

Headache

Series Editor: Paolo Martelletti

Antoinette Maassen van den Brink  
E. Anne MacGregor *Editors*

# Gender and Migraine



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# Headache

**Series Editor:**

Paolo Martelletti  
Roma, Italy

The purpose of this Series, endorsed by the European Headache Federation (EHF), is to describe in detail all aspects of headache disorders that are of importance in primary care and the hospital setting, including pathophysiology, diagnosis, management, comorbidities, and issues in particular patient groups. A key feature of the Series is its multidisciplinary approach, and it will have wide appeal to internists, rheumatologists, neurologists, pain doctors, general practitioners, primary care givers, and pediatricians. Readers will find that the Series assists not only in understanding, recognizing, and treating the primary headache disorders, but also in identifying the potentially dangerous underlying causes of secondary headache disorders and avoiding mismanagement and overuse of medications for acute headache, which are major risk factors for disease aggravation. Each volume is designed to meet the needs of both more experienced professionals and medical students, residents, and trainees.

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Antoinette Maassen van den Brink  
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# Gender and Migraine

 Springer

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# Foreword

In the last 50 years, medicine has considered and studied patients regardless of gender, sociocultural, and environmental characteristics. Clinical trials are a typical example; experimental clinical studies composed mainly, especially in the phase II studies, voluntary samples of the male population. In migraine, this is not epidemiologically possible, but this reverses and comforts this disparity. The consequence is a reduced personalization and standardization of care measured on the male subject without taking into account variables such as gender, social status, education, culture, education, access to care, and the type of multiple therapies required for intercurrent comorbidity or transient diseases.

This so-called neutral approach of contemporary medicine is badly combined with a disease, migraine, which intersects the patient's entire health life, whatever gender it belongs to or wishes to belong to.

We must therefore speak about gender-specific headache medicine, and this brilliant volume, edited by Antoinette Maassen van den Brink and Anne MacGregor, authoritative area scientists, will help experts to reshape clinical and research activity in the light of this not beyond derogable vision of primary headaches.

Rome, Italy

Paolo Martelletti

# Preface

We are delighted to produce this book, dedicated to gender and migraine, endorsed by the European Headache Federation. Migraine is recognized to affect more women than men and is widely considered to be consequent to the effect of female sex hormones. Yet, despite this recognition, basic research still often uses male animal models, without a justification of the sex used. Further, clinical trials fail to analyze data from men and women separately. With increasing numbers of transgender men and women undergoing hormone therapy, we also need to consider how treatment will affect migraine. Moreover, a proper study of the effect of hormone treatment in such specific groups may shed more light on the mechanisms involved in the effects of sex hormones on the pathophysiology of migraine. In this book, we aim to address many of these issues and discuss opportunities for future research.

We are extremely grateful to each of the renowned authors involved in this project who are all experts in their fields. The authors present their personal opinions supported by evidence. Given the variations in drugs and doses worldwide, we urge readers to refer to their local formularies when considering the recommendations presented.

We also thank Angela Schulze-Thomin and Donatella Rizza at Springer, with particular thanks to the project coordinator, Madona Samuel.

Rotterdam, The Netherlands  
London, UK

Antoinette Maassen van den Brink  
E. Anne MacGregor

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# Chapter 1

## Epidemiology of Migraine in Men and Women



Kjersti Grøtta Vetvik

### 1.1 Introduction

Migraine is a primary headache disorder—a headache without underlying cause [1]. The diagnosis is based on the patients' reported symptoms during attacks and can to date not be confirmed by any specific diagnostic tests, e.g., blood tests or radiological investigations.

The International Classification of Headache Disorders (ICHD) defines two major subtypes of migraine which may coexist; migraine without aura and migraine with aura [1]. The main feature of migraine without aura is a unilateral throbbing headache of moderate to severe intensity. Headache is often aggravated by routine physical activity and is accompanied by photo- and phonophobia, as well as nausea with or without vomiting. The migraine headache is thought to be a result of activation of trigeminovascular pathways, the brain stem, and diencephalic nuclei with subsequent release of neuropeptides and sensitization of second- and third-order central neurons [2].

Migraine with aura affects about one third of migraineurs and is characterized by one or more transient and fully reversible focal neurological symptoms developing gradually over minutes, of which each symptom lasts for up to an hour [1, 3, 4]. The most common aura symptoms are visual disturbances, followed by sensory symptoms and speech problems. In rare cases, the migraine aura can also include motor symptoms and retinal or brain stem symptoms. The migraine aura is in most cases followed, by or accompanied by, a headache that may or may not have migrainous features, but in fewer than 5%, no headache occurs [5]. A slowly propagating wave of neuronal depolarization, the so-called

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cortical spreading depression, is the anticipated underlying pathophysiological mechanism for the aura [6].

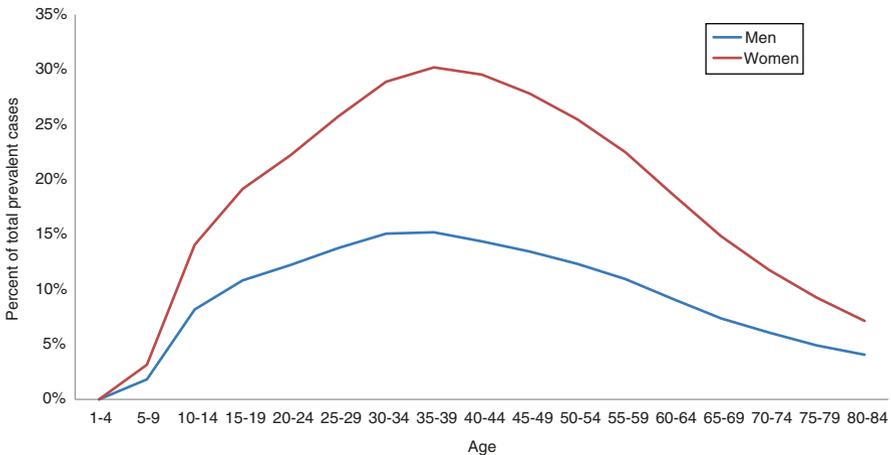
Migraine may also be subdivided into episodic and chronic migraine, depending on the total headache frequency per month. Chronic migraine is defined as headache occurring on 15 or more days per month for more than 3 months, which has the features of migraine headache on at least 8 days per month [1]. In episodic migraine, headache occurs less than 15 days per month.

The distinction between episodic and chronic migraine has mainly implications for the treatment, while the subclassification of migraine with and without aura additionally is relevant to comorbidity, assessment of risk factors (e.g., vascular diseases), and prognosis—especially in women.

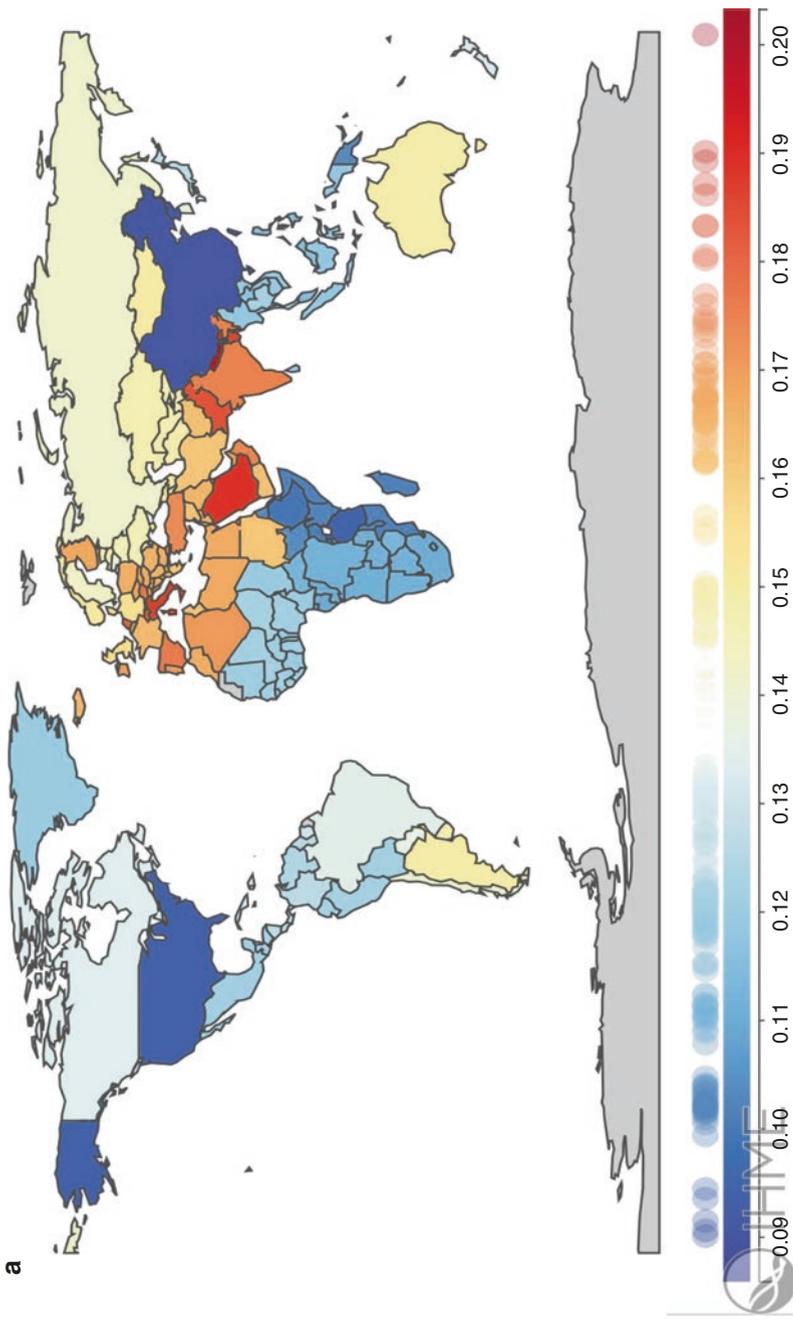
## 1.2 Prevalence of Migraine

The prevalence of migraine is significantly influenced by age and sex. In prepubertal children, the prevalence is about 3–7% with no significant difference between boys and girls [7–11]. From the age of 10–14 years, and during all the following years, the prevalence is two to three times higher in women than in men. The maximum sex difference is between age 30 and 45 (Fig. 1.1) when the migraine prevalence peaks in both men and women [12–16]. After the age of 50 years, the prevalence declines in both sexes, most markedly for women. New onset of migraine after the age of 50 years is rare in both sexes [17].

The prevalence of migraine varies across continents with the highest figures in Australia, Europe, and North America and the lowest in Africa, Central/South America, and Southeast Asia (Fig. 1.2a, b). The male to female prevalence ratio is



**Fig. 1.1** Prevalence of migraine by age and sex. Data from the Global Burden of Disease Study 2016 (GBD 2016) [18]



**Fig. 1.2** (a) Global prevalence of migraine among men aged 15–49 years. (b) Global prevalence of migraine among women aged 15–49 years [18]

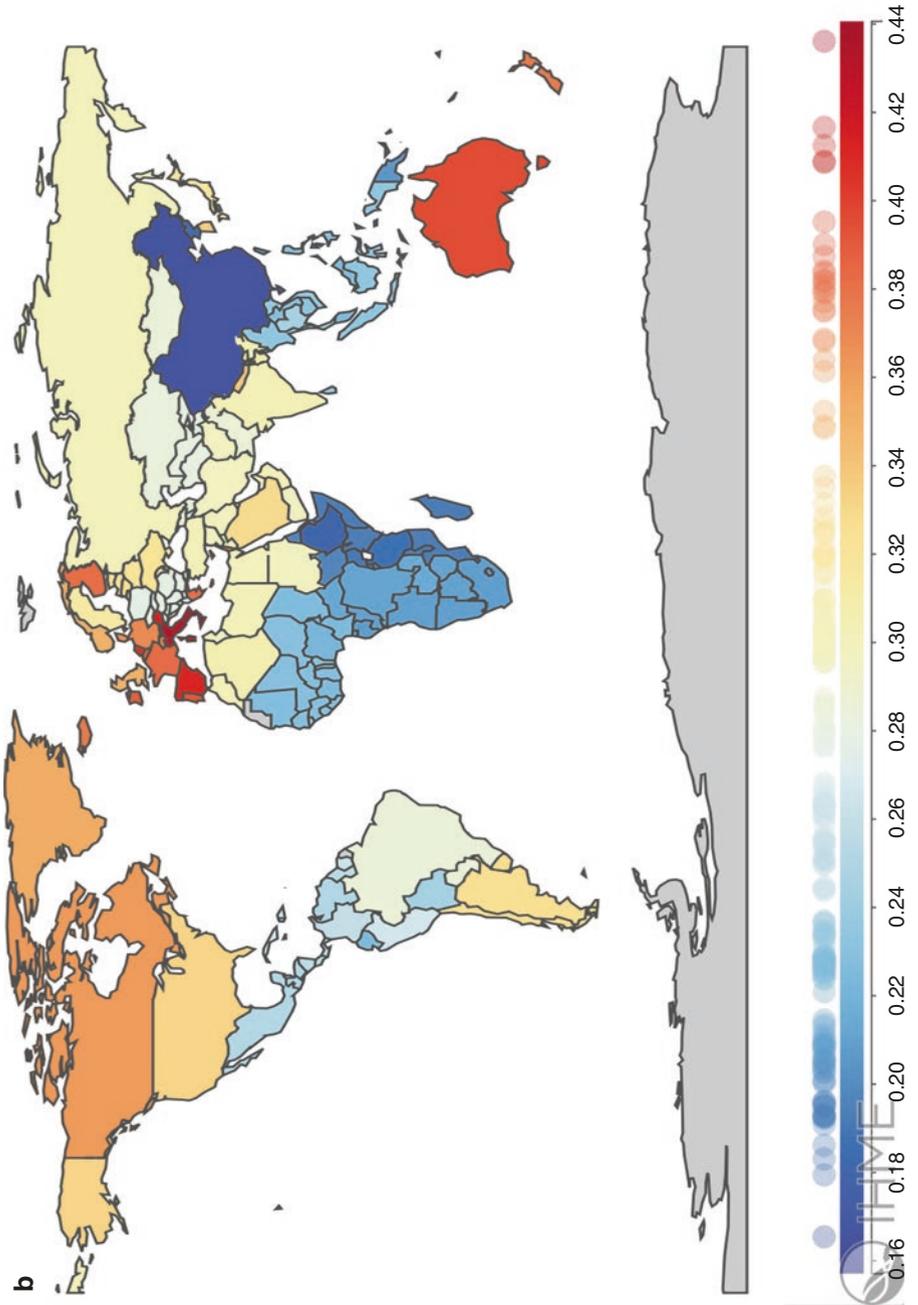


Fig. 1.2 (continued)

however consistently reported. Large population-based studies indicate that the 1-year prevalence and sex ratio are stable over time, with the numbers of men and women reporting migraine increasing in proportion to the population growth [12, 14, 16, 19].

### **1.2.1 Subtypes of Migraine**

In both men and women, migraine without aura occurs about twice as often as migraine with aura, and the prevalence of migraine with aura is two to three times higher in women than men. Among men, the 1-year prevalence is within the range 0.6–3.4% with corresponding figures for women 1.9–7.4% [4, 16, 20–24]. A Danish study reported slightly higher figures for the lifetime prevalence of migraine with aura: 3.6% for men and 7.5% for women [25].

Chronic migraine accounts for about 8% of all migraine cases with prevalence estimates typically in the range of 1.4–2.2% [26]. Similar to the total migraine prevalence, the prevalence of chronic migraine peaks in the 40s in both sexes [27]. Chronic migraine is 4.7 times more common in women than men among young adults aged <30 years [28]. Thereafter, the prevalence is two to three times higher in women than in men, mirroring the sex ratio of the total migraine prevalence [27–29]. However, in the general population, chronic migraine is more prevalent within the total male migraine population than within the total female migraine population. This becomes specifically evident after the age of 40 when chronic migraine accounts for 9.9–11.7% of all male migraine cases as compared to 7.3–8.4% of all female migraine cases [27].

### **1.2.2 Incidence and Age at Onset**

Age- and sex-specific incidence rates for migraine have been presented in both longitudinal and cross-sectional studies, although there is a dearth of longitudinal studies among adults [21, 30–33]. Common to all studies are the significant higher annual and cumulative incidence rates of migraine in women.

In a 12-year longitudinal Danish population-based study of 673 adults aged 25–64 years, the annual incidence rate of migraine was 8.1 per 1000 person-years with a male to female ratio of 1:6 [30]. Among both sexes, the incidence decreased significantly by age. The highest incidence was found among participants aged 25–34 years, with annual incidence rates of 6.5 per 1000 person-years for men and 22.8 per 1000 person-years for women.

Cross-sectional studies from the USA consistently report an earlier peak incidence in men [17, 34, 35]. The American Migraine Prevalence and Prevention (AMPP) study included more than 160,000 participants aged  $\geq 12$  years [17]. Migraine incidence peaked between the ages of 20 and 24 years in women (18.2 per