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## Are infrequent episodic, frequent episodic and chronic tension-type headache inherited? A population-based study of 11 199 twin pairs

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**Abstract** The objective was to investigate the importance of genetic and environmental factors for infrequent episodic, frequent episodic and chronic tension-type headache. Twin pairs recruited from the population-based Danish Twin Registry received a posted questionnaire. Only twin pairs where both twins replied were included. A total of 3523 monozygotic (MZ), 4150 dizygotic (DZ) same-gender and 3526 DZ opposite-gender twin pairs were included. The prevalence of frequent episodic and chronic tension-type headache was significantly more frequent in women than men, and significantly higher in those with co-occurrence of migraine. The concordance rates were significantly higher in MZ than same-gender DZ twin pairs with no or frequent episodic tension-type headache, while the difference was not significant in chronic tension-type headache. The concordance rates of infrequent episodic tension-type headache in

MZ and same-gender DZ twin pairs was significantly different in women but not in men, although the difference was small in both genders. We conclude that genetic factors play a role in no and frequent episodic tension-type headache, while infrequent episodic tension-type headache is caused primarily by environmental factors. The data regarding chronic tension-type headache were limited, so no firm conclusion could be drawn.

**Keywords** Tension-type headache • Genetics • Twins • Inheritance

### Introduction

The International Classification of Headache Disorders classifies tension-type headache as infrequent episodic,

frequent episodic and chronic tension-type headache [1]. The last year prevalence of infrequent episodic tension-type headache is 64%; 61% among women and 67% among men [2]. The high prevalence causes a positive family history of infrequent tension-type headache simply

by chance in more than 98% of the families, if the proband has four first-degree relatives. One or both parents are affected by chance in 87% of the families. A genetic epidemiological survey is therefore not likely to elucidate the importance of genetic and environmental factors in infrequent episodic tension-type headache. The last year prevalence of frequent episodic tension-type headache is 21%; 31% among women and 12% among men [2]. This gender ratio is different from that of infrequent episodic tension-type headache and similar to that of chronic tension-type headache [2, 3]. A family study of chronic tension-type headache suggested that genetic factors are important. Compared with the general population, first degree relatives had a 3-fold significantly increased risk of chronic tension-type headache [4]. A complex segregation analysis was in favour for multifactorial inheritance [5].

The present study is based on the population-based Danish Twin Register [6]. The concordance rates for infrequent episodic, frequent episodic and chronic tension-type headache in monozygotic (MZ) and dizygotic (DZ) twin pairs were compared in order to measure the influence of genetic and environmental factors.

## Subjects and methods

### Identification of twins

The New Danish Twin Register is population-based and comprises Danish twins born from 1953 to 1982 [6]. It is based on the Danish Civil Registration System, which registers inhabitants and newborns in Denmark. The zygosity of the twin pairs was determined by using a questionnaire focusing on the similarity within the twin pairs. This method is reportedly reliable in large twin populations, as it classifies 90%–95% of the twin pairs correctly [7–9].

### Questionnaire

This study included MZ and DZ twin pairs. They received a posted questionnaire in 1994 with a single question about self-reported tension-type headache and its frequency within the last year, i.e., 0, 1–7, 8–14, 15–30, 31–179 or  $\geq 180$  days. Questions about migraine were: Have you ever had migraine? Have you ever had a severe headache accompanied by nausea? Have you ever had a severe headache accompanied by hypersensitivity to light or sound? Have you ever had visual disturbances lasting 5–60 min followed by headache? We used a combination of the first and the last migraine questions to screen for migraine. A total of 16 882 twin pairs age 12–41 years old were eligible. Inclusion required that both twins in a pair replied on the questionnaire as well as known zygosity. Detailed description of the epidemiological data has been published elsewhere [2].

### Classification

The International Classification of Headache Disorders defines infrequent episodic tension-type headache to be less than 12 days per year and frequent episodic tension-type headache to be between 12 and 179 days per year [1]. The present study delineated infrequent episodic tension-type headache to be less than 15 days per year and frequent episodic tension-type headache to be between 15 and 179 days per year.

### Concordance

The pairwise concordance rate is the number of twin pairs with double-affected twins in relation to the total number of twin pairs [10, 11]. It expresses the relative influence of genetic and environmental factors. The risk of no tension-type headache, infrequent episodic, frequent episodic and chronic tension-type headache in co-twins to those affected was calculated as the proportion of affected co-twins of probands in relation to the total number of affected. This proportion is the probandwise concordance rate [10]. It was estimated by  $(2C1+C2)/(2C1+C2+D)$ .  $C1$  is the number of doubly ascertained concordant pairs,  $C2$  is the number of singly ascertained concordant pairs and  $D$  is the number of discordant pairs. The probandwise concordance rate does not vary with ascertainment and it is comparable with the recurrence risk in other groups of relatives [12, 13].

### Statistical analyses

Statistical analyses were performed using SPSS base 13.0 for Windows using a 5% significance level. The study was approved by the Danish ethical committees and the Danish data protection agency.

## Results

### Characteristics of twins

Questionnaire information could be ascertained from both twins in 11 199 twin pairs. The study population included 3523 (1572 male and 1951 female) MZ twin pairs, 4150 (1979 male and 2171 female) DZ same-gender twin pairs and 3526 DZ opposite gender twin pairs.

### Last year prevalence of tension-type headache

Table 1 shows the last year prevalence of the different types of tension-type headache in relation to migraine.

**Table 1** The one-year prevalence of tension-type headache in relation to co-occurrence of migraine

	Tension-type headache				Total % (n)
	No % (n)	Infrequent % (n)	Frequent % (n)	Chronic % (n)	
<b>Men</b>					
No migraine	23.3 (2137)	67.5 (6188)	9.0 (823)	0.2 (21)	100 (9169)
Migraine	8.2 (119)	63.3 (923)	26.8 (391)	1.8 (26)	100 (1459)
<b>Women</b>					
No migraine	9.4 (850)	66.1 (5961)	23.9 (2153)	0.6 (51)	100 (9015)
Migraine	2.3 (62)	44.5 (1227)	50.2 (1382)	3.0 (84)	100 (2755)

The prevalence of frequent episodic and chronic tension-type headache is significantly more frequent in women than men ( $p < 0.001$ ) and significantly higher in those with than those without co-occurrence of migraine in both genders ( $p < 0.001$ ). The opposite effect was observed for no and infrequent tension-type headache with the exception that infrequent tension-type headache was not significantly different in men and women without co-occurrence of migraine.

The prevalence of tension-type headache was independent on whether it was twin A or B, or whether it was a MZ, DZ same- or opposite-gender twin pair. Twins that replied on the questionnaire, but were excluded due to incomplete information from the twin pair were not significantly different from those twins included in the study regarding tension-type headache analysed separately by zygoty and gender (data not shown).

### Concordance rates

Table 2 shows the concordance rates of no, infrequent episodic, frequent episodic and chronic tension-type headache in twin pairs without co-occurrence of migraine. The concordance rates were significantly higher in MZ than same-gender DZ twin pairs with the exception of chronic tension-type headache and infrequent episodic tension-type headache in men. The difference of the significant different concordance rates in MZ and same gender DZ twin pairs varied from 8 to 15%. The concordance rates for migraine without aura and migraine with aura are added for comparisons. The difference in probandwise concordance rates of MZ and same-gender DZ twin pairs is 11%, 14% and 12% in those with no or frequent episodic tension-type headache and migraine without aura, respectively, while the difference is higher, i.e., 29% in migraine with aura.

Table 3 shows concordance rates of tension-type headache in twin pairs where at least one of the twins in

a pair has co-occurrence of migraine. The concordance rates were significantly different in MZ and same-gender DZ twin pairs regarding infrequent episodic tension-type headache in women and frequent episodic tension-type headache. Chronic tension-type headache showed a nonsignificant difference in MZ and same-gender DZ twin pairs.

Table 4 shows the concordance rates of opposite-gender DZ twin pairs. The concordance rates were lower than observed in same-gender DZ twin pairs with the exception of infrequent tension-type headache. This can partly be explained by the different prevalence of tension-type headache in men and women, which causes a lower concordance rate by chance in opposite- than same-gender DZ twin pairs, an effect that is less pronounced if the prevalence of men and women is equal, as seen in infrequent episodic tension-type headache without co-occurrence of migraine (Table 1).

## Discussion

### Methodological considerations

A twin registry is a valuable resource for studies of the cause of illnesses, provided the registry is representative of all twins in a population. The New Danish Twin Register has been established on an epidemiological basis and shows no evidence of disproportionate sampling of MZ and DZ twins [6]. The twin sample in the present study was ascertained independently of zygoty and tension-type headache status, minimising selection bias. Participation was restricted to those twin pairs where both twins replied on the questionnaire. The deviation from the International Classification of Headache Disorders redefining infrequent and frequent episodic tension-type headache is minor, as the cut-off point is changed from 12 to 14 days per year [1]. This is not likely to cause a major difference and it is important to remember that the fre-

**Table 2** The number of concordant and discordant monozygotic (MZ) and same-gender dizygotic (DZ) twin pairs with tension-type headache and no co-occurrence of migraine

Tension-type headache	Men		Women		Total	
	MZ	DZ	MZ	DZ	MZ	DZ
No						
Number of pairs						
Concordant pairs	143	146	61	41	204	187
Discordant pairs	285	431	116	169	401	600
Concordance rates						
Pairwise (95% CI)	33 (29–38)	25 (22–29)	35 (28–42)	20 (14–25)	33 (30–38)	24 (21–27)
<i>p</i> -values	0.005		0.001		<0.001	
Probandwise	50 (43–57)	40 (33–48)	51 (40–62)	33 (20–46)	50 (45–56)	38 (32–45)
<i>p</i> -values	<0.001		<0.001		<0.001	
Infrequent episodic						
Number of pairs						
Concordant pairs	630	757	674	642	1304	1399
Discordant pairs	413	539	377	519	790	1058
Concordance rates						
Pairwise	60 (57–63)	58 (56–61)	64 (61–67)	55 (52–58)	62 (60–64)	57 (55–59)
<i>p</i> -values	n.s.		<0.001		<0.001	
Probandwise	75 (73–78)	74 (71–76)	78 (76–81)	71 (68–74)	77 (75–79)	73 (71–74)
<i>p</i> -values	n.s.		<0.001		<0.001	
Frequent episodic						
Number of pairs						
Concordant pairs	40	20	148	119	188	139
Discordant pairs	153	188	297	401	450	589
Concordance rates						
Pairwise	21 (15–26)	10 (6–14)	33 (29–38)	23 (19–27)	30 (26–33)	19 (16–22)
<i>p</i> -values	0.002		<0.001		<0.001	
Probandwise	34 (21–48)	18 (2–34)	50 (43–57)	37 (29–45)	46 (39–52)	32 (25–39)
<i>p</i> -values	<0.001		<0.001		<0.001	
Chronic						
Number of pairs						
Concordant pairs	0	0	1	1	1	1
Discordant pairs	7	6	11	15	18	21
Concordance rates						
Pairwise	0 (–)	0 (–)	8 (–7–24)	6 (–5–18)	5 (–5–15)	5 (–4–13)
<i>p</i> -values	–		n.s.		n.s.	
Probandwise	0 (–)	0 (–)	15 (–52–83)	12 (–50–73)	10 (–47–67)	9 (–45–63)
<i>p</i> -values	–		n.s.		n.s.	
Migraine without aura						
Probandwise <sup>23, 24</sup>	29 (3–55)	15 (–19–49)	50 (41–59)	37 (31–43)	43 (37–49)	31 (26–36)
Migraine with aura						
Probandwise <sup>25, 26</sup>	53 (35–71)	29 (15–43)	48 (32–64)	15 (4–26)	50 (38–62)	21 (12–30)

The concordance rates are in percentage and the 95% confidence intervals are in parenthesis  
*n.s.*, not significant

quency cut-off point is not based on scientific evidence, but is set arbitrarily. The definition of frequent and chronic tension-type headache was based on the frequency within the last year, while the International Classification of Headache Disorders defines the frequency of frequent and chronic tension-type headache for at least 3 months as well as for one year [1]. Our definition of frequent and

chronic tension-type headache is not likely to have a major influence on the prevalence of frequent and chronic tension-type headache, since the vast majority have these types of headache year around and not in specific periods of the year. The study population was not directly interviewed by a physician, but the data were ascertained by a questionnaire sent to the entire twin population [6]. The

**Table 3** The number of concordant and discordant monozygotic (MZ) and same-gender dizygotic (DZ) twin pairs with tension-type headache and co-occurrence of migraine in at least one of the twins in a pair

	Men		Women		Total	
	MZ	DZ	MZ	DZ	MZ	DZ
None						
Number of pairs						
Concordant pairs	10	10	1	4	11	14
Discordant pairs	59	100	48	64	107	164
Concordance rates						
Pairwise	15 (6–23)	9 (4–15)	2 (–2–6)	6 (0–12)	9 (4–15)	8 (4–12)
<i>p</i> -values	n.s.	n.s.	n.s.			
Probandwise	25 (0–51)	17 (–5–39)	4 (–34–42)	11 (–18–41)	17 (–4–38)	15 (–3–32)
<i>p</i> -values	n.s.		n.s.		n.s.	
Infrequent episodic						
Number of pairs						
Concordant pairs	149	202	207	234	383	436
Discordant pairs	132	224	271	397	403	674
Concordance rates						
Pairwise	53 (47–59)	47 (43–52)	43 (39–48)	37 (33–41)	49 (45–52)	39 (36–42)
<i>p</i> -values	n.s.	0.036	<0.001			
Probandwise	69 (63–75)	64 (59–70)	60 (55–66)	54 (49–60)	66 (62–69)	56 (53–60)
<i>p</i> -values	n.s.		0.012		<0.001	
Frequent episodic						
Number of pairs						
Concordant pairs	27	19	151	132	178	151
Discordant pairs	85	151	266	391	351	542
Concordance rates						
Pairwise	24 (16–32)	11 (6–16)	36 (32–41)	25 (22–29)	34 (30–38)	22 (19–25)
<i>p</i> -values	0.004	<0.001	<0.001			
Probandwise	39 (22–55)	20 (3–37)	53 (46–60)	40 (33–48)	50 (44–57)	36 (29–43)
<i>p</i> -values	<0.001		<0.001		<0.001	
Chronic						
Number of pairs						
Concordant pairs	2	1	2	1	4	2
Discordant pairs	8	9	27	38	35	47
Concordance rates						
Pairwise	20 (–4–45)	10 (–8–29)	7 (–2–16)	3 (–2–8)	10 (1–20)	4 (–1–10)
<i>p</i> -values	n.s.	n.s.	n.s.			
Probandwise	33 (–26–93)	18 (–54–90)	13 (–32–58)	5 (–37–47)	19 (–17–55)	8 (–29–44)
<i>p</i> -values	n.s.		n.s.		n.s.	

The concordance rates are in percentage and the 95% confidence intervals are in parenthesis

*n.s.*, not significant

validity of the questionnaire has previously been evaluated in three steps. Firstly, the single question self-reported tension-type headache, evaluated against a clinical interview by a physician, showed that self-reported tension-type headache is a valid measure in the Danish population, as the observed agreement rate was 0.91 and the chance-corrected agreement rate Kappa was 0.74, i.e., a good strength of agreement [14]. Secondly, self-reported frequency of tension-type headache was evaluated against a clinical interview in the same population on the same day

in those who had self-reported tension-type headache. The observed agreement rate was 0.87, and the chance corrected agreement rate Kappa was 0.77, i.e., a good strength of agreement [15]. Thirdly, self-reported migraine evaluated against a clinical interview shows an observed agreement rate of 0.83 and the chance corrected agreement rate Kappa was 0.62 [16]. Although an interview by a physician is the golden standard diagnosing headache, the evaluations of the questionnaire indicate that the results are valid.

**Table 4** The number of concordant and discordant opposite-gender dizygotic (DZ) twin pairs with tension-type headache. Co-occurrence of migraine indicate that a least one of the twins in a pair had migraine

Tension-type headache	Opposite-gender DZ twin pairs	
	Without co-occurrence of migraine	With co-occurrence of migraine
No		
Number of pairs		
Concordant pairs	94	13
Discordant pairs	636	224
Concordance rates		
Pairwise	13 (10–15)	6 (3–8)
<i>p</i> -value	0.001	
Probandwise	23 (15–31)	10 (–5–27)
<i>p</i> -value	<0.001	
Infrequent episodic		
Number of pairs		
Concordant pairs	1015	398
Discordant pairs	617	602
Concordance rates		
Pairwise	62 (60–65)	40 (37–43)
<i>p</i> -value	<0.001	
Probandwise	77 (75–79)	57 (53–61)
<i>p</i> -value	<0.001	
Frequent episodic		
Number of pairs		
Concordant pairs	75	100
Discordant pairs	606	559
Concordance rates		
Pairwise	11 (9–13)	15 (12–18)
<i>p</i> -value	0.024	
Probandwise	20 (11–28)	26 (18–34)
<i>p</i> -value	0.003	
Chronic		
Number of pairs		
Concordant pairs	0	0
Discordant pairs	6	39
Concordance rates		
Pairwise	0 (–)	0 (–)
<i>p</i> -value	–	–
Probandwise	0 (–)	0 (–)
<i>p</i> -value	–	–

The concordance rates are in percentage and the 95% confidence intervals are in parenthesis *n.s.*, not significant

The results were based on tension-type headache within the last year. This was chosen in order to reduce recall bias. As tension-type headache is not a disabling or life-threatening disorder, recall bias is likely to occur if one asks about tension-type headache years ago. Actually the use of the last year prevalence is likely to secure more precise data, as both twins in a pair provide more precise data. Thus, the methodological precautions should ensure that the data are both representative and can be generalised.

#### Present results

Tension-type headache is very common in industrial countries. The one-year prevalence of tension-type headache varies from 40% to 86% [2, 15, 17–21]. The highest prevalence is found in Danish population-based epidemiological surveys [2, 15, 19]. The International Headache Society's 1988 classification defined tension-type headache as episodic or chronic, while the revised classification the International Classification of Headache Disorders from

2004 separated episodic tension-type headache into infrequent and frequent forms [1, 22]. Our data confirm the high prevalence of tension-type headache. The prevalence of infrequent episodic, frequent episodic and chronic tension-type headache was slightly different from another Danish population-based sample of 40 years old [2]. Infrequent tension-type headache occurred more frequently in the present than previous study, i.e., men 68% vs. 54% and women 66% vs. 50%, while the opposite effect was observed for frequent episodic and chronic tension-type headache, i.e., men 9% vs. 20% and 0.2% vs. 0.7%, and women 24% vs. 37% and 0.6% vs. 2.7%, respectively. No tension-type headache within the last year was similar in the two populations. This difference can be explained by different age composition in the two population-based samples. Although the two studies showed minor difference in the prevalence of the subtypes of tension-type headache, both studies clearly showed that co-occurrence of migraine significantly increased the prevalence of frequent episodic and chronic tension-type headache, and the opposite obligate effect regarding no and infrequent episodic tension-type headache (Table 1) [2]. Tension-type headache and migraine are clinically distinct headache disorders and are defined as such in the International Classification of Headache Disorders [1]. To our knowledge there exist no scientific data proving that tension-type headache can lead to migraine or vice versa. The relationship between tension-type headache and migraine is not within the scope of our paper. However, the prevalence data clearly show a relationship and for that reason we did all the genetic analyses excluding twin pairs with co-occurrence of migraine in at least one of the twins (Table 2). For completeness we also present the concordance rates of tension-type headache in twin pairs with co-occurrence of migraine in at least one of the twins (Table 3). Our main results are:

1. *Infrequent episodic tension-type headache is not likely to be inherited* due to a minor difference in concordance rates in MZ and same-gender DZ twin pairs, a nonsignificant difference in men and significant difference in women. However, even minor differences will be significant due to inclusion of 4551 twin pairs in this analysis.
2. *Frequent episodic tension-type headache is inherited*. The difference in concordance rates in MZ and same-gender DZ twin pairs is very similar to that found in migraine without aura, but less than that found in migraine with aura (Table 2) [23–26]. Furthermore, the prevalence of frequent episodic tension-type headache is very similar to that of migraine without aura (men 9% and women 20%) in Denmark [27]. Migraine without aura has multifactorial inheritance, although two families with autosomal dominant inheritance are described in the literature [23, 24, 28–30]. The concordance rates of frequent episodic tension-type headache suggest that the inheritance is multifactorial, i.e., caused by a combination of genetic and environmental factors. A previous twin study of episodic tension-type headache concluded that environmental influence is of major importance for episodic tension-type headache and a genetic factor, if it exists, is minor [31]. This study was based on twin pairs selected for migraine features and the inter-relation of tension-type headache and migraine was not addressed [16]. Infrequent and frequent episodic tension-type headache were analysed together, as the headache classification of the International Headache Society was used [22]. Thus, the methodological shortcoming suggests that the results should be interpreted with caution.
3. The data regarding chronic tension-type headache were limited, so no firm conclusion could be drawn. Only 41 twin pairs were included in the analysis. However, if a genetic factor had been important, one would expect a difference in the concordance rate of MZ and same-gender DZ twin pairs, as well as more than 2 concordant twin pairs (Table 2). The difference in concordance rate tended to be higher in twin pairs with co-occurrence of migraine, although the difference was not significant due to small numbers of twin pairs (Table 3). The latter may explain the effect observed in a previous family study of chronic tension-type headache, as these data were not analysed for co-occurrence of migraine [2, 3].
4. *No tension-type headache is likely to be inherited*. The difference of concordance rate of MZ and same-gender DZ twin pairs was statistically significant in both genders. The difference in concordance rates was similar to that observed in migraine without aura (Table 2). The inheritance of no tension-type headache is probably caused by the absence of factors that increase the disposition for tension-type headache, but it may also be the existence of protective factors or a combination of the two. Another example is symptomatic generalised epilepsy. Only a minority of those with brain tumours or stroke will experience seizures. A twin study of epilepsy showed that the probandwise concordance rate of symptomatic generalised epilepsy was 0.83 in MZ and 0 in DZ twin pairs, indicating that genetic factors are important [32]. However, whether this genetic factor is a protective factor or factor that increase the risk of seizures is unknown.

We conclude that genetic factors play a role in no and frequent episodic tension-type headache, while infrequent episodic tension-type headache is caused primarily by environmental factors. The data regarding chronic tension-type headache were limited, so no firm conclusion could be drawn.

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