparison to men, the prevalence risk for women was 2.1 (7.1% versus 13.8%; 95% CI: 1.9, 2.4). The prevalence of mixed headache was 4.7% for men, 7.0% for women, and 5.9% for men and women pooled together, and the prevalence risk for women 1.5 (95% CI: 1.3, 1.8). The prevalence of migrainous headache was 2.4% for men, 6.8% for women, and 4.8% for men and women pooled together, and the prevalence risk for women 3.0 (95% CI: 2.4, 3.6). For mixed headache, there was no significant difference between age groups in regard to the prevalence risk (Table 3). As compared to the youngest of the four age groups, the prevalence risk of migrainous headache was significantly higher in the two oldest age groups among men and in the three oldest age groups among women (Table 3).

Twin Similarity

Tables 4 and 5 summarize twin similarity for expression of severe disabling recurrent headaches. For this purpose, and in further analyses of this paper, men were divided into two

Table 3

Prevalence Risk for Expression of Severe Disabling Recurrent Headaches in Male and Female Swedish Twins by Age Group: Odds-ratio (OR) and Ninety-five Per cent Confidence Interval (95% CI)

	Mixed headache		Migrainous headache	
	%	OR (95% CI)	%	OR (95% CI)
Men				
15–20 yrs	3.9	1.0 (reference)	1.3	1.0 (reference)
21–30 yrs	4.6	1.2 (0.8, 1.7)	1.8	1.4 (0.8, 2.6)
31–40 yrs	5.4	1.4 (1.0, 2.0)	3.3	2.7 (1.5, 4.6)
41–47 yrs	5.0	1.3 (0.8, 1.9)	3.9	3.1 (1.7, 5.6)
Women				
15–20 yrs	6.4	1.0 (reference)	2.7	1.0 (reference)
21–30 yrs	7.6	1.2 (0.9, 1.6)	6.3	2.4 (1.7, 3.4)
31–40 yrs	6.8	1.0 (0.8, 1.4)	9.0	3.5 (2.4, 5.0)
41–47 yrs	6.7	1.0 (0.8, 1.4)	9.3	3.6 (2.5, 5.3)

Note: One random member of each MZ and DZ twin pair was selected from the total sample of respondents regardless of whether both twins participated in the study or not (N = 12,759 twins).

age groups, 15 to 30 years and 31 to 47 years, respectively, due to low prevalence of severe disabling recurrent headaches in men. Regardless of age, the correlation in liability of twin pairs for mixed headache tended to be higher in MZ twins than in DZ twins indicating the importance of additive genetic effects (Table 4). The MZ:DZ correlation ratio differed from two in some age groups suggesting the possibility of non-additive genetic and shared environmental influences, respectively. Although the MZ correlation for women tended to be high in the youngest age group as compared to the older ones, differences were not significant. The MZ:DZ correlation ratio for migrainous headaches was higher than two indicating the possibility of non-additive genetic effects (Table 5). The MZ correlation for women was significantly higher in the youngest age group as compared to the older groups, suggesting age group differences in the importance of genetic and environmental effects.

Genetic and Environmental Influences: Relative Importance

As determined by MZ and DZ correlations, full structural equation models were fitted to headache data and the relative importance of genetic and environmental influences by age group was computed (Table 6). Twin similarity for mixed headache in men was due to non-additive genetic influences in the youngest age group (49%), and a combination of additive genetic and shared environmental influences in the oldest age group (28%). In women, the proportion of the total phenotypic variance that was explained ranged from 12% to 61%. This proportion was mainly attributed by additive genetic influences, and to lesser extent non-additive genetic and shared environmental influences, respectively. Twin similarity for migrainous headache in men was attributed by non-additive genetic influences and this contribution was significant in the oldest age group. In women, the proportion of variation in liability to migrainous headache that was explained by genetic influences ranged from 37% to 91% across age groups, with major contributions by additive genetic influences in the two intermediate age groups, and non-additive genetic influences in the youngest and the oldest age groups.

Table 4

Similarity of Twin Pairs for Mixed Headache

	Men				Women			
	Number of affected twins				Number of affected twins			
	None	One	Both	r (95% CI)	None	One	Both	r (95% CI)
15–20 yrs								
MZ	1224	89	13	0.49 (0.31, 0.64)	509	50	13	0.60 (0.40, 0.76)
DZ	1898	187	6	0.06 (–0.13, 0.24)	695	95	9	0.26 (0.05, 0.46)
21–30 yrs								
MZ					858	137	12	0.24 (0.06, 0.42)
DZ					1217	202	15	0.15 (–0.01, 0.30)
31–40 yrs								
MZ	844	79	6	0.28 (0.04, 0.49)	608	75	12	0.43 (0.23, 0.61)
DZ	1365	147	9	0.19 (0.01, 0.37)	961	128	9	0.19 (–0.01, 0.37)
41–47 yrs								
MZ					368	49	3	0.15 (–0.18, 0.45)
DZ					626	95	3	–0.04 (–0.31, 0.22)

Note: r denotes the tetrachoric correlation coefficient. In men, age groups were from 15 to 30 years and from 31 to 47 years, respectively.

Table 5

Similarity of Twin Pairs for Migrainous Headache

	Men				Women			
	Number of affected twins				Number of affected twins			
	None	One	Both	*r* (95% CI)	None	One	Both	*r* (95% CI)
15–20 yrs								
MZ	1284	40	2	0.35 (0.0, 0.63)	555	10	7	0.90 (0.73, 0.97)
DZ	2039	52	0	–0.65 (–1.0, 0.32)	754	43	2	0.24 (–0.12, 0.55)
21–30 yrs								
MZ					897	90	10	0.37 (0.16, 0.55)
DZ					1261	162	11	0.18 (0.01, 0.35)
31–40 yrs								
MZ	872	51	6	0.47 (0.22, 0.67)	613	67	15	0.55 (0.36, 0.70)
DZ	1409	110	2	–0.01 (–0.29, 0.25)	906	172	20	0.25 (0.09, 0.40)
41–47 yrs								
MZ					351	59	10	0.39 (0.15, 0.60)
DZ					600	118	6	0.01 (–0.22, 0.23)

Note: *r* denotes the tetrachoric correlation coefficient. In men, age groups were from 15 to 30 years and from 31 to 47 years, respectively.

Table 6

Relative Importance (%) of Genetic and Environmental Influences on the Expression of Severe Disabling Recurrent Headache by Age Group with Ninety-five Percent Confidence Interval Between Parentheses

	Mixed headache		Migrainous headache	
	Men	Women	Men	Women
15–20 yrs				
A	0 (0, 0)	44 (0, 74)	0 (0, 55)	4 (0, 96)
C or D	49 (0, 64)**	17 (0, 75)**	32 (0, 60)**	87 (0, 98)**
E	51 (36, 69)	39 (24, 59)	68 (40, 100)	9 (2, 24)
21–30 yrs				
A		20 (0, 41)		35 (0, 54)
C or D		5 (0, 30)*		3 (0, 55)**
E		75 (59, 92)		62 (44, 80)
31–40 yrs				
A	18 (0, 49)	32 (0, 58)	0 (0, 53)	40 (0, 69)
C or D	10 (0, 36)*	11 (0, 60)**	45 (20, 66)**	18 (0, 71)**
E	72 (51, 92)	57 (40, 76)	55 (34, 80)	42 (27, 60)
41–47 yrs				
A		0 (0, 0)		0 (0, 47)
C or D		12 (0, 42)**		37 (0, 57)**
E		88 (58, 100)		63 (43, 87)

Note: A denotes additive genetic influences, D non-additive genetic influences, C shared environmental influences, and E individual specific environmental influences. The relative importance of genetic and environmental influences is calculated through expressions such as A = V(A)/V(P), where V(A) is the additive genetic variance and V(P) the total phenotypic variance. In men, age groups were from 15 to 30 years and from 31 to 47 years, respectively. *Shared environmental influences (C). ** Non-additive genetic influences (D).

Genetic and Environmental Influences: Raw Variance

The raw variance was extracted for each component of the full structural equation models shown in Table 6. The pattern of genetic and environmental influences for mixed headache across age groups when measured as the raw variance was similar to that measured as the relative importance (Figures 1A and B). The age group difference of non-additive genetic influences for migrainous headache in men tended to be more apparent on an absolute scale than on a relative scale because total phenotypic variance differed between the two age groups (Figure 1C). In contrast to the large difference in the relative importance of genetic influences (additive + non-additive) for migrainous headache between adolescent and adult women, the level of absolute genetic variance (additive + non-additive) tended to be rather stable across age groups (Figure 1D). Total phenotypic variance and individual specific environmental variance were lower in the youngest age group as compared to the older age groups.

Test of Age Heterogeneity

Equality of raw variance for genetic and environmental parameters across age groups was examined using constrained sub-models. When parameters of additive genetic (a) and individual specific environmental (e) variance were set to be equal across age groups for mixed headache in

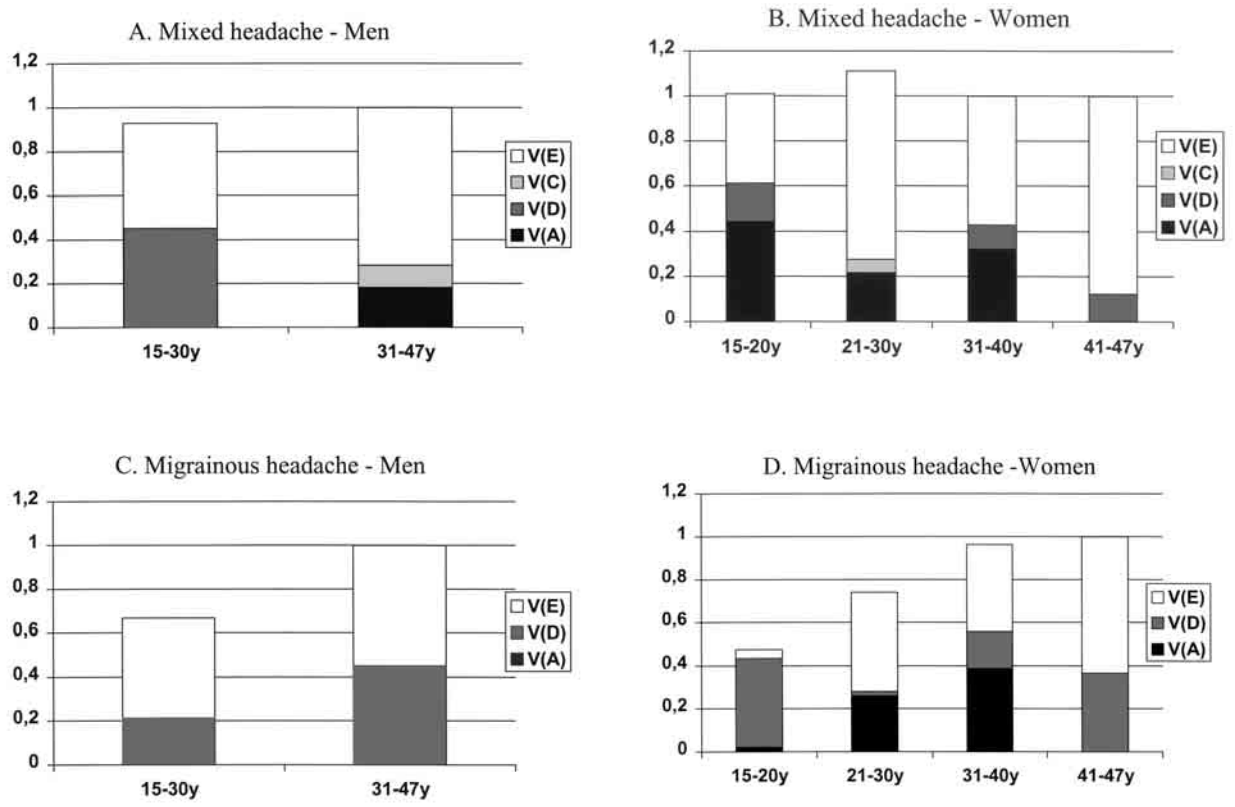

Figure 1

Genetic and environmental components of variance for liability to mixed headache and migrainous headache, respectively, as a function of age. V(A) denotes additive genetic variance, V(D) non-additive genetic variance, V(C) shared environmental variance, and V(E) individual specific environmental variance. The total variance is obtained as follows: V(P) = V(A)+V(D)+V(C)+V(E). The total variance is set to be 1 in the oldest age group. $V(A) = a^2$, $V(D) = d^2$ and so forth., where a, d, c, and e are structural equation modeling parameters.

men, model fit did not deteriorate significantly, indicating no substantial age group differences in these variance components (Table 7). In women, an equality constraint of the e parameter resulted in significant worsening of model fit, indicating that individual specific environmental variance differs between age groups (Table 7). Out of 10 possible comparisons for mixed headache in women, the parameter value of individual specific environmental variance differed significantly between the two youngest age groups ($\Delta\chi^2 = 9.83$, $\Delta df = 1$, $p < 0.005$). There were no significant differences in parameter estimates for migrainous headache in men between age groups (Table 8). When all parameter values were set to be equal across age groups model fit deteriorated significantly, reflecting a difference in total phenotypic variance between age groups (Table 8). In women, genetic parameters for migrainous headache did not differ significantly between age groups, whereas the e parameter and the total phenotypic variance did (Table 8). The parameter value of individual specific environmental variance differed significantly between the youngest age group and all the older age groups ($\Delta\chi^2 = 26.45$, 20.50, and 32.51, respectively, $\Delta df = 1$, $p < 0.005$).

Discussion

The major purpose of this study was to evaluate age differences of genetic and environmental influences on expression of severe disabling recurrent headaches using questionnaire data collected in 1973 for the Middle cohort of the Swedish Twin Registry. We have previously examined the same cohort of twins but without consideration of the reporting age (15 to 47 years). In the present study, the extent genetic effects were partitioned into additive and non-additive variance and the level of individual specific environmental variance, respectively, tended to differ between age groups, in particular among women.

Results from previous twin studies show a significant importance for genetic factors in recurrent headache, especially in migraine. Our present data suggests that a genetic predisposition is required for expression of recurrent headache from adolescence to mid-life, although there may be a substantial variation in the relative importance of genetic influences across age groups. However, the absolute level of genetic variance may show minor variation between age groups. Further, the extent by which the genotypic effect deviates from the effects of segregating alleles taken

Table 7

Test of Age Differences in Genetic and Environmental Variance on Liability to Mixed Headache

Equality constraint	df	χ^2	AIC	*p*	Test of age heterogeneity $\Delta\chi^2(\Delta df)$	*p*-value
Men						
Full	6	2.53	–9.47	0.87	—	—
a	7	2.88	–11.12	0.90	0.35 (1)	*ns*
e	7	5.48	–8.52	0.60	2.95 (1)	*ns*
a, e	8	7.34	–8.66	0.50	4.81 (2)	*ns*
Women						
Full	12	7.38	–16.62	0.83	—	—
a	15	8.47	–21.53	0.90	1.09 (3)	*ns*
d	14	7.39	–20.61	0.92	0.01 (2)	*ns*
e	15	19.83	–10.17	0.18	12.45 (3)	< 0.01
a, d	17	15.97	–18.03	0.53	8.59 (5)	*ns*
a, d, e	20	22.72	–17.28	0.30	15.34 (8)	*ns*

Note: Equality of genetic and environmental variance across age groups was examined, where a, d, and e reflect structural equation modeling parameters corresponding to additive genetic, non-additive genetic, and shared environmental variance, respectively. Significance level is 0.01 due to multiple comparisons. *ns* = Non-significant.

Table 8

Test of Age Differences in Genetic and Environmental Variance on Liability to Migrainous Headache

Equality constraint	df	χ^2	AIC	*p*	Test of age heterogeneity $\Delta\chi^2(\Delta df)$	*p*-value
Men						
Full	6	11.22	–0.78	0.08	—	—
a	7	11.22	–2.78	0.13	0.0 (1)	*ns*
d	7	12.04	–1.96	0.10	0.82 (1)	*ns*
e	7	11.56	–2.44	0.12	0.34 (1)	*ns*
a, d	8	11.56	–4.44	0.17	0.34 (2)	*ns*
a, d, e	9	69.48	51.48	0.00	58.26 (3)	< 0.01
Women						
Full	12	20.10	–3.90	0.06	—	—
a	15	21.58	–8.42	0.12	1.48 (3)	*ns*
d	15	21.34	–8.66	0.13	1.24 (3)	*ns*
e	15	57.30	27.30	0.00	37.20 (3)	< 0.01
a, d	18	28.63	–7.37	0.05	8.53 (6)	*ns*
a, d, e	21	169.06	127.06	0.00	148.96 (9)	< 0.01

Note: Equality of genetic and environmental variance across age groups was examined, where a, d, and e reflect structural equation modeling parameters corresponding to additive genetic, non-additive genetic, and shared environmental variance, respectively. Significance level is 0.01 due to multiple comparisons. *ns* = Non-significant.

separately differed between age groups, and this was most apparent for mixed headache in men and migrainous headache in women. Human development includes variation across ages of which genes are transcribed and at what level they are expressed. In addition, gene products usually do not act in isolation but rather within an assembly or pathway involving many other proteins. One interpretation of our findings is that one or several specific genetic polymorphisms are important for expression of recurrent headache at some ages as flagged by non-additive genetic effects. However, at other ages they are of less importance due to modulation of the expression level as flagged by a shift from non-additive to additive genetic effects. Alternatively, specific genetic polymorphisms play important roles for certain aspects of recurrent headache, such as onset and prognosis.

A polymorphism of the insulin receptor gene located on chromosome 19 has recently been proposed as one susceptibility gene for non-familial migraine (McCarthy et al., 2001). Linkage studies of familial migraine have revealed candidate loci at chromosomes 1 (Ducros et al., 1997; Gardner et al., 1997), 3 (Ophoff et al., 2001), 4 (Wessman et al., 2002), 19 (Jones et al., 2001; Joutel et al., 1993; Nyholt et al., 1998; Tournier-Lasserve et al., 1993) and X (Nyholt et al., 2000). The gene has been identified for two loci mapped to chromosome 19 (Joutel et al., 1996; Ophoff et al., 1996) — the CACNA1A gene and the Notch3 gene — and encoded proteins have key regulatory functions in neurotransmitter release and gene transcription, respectively. In all age groups of the present study, shared family environmental variance was of no or little importance for the expression of recurrent headache.

The importance of individual specific environmental variance for expression of recurrent headache was stable across all age groups of the present study, with a major exception of migrainous headache in adolescent women. The low level of individual specific environmental variance for migrainous headache in adolescent women as compared

to adult women was the major explanation for large age group differences in the relative importance of genetic influences. There are several possible reasons for this marked age dependence in environmental variance. First, as discussed above expression of migrainous headache in adolescent women may largely be related to a major susceptibility allele, with little contribution from environmental variance. Second, the step from youth to young adulthood may represent a subtle developmental transition, with modulation of gene expression and subsequent increase in gene environment interaction. Third, the psychosocial environment probably exhibits qualitative differences across age, where the social network changes, minor life events or daily hassles predominate in youngsters, and major life events and negative stress become more common in adults. Lifestyle changes may also contribute to an increase in individual specific environmental variance for migrainous headache across age groups.

The female hormonal environment and psychosocial stress seem to be the major candidate predisposing factors of non-genetic origin (Olesen & Goadsby, 2000). As mentioned in the introduction, the threshold for migraine attacks among women is lowered substantially at menarche. An association between neuroticism and migraine (Breslau & Rasmussen, 2001) suggests that emotional instability and increased sensitivity to stress (Eaves et al., 1989) increase the risk to express migraine. In one prospective cohort study of 21- to 30-year-old women (Breslau et al., 1996), neuroticism at baseline predicted migraine at follow-up 3.5 to 5.5 years later. Further, menstruation and stress often act as provoking factors in attacks of migraine (Drummond, 2000; Rasmussen, 1993). Migraine in relation to menstruation is especially common among women with migraine onset at puberty (Russell et al., 1996). One speculation is that major changes of endogenous or exogenous environments per se represent key stimuli for expression of migraine. A genetic susceptibility for migraine might be related to a reduced ability to adapt to environmental changes (Olesen & Goadsby, 2000).

Our findings of age differences in genetic and environmental effects for recurrent headache may be related to aspects of disease variation, such as age at onset (Rasmussen, 1993) and prognosis (Bille, 1997). A positive family history for migraine ascertained clinically was more frequently reported in cases with early onset as compared to late onset cases (Devoto et al., 1986; Steiner et al., 1980). In migraine with aura, there is evidence of multiple distributions of the age at migraine onset with peaks in late adolescence and after 30 years of age, respectively (Russell et al., 1996; Stewart et al., 1991). Onset of menstruation migraine at menarche (Russell et al., 1996), and onset of migraine in association with pregnancy (Massiou & Bousser, 2000) or metabolic disease (Split & Szydlowska, 1997) represent specific manifestations of migraine, which indirectly are related to age at onset. Various age-related endogenous processes such as the function of endocrine, immune, and vascular systems, plasticity of the central nervous system, and normal aging, may be of importance for the self-limiting capacity of the condition. Access to health care and medication (Lipton et al., 2001; Stewart et al., 1992), and success in development of coping strategies are other prognostic factors that may differ between age groups.

A follow-up assessment of recurrent headaches provided convincing evidence of validity for the headache classification that was used in the present study. Similar examples of predictive validity and long-term stability of headache diagnoses in the literature are few (Bille, 1997) but highly warranted. The prevalence of severe disabling recurrent headaches during the latest years in the present study (11%) is in agreement with estimates of the one-year prevalence of migraine (10–15%) from several population-based surveys (Breslau & Rasmussen, 2001), including one recent Swedish study (Dahlöf & Linde, 2001). In the present study, the prevalence distribution by gender and age support features of tension-type headache in the category of "mixed headache" (weak female preponderance and increase by age) and migraine in the category of "migrainous headache" (pronounced female preponderance and increase by age) (Rasmussen, 1993; Rasmussen & Olesen, 1994). Almost 80% of the Swedish general population suffering from a severe headache that could be considered very troublesome during the last year had migraine (Dahlöf & Linde, 2001). As pointed out previously, a severe grade of various headache symptoms is an indication for migraine rather than tension-type headache (Rasmussen, 1995). Although visual disturbance is the most frequent aura symptom, only about one half of migraine sufferers report aura symptoms (Rasmussen, 1995). Approximately half the proportion of migraine sufferers vomits during their attacks (Rasmussen, 1995). In summary, headache classification in our study was characterized by high diagnostic stability over time where "mixed headache" probably reflects predominantly migraine and to a less extent tension-type headache, and "migrainous headache" a more homogenous sub-population of migraine.

In the present study, the possibility of age group analyses in men was limited due to low headache prevalence. Further, the classical twin study has limited power to reach statistical significance for non-additive genetic and shared environmental influences, respectively, in particular when categorical data is analyzed (Martin et al., 1978; Neale et al., 1994). To study etiologic relationships such as age-related processes, the time period of consideration in this study, the latest years, is advantageous as compared to the lifetime period. Although less precise than the commonly used one-year period, it is also less prone for recall biases as compared to lifetime assessment. In future research, however, our study might be improved by analyses of the age at headache onset, longitudinal data (Eaves et al., 1986), and gene environment interaction (Neale & Cardon, 1992).

In conclusion, our data suggests that a genetic predisposition is necessary for expression of migraine regardless of the actual age. The extent by which genetic variance reflects non-additive effects and the contribution of individual specific environmental variance, respectively, may at times differ between age groups, and this seem to be especially true in women. When comparison of various disease groups is made, our results underscore the importance of analyzing

the raw variance of genetic and environmental influences rather than the relative importance.

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