



Comorbidities of migraine

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- Comorbidity is greater than coincidental association of two (or more) conditions in the same individual.



Feinstein 1963



- Migraine has been noted to be comorbid with a number of other illnesses in specialty care and in population samples.

Why is important to learn about comorbidities?

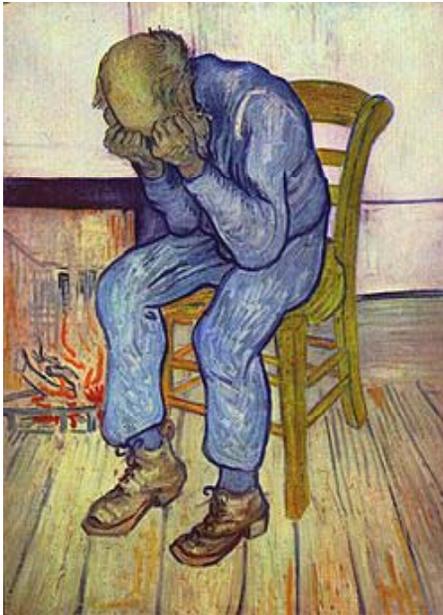
- Raise the global burden of migraine
- In clinical practice: acute and prophylactic treatment
- Insight in pathophysiology of migraine



Conditions comorbid with migraine

Psychiatric	Depression Anxiety Panic disorders Bipolar
Neurologic	Epilepsy Tourette's*
Cardiovascular	Raynaud's phenomenon Stroke: ischemic, lacunar Patent foramen ovale*, mitral valve prolapse*, atrial septal aneurysm*
Other	Snoring/sleep apnea* Asthma/allergy Systemic lupus erythematosus* Non-cephalic pain

* Data from clinical samples only



- Depressive disorders are among the leading causes of disability worldwide.

- WHO estimates that major depressive disorder will become the second leading cause of disease burden by the year 2020, second only to ischemic heart disease.

Migraine and depression – bidirectional association



Detroit metropolitan area

- Population-based cohort study

- migraine 496
- other headaches 151
- control subjects 539

- Interviews in 1997, 1999

- Major depression at baseline

Migraine OR = **3.4** (1.4- 8.7)

Other headaches OR = 0.6 (0.1- 4.6)

- Migraine at baseline

Depression OR = **5.8** (2.7- 12.3)

Other headaches at baseline

Depression OR= 2.7 (0.9- 8.1)

Breslau et al. 2003

Migraine, depression and anxiety disorder



*Nord-Trøndelag County
in Norway*

- Cross-sectional population-based study
- 64 560 participants
- Depression
 - Migraine OR = **2.7** (2.3- 3.2)
 - Non-migraine headaches OR = **2.2** (2.0- 2.5)
- Anxiety disorder
 - Migraine OR = **3.2** (2.8-3.6)
 - Non-migraine headaches OR= **2.7** (2.4- 3.0)
- Stronger for anxiety disorder
- The ORs increased with increasing headache frequency

Zwart et al. 2003

Migraine and depression: Meta-analysis

- 47 cross-sectional and case control studies, 12 relevant

Ratcliffe et al. 2009, Hung et al.2009, Jette et al. 2008, Camarda et al. 2008, Merikangas et al. 1994, Breslau et al. 2000 and 2003, Samaan et al. 2009, Lipton et al. 2000, Lanteri-Minet et al. 2005, Kececi et al. 2003, McWilliams et al. 2004

- The prevalence of depression
 - without migraine 3.4 - 24.4%
 - migraine 8.6 - 47.9%
- Overall OR **2.2** (2.0-2.3)

Antonaci et al. 2011

Migraine and other psychiatric disorders

- Anxiety disorders
 - Panic attacks and phobias – increased risk
 - Conflicting results: obsessive–compulsive disorder
 - generalized anxiety disorder
- Other affective disorders
 - Bipolar disorder – increased risk
- Substance - related disorders
 - Association between migraine and drug, alcohol or substance abuse/dependence is not proven.

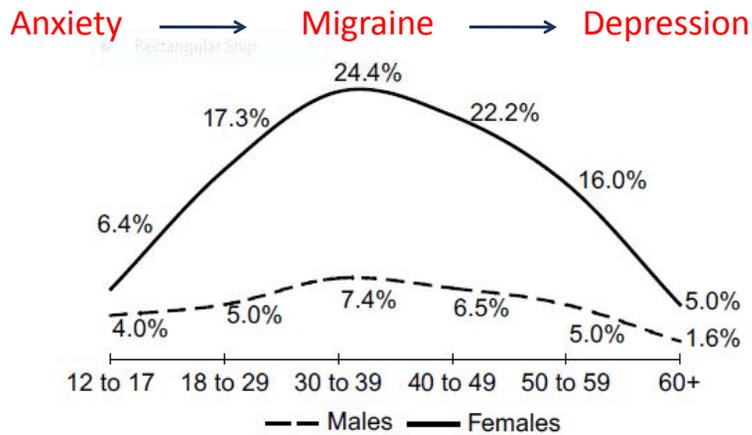
Breslau et al. 1991, Swartz et al. 2000, Jette et al. 2008, Ratcliffe et al. 2009

Migraine subtypes and depression

- Migraine with aura
 - Ball et al. 2009, Samaan et al. 2009*
- Chronic headache, and particularly chronic migraine, as compared to episodic migraine
 - Juang et al. 2000, Hung et al 2009*
- Suicide risk is higher:
 - migraine with aura
 - higher headache frequency
 - females with migraine
 - adolescents with chronic headaches

Wang et al. 2009, De Filippis et al. 2008, Ilgen et al. 2008

From children to grown-up



Merikangas 1990, 1993, 1994, Breslau and Davis 1993

History of abuse

- Migraineurs with current depression reported more frequent physical and sexual abuse compared to those without depression.
- Women with major depression were more likely to report sexual abuse occurring before 12 years.
- Women with migraine and depression were 4 times more likely to have a history of some type of childhood maltreatment.

Tietjen et al. 2007

Pathophysiology of the comorbidity

- At present, these mechanisms are poorly understood.
- Dopamine D2 receptor genotype and comorbid migraine with aura, major depression and generalized anxiety disorder
Peroutka et al. 1998
- 5-HT receptors and transporters, other neurotransmitters are under investigation.

Pain conditions and psychiatric disorders

- A large sample (3032 adults), Canada
- Association between
pain conditions: migraine, arthritis and back pain
psychiatric disorders: depression, panic attacks and generalized anxiety disorder
- Significant positive associations between each pain condition and the psychiatric disorders
- The associations between the pain conditions and the anxiety disorders were generally larger than those between the pain conditions and depression.

Williams et al. 2004

Comorbid pain



Musculoskeletal pain



Low back pain



Neck pain

Migraine and pain



Finland, Turku

- Prospective follow-up study
- 1756 school children (mean age 10.8 years)
- musculoskeletal pain
- At baseline 32.1%
After 1 year 53.8%
After 4 years 63.5%
- Neck pain was the most persistent
- Baseline headache once or twice a week was found to be a prognostic factor for pain persistence.

El-Metwally et al. 2004

Migraine and pain

- Headache was associated with low back pain in a cross-sectional population-based study of 9000 adolescents and young adults. Both conditions were associated with asthma.
- Individuals with headache were roughly twice as likely to report musculoskeletal symptoms as those without headache. The risk was similar in those with nonmigraineous and migraineous headaches. **Headache frequency** was a stronger predictor than headache type.
- Chronic spinal pain was associated with other chronic pain (arthritis, migraine, other headache and other chronic pain), as well as mood disorders, anxiety disorders, and substance use disorders, primarily alcohol abuse or dependence.

*Hestbaek et al. 2006, Hestbaek et al. 2004,
Hagen et al. 2002, Von Korff et al. 2005*

Migraine and epilepsy



- Chronic disorders with episodic manifestations
- Frequently occur together
- Share similar triggers and some clinical features
- Pathophysiology: Ion channels
- The therapeutic options for the disorders overlap.

Migraine and epilepsy

- The prevalence of
migraine in patients with epilepsy 14-24%
epilepsy in migraine subjects 1.1- 17%

*Andermann and Andermann 1987,
Leniger et al. 2003, Tèllez-Zenteno et al. 2005*

- Comorbidity of epilepsy included migraine, a national survey,
Canada

Hinnell et al. 2010

- A higher risk of unprovoked seizures among children with
migraine with aura, a population-based case–control study,
Iceland.

Ludvigsson et al. 2006

Migraine and epilepsy

- Other studies have found no correlation between
migraine and epilepsy, with conflicting results and
questioning the existence of a definite comorbidity.

*Nuyen et al. 2006, Matias-Guiu et al. 1992,
Tietjen et al. 2007, Brodtkorb et al. 2008*

Migraine and epilepsy



Italy

- 9 Headache, 11 Epilepsy Centers, cross-sectional study, adults
- Headache 675
migraine 68.8%
- Epilepsy 336
- Both disorders 156 (13.4%)
- The prevalence of H/E comorbidity
30.0% from Epilepsy centers
1.6% from Headache centers
- These rates are similar to those expected in general population.

Tonini et al. 2012

Temporal coincidence of migraine and epilepsy

Headaches attributed to epileptic seizures

• 7.6.1 **Hemicrania epileptica**

Headache with migraine features lasting seconds to minutes synchronously with the partial epileptic seizure and is ipsilateral to the ictal discharge.

• 7.6.2 **Post-ictal headache**

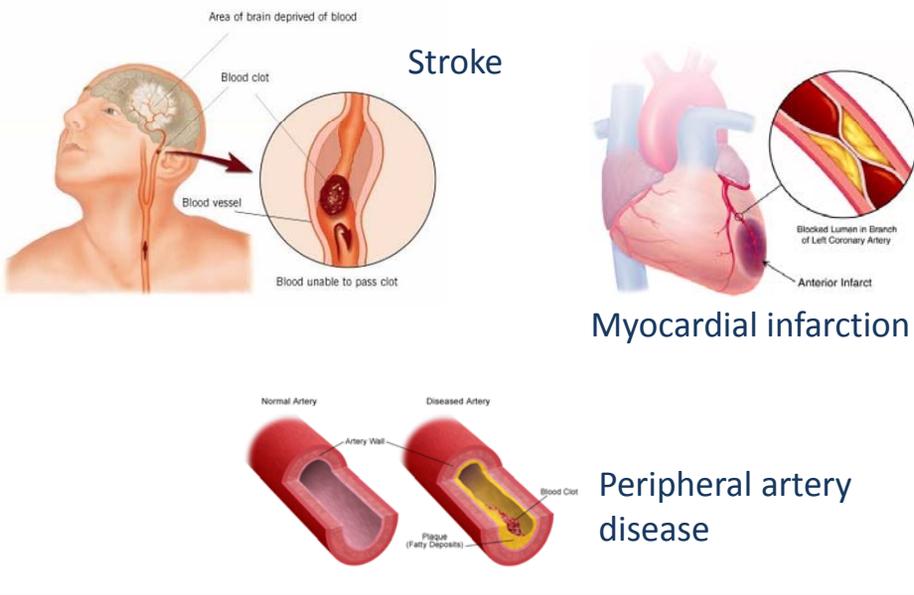
Complication of migraine

• 1.5.5 **Migraine-triggered seizures** previously termed “migralepsy”

A seizure fulfilling diagnostic criteria for one type of epileptic attack occurs during or within 1 hour after a migraine aura.

ICHD-II

Vascular disorders



Migraine and ischemic stroke: Meta-analysis of studies before 2004

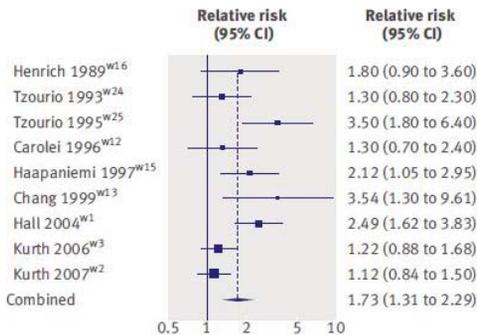
- 11 case-control studies and 3 cohort studies

Migraine **2.16** (1.9–2.5).

Migraine with aura **2.27** (1.61–3.19)

Migraine without aura **1.83** (1.06–3.15)

Migraine and ischemic stroke: Meta-analysis

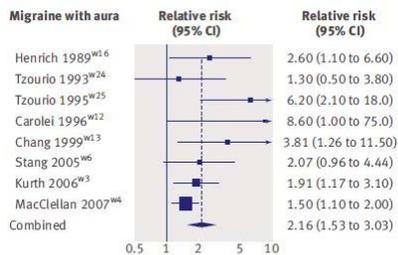


Heterogeneity: $Q=22.9$, $df=8$, $P=0.004$, $I^2=65\%$

- 9 studies:
 - six case-control
 - three cohort
- The pooled relative risk **1.73** (1.31-2.29)
- An increased risk
 - women
 - age < 45 years
 - smokers
 - oral contraceptives

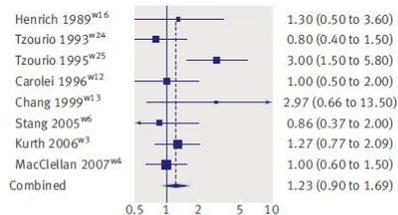
Schürks et al. 2009

Migraine subtype and stroke: Meta-analysis



Heterogeneity: $Q=11.5$, $df=7$, $P=0.12$, $I^2=39\%$

Migraine without aura



Heterogeneity: $Q=11.4$, $df=7$, $P=0.12$, $I^2=39\%$

- 8 studies
- Migraine with aura **2.16** (1.53-3.03)
- Migraine without aura **1.23** (0.9-1.69)

Schürks et al. 2009

Migraine and other stroke subtypes: Meta-analysis

- 3 studies: an association between migraine and TIA

2.34 (1.90-2.88)

*Higgins et al. 2003,
Egger et al. 1997,
Buring et al. 1995*

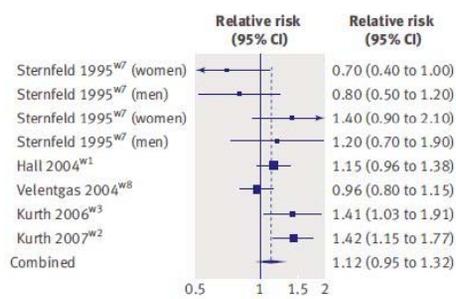
- 3 studies: an association between migraine and haemorrhagic stroke

1.18 (0.87-1.60)

*Haut et al. 2006,
Cook et al. 2002,
Nightingale et al. 2004*

Schürks et al. 2009

Migraine and myocardial infarction: Meta-analysis



Heterogeneity: $Q=17.1$, $df=7$, $P=0.02$, $I^2=59\%$

- 8 studies:
four cohort
- The pooled relative risk
1.12 (0.95-1.32)
- 1 study:
migraine with aura
2.08 (1.30 to 3.31)

Silberstein 2004

Schürks et al. 2009

Migraine and angina pectoris: Meta-analysis

- 3 studies – slightly increased risk, especially in women

1.29 (1.12-1.47)

*Lipton and Bigal 2005,
Silberstein 2004,
Higgins et al. 2003*

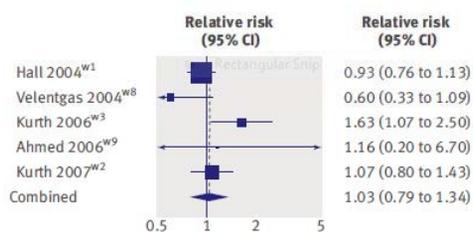
- 1 study: migraine with aura

1.71 (1.16-2.53)

Silberstein 2004

Schürks et al. 2009

Migraine and vascular death: Meta-analysis



Heterogeneity: $Q=8.6$, $df=4$, $P=0.07$, $I^2=54\%$

- 5 studies

- The pooled relative risk **1.03 (0.79-1.34)**

- An increased risk:
women
migraine with aura

Schürks et al. 2009

Increased risk: **peripartum** migraine

Vascular disorder	≈ RR
Brain infarction	15
Myocardial infarction and heart disease	2
Pulmonary embolus and deep venous thrombosis	3
Hypertension	8
Pre-eclampsia and gestational hypertension	1,8 - 5

Scher et al. 2005, Sanchez et al. 2008, Facchinetti et al. 2009, Sanchez et al. 2010, Bushnell et al. 2009, Blair and Nelson 2010, Chen et al. 2010

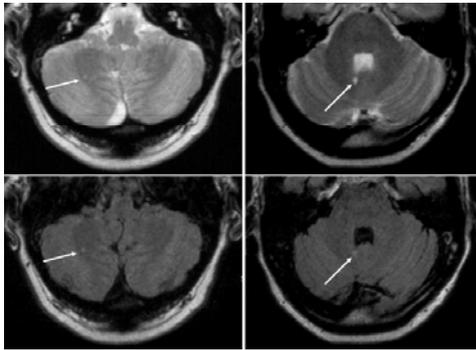
Migraine and subclinical brain lesions



- Population-based study
- Migraine without aura 134
Migraine with aura 161
Controls 140
- Exclusion criteria:
 - stroke
 - TIA
 - abnormal examination
- Neuroradiologist : MRI
Neurologist: headache

Kruit et al. 2004

Migraine and subclinical brain lesions



T2 and FLAIR images of 2 cases with cerebellar hyperintense lesions.

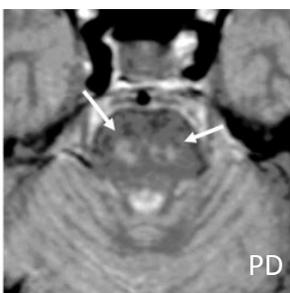
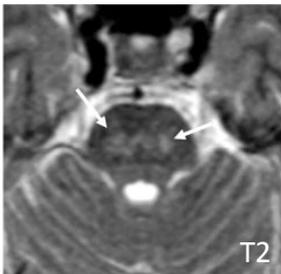
- No differences in the overall infarct prevalence between migraineurs and controls.

- Cerebellar region migraine vs. controls
OR = **7.1** (0.9-55)

- The highest risk migraine with aura > 1 attack per month women
OR = **15.8** (1.8-140)

Kruit et al. 2004

Migraine and subclinical brain lesions



- An increased prevalence of infratentorial, mostly pontine, hyperintensities in migraineurs.

- The etiology: small-vessel disease or/and repetitive perfusion deficits.

Kruit et al. 2006

Migraine and patent foramen ovale (PFO)

Migraine studies	Method	MA	MWA	Controls
Del Sette 1998.	TCD	18/44 (41%)	/	8/50 (16%)
Anzola 1999.	TCD	54/113 (48%)	12/53 (23%)	5/25 (20%)
Schwerzmann 2005.	TEE	44/93 (47%)	/	16/93 (17%)
Dowson 2005.	TTE	220/370 (59%)	/	/
overall		336/620 (54%)	12/53 (23%)	29/68 (17%)

PFO studies	Method	MA	MWA
Wilmshurst 2001.	TTE	42/120 (35%)	11/120 (9%)
Wilmshurst 2005.	TTE	59/119 (50%)	4/119 (3%)
Schwerzmann 2004.	OP	37/215 (17%)	11/215 (5%)
Reisman 2005.	OP	39/162 (24%)	18/162 (11%)
Morandi 2003.	OP	8/62 (13%)	9/62 (15%)
Post 2004.	OP	12/66 (18%)	14/66 (21%)
Azarbel 2005.	OP	22/66 (30%)	10/66 (15%)
overall		217/810 (27%)	77/810 (10%)

Migraine and PFO: Systematic review

- 18 observational studies
 - PFO and migraine OR = 5.13 (4.67-5.59)
 - PFO and migraine with aura OR = 3.21 (2.38-4.17)
 - Migraine and PFO OR = 2.54 (2.01-3.08)
- low to moderate grade of evidence
- 6 studies of PFO closure suggested improvement in migraine, but had a very low grade of evidence.

Migraine with aura and R-L shunt

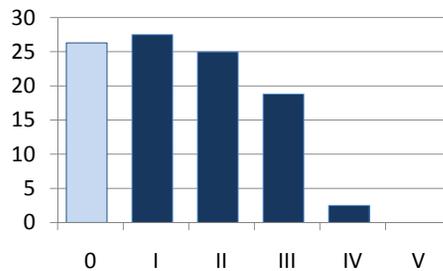
86 pts.

77.9% females

35.3 ± 12.4 years

Grade	Number of bubbles
0	0
I	1 (3) - 10
II	11-30
III	31-100
IV	101-300
V	> 300

Bubble-test 80 pts.: 73.7%



Headache Center, Belgrade

New comorbidities



Denmark

- Population-based study
31865 adult twins
- Previously documented diseases:
asthma, epilepsy, stroke
- New conditions: **kidney stone, psoriasis, rheumatoid arthritis and fibromyalgia.**
- MA had more comorbidities than MO and females more than males.

Le et al. 2011

Migraine, lifestyle and socioeconomic factors



Denmark

- Population-based study
- 31865 adult twins
- An increased risk of migraine:
 - lower level of schooling
 - lower level of education
 - retirement
 - unemployment
 - smoking

Le et al. 2011

Migraine and obesity



- Obesity was associated with increased frequency of attacks and might be a risk factor for migraine progression.

Bigal et al. 2006, Bigal et al. 2007

Comorbidities in cluster headache and migraine

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The most frequent comorbidities in CH group

Comorbid disorder	N (%) of patients
Chronic sinusitis (J32)	31 (23.8)
Hypertension (I10)	17 (13.1)
Gastric and duodenal ulcers (K25, K26)	12 (9.2)
Cervical spondylosis (M47.8)	10 (7.7)
Depression (F32) and anxiety disorders (F41)	6 (4.6)
Diabetes mellitus (E11)	5 (3.8)
Malignant tumors (C50, C54, C75.0)	4 (3.1)

130 pts

56.9%

The most frequent comorbidities in migraine group

Comorbid disorder	N (%) of patients
Hypertension (I10)	146 (14.9%)
Gastric and duodenal ulcers (K25, K26)	122 (12.4%)
Cervical spondylosis (M47.8)	61 (6.2%)
Depression (F32) and anxiety disorders (F41)	50 (5.1%)
Epilepsy (G40)	43 (4.4%)
Immunologically mediated disorders (D68.3, D86, J30, M05, M32, M35.0)	38 (3.9%)
Chronic sinusitis (J32)	35 (3.6%)
Iron deficiency anaemia (D50)	31 (3.2%)
Intracranial injury (S06)	30 (3.1%)
Cerebral infarctions (I63)	23 (2.3%)

982 pts

56.7%

- Comorbid disorders in cluster headache patients were frequent and similar to those noticed in migraine patients, except chronic sinusitis and diabetes mellitus.