Chapter 7

# Panic Disorder and Panic Attacks

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## Introduction

Panic attacks (PAs) are an important set of anxiety symptoms and are defined in different editions of the *Diagnostic and Statistical Manual*: DSM (APA 1987, 1994). PAs are a common phenomenon that many people will experience at some point during their lives. A distinction is made between PAs and Panic Disorder (PD); the latter being characterized by recurrent PAs (Horwath, Gould & Weissman 2011). Despite some minor changes, the definition of PAs is largely comparable across the recent editions of the DSM (DSM-III, DSM-IV, DSM-5) (APA 1987, 1994, 2013). These are defined as periods of intense fear or discomfort in which at least 4 of the following 13 symptoms develop quickly, reaching a peak within 10 minutes:

(1) palpitations, pounding heart, or accelerated heart rate,
(2) sweating,
(3) trembling or shaking,
(4) sensations of shortness of breath or smothering,
(5) feeling of choking,
(6) chest pain or discomfort,
(7) nausea or abdominal distress,
(8) feeling dizzy, unsteady, lightheaded, or faint,
(9) derealization or depersonalization,
(10) fear of losing control or going crazy,
(11) fear of dying,
(12) numbness or tingling sensations,
(13) chills or hot flushes.

To diagnose PD, PAs should not be attributable to a general medical condition (such as hyperthyroidism or myocardial ischemia) or to substances (such as caffeine or amphetamine; Roberson-Nay & Kendler 2011). It should be noted that in DSM-IV, PAs were only coded in the context of a specific diagnosis, such as PD or agoraphobia. However, in DSM-5 PAs are conceptualized as a generic specifier and prognostic factor for severity of diagnosis, course, and comorbidity across different disorders. Thus, for example, an individual may have a major depressive disorder with PAs. Therefore, although the epidemiological data we present in this chapter are for DSM-IV PD, we also present the epidemiological data on PAs separately from PD (see also de Jonge *et al.* 2016).

In DSM-IV, the essential feature of PD is the presence of recurrent, unexpected PAs. In addition, at least one of the attacks must be followed by one month or more of at least one of the following:

(1) Persistent concern about having additional attacks.
(2) Worry about the implications of the attack or its consequences (such as losing control, having a heart attack, going crazy).
(3) A significant change in behaviour related to the attack.

In DSM-III and DSM-IV, PD was closely linked to the presence of agoraphobia such that explicit distinctions were made between PD with and without agoraphobia, and agoraphobia without PD. Agoraphobia was described as a condition accompanying PD, while agoraphobia without a history of PD described individuals where avoidance was a key symptom. The link between the disorders was based on research in clinical samples (Klein 1993) where agoraphobia mostly occurred after PD or PAs. However, it has become increasingly apparent that PAs may be a marker of psychopathology in general rather than being specific to PD or agoraphobia (Goodwin & Hamilton 2001; Batelaan *et al.* 2007, 2012) and that PD and agoraphobia are not expressions of a single disorder (Wittchen *et al.* 2010). In DSM-5, diagnostic criteria for PD and agoraphobia have therefore been unlinked, to emphasize that they are two independent diagnoses.

Anxiety disorders are among the major contributors to the worldwide burden of disease (Murray *et al.* 2010; Whiteford *et al.* 2013). The epidemiology of PD is well described. Several studies have reported



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the prevalence rates of PD, including the National Comorbidity Study (NCS), the National Comorbidity Study Replication (NCS-R), the Epidemiological Area Catchment Study (ECA), and the National Epidemiological Survey on Alcohol and Related Conditions (NESARC) (Regier, Narrow & Rae 1990; Kessler & Walters 2002; Kessler & Merikangas 2004; Grant & Dawson 2006). Lifetime rates are generally found in the order of 1–4%, with some exceptions at the higher end in specific studies or countries (e.g. NCS-R: 4.7%) and the lower end (e.g. in Taiwan: <0.5%). As recently summarized, risk factors for PD are fairly consistent and include female gender, smoking and alcohol problems, mental comorbidity, and low socio-economic status (Moreno-Peral *et al.* 2004). Age-of-onset (AOO) of PD is mostly in early to middle adulthood, regardless of presence or absence of agoraphobia (Weissman *et al.* 1997; Kessler *et al.* 2006). In comparison to other mental disorders, PD is characterized by relatively high levels of help-seeking (Iza *et al.* 2013) (see also Chapter 21), predominantly due to the extreme discomfort associated with PAs and the concern among sufferers that the symptoms may indicate a heart attack or some other medical problem.

Several authors have reported high levels of psychiatric comorbidity (Chen & Dilsaver 1995; Roy-Byrne *et al.* 2000; Kessler *et al.* 2006), especially with other anxiety disorders, but also with mood disorders (Grant *et al.* 2005). In the NCS, half of the respondents with lifetime PAs (50.9%) or with lifetime PD (55.6%) also met lifetime criteria for depression (Kessler *et al.* 1998). In addition, personality disorders have been associated with the presence of PD (Grant *et al.* 2005). In the NESARC study, avoidant and dependent personality disorders were strongly associated with PD, but paranoid, schizoid, histrionic, and antisocial personality disorders also had some association with PD.

Prior research based on the WMH survey in the United States (the NCS-R) found that PD is associated with substantial levels of impairment (Kessler *et al.* 2006). As many as 84.7% of individuals with PD and agoraphobia reported severe impairment on at least one of the four Sheehan domains (work, home, social, and personal relationship), while this percentage was 56.2% for people with PD without agoraphobia. Substantially less severe impairment (11.1%) was reported by individuals with PAs without PD and agoraphobia. In the same report, it was found that treatment rates varied in a similar way, in that high lifetime treatment rates were reported for individuals with lifetime PD (84.8% lifetime treatment for PD only and 96.1% for PD with agoraphobia) and somewhat lower rates for people with lifetime PAs (61.1%). Based on several reports it was concluded that most individuals with PD eventually receive treatment. Also, of those with a past 12-month diagnosis of PD, most receive treatment, although it was noted that most treatment fails to meet basic treatment guidelines (Wang *et al.* 2005).

Most of the available epidemiological data on PD and PAs comes from the United States. However, it has been suggested that considerable cross-cultural variation exists in the prevalence and presentation of the anxiety disorders (Marques *et al.* 2011). The first study on the cross-national epidemiology of PD was reported by Weissman *et al.* (1997). It was concluded that the rates and patterns of PD were fairly consistent across countries. However, while the lifetime prevalence rates varied between 1.4% (Alberta) and 3.5% (United States), in Taiwan this was considerably lower (0.4%). Mean AOO of PD was between 23 and 25 years of age and fairly consistent across the samples. Comorbidity with agoraphobia was consistently high, with a 10–20-fold increased risk across the samples. However, comorbidity with depression varied substantially, with ORs of 1.3 and 2.5 for Taiwan and Korea, and 16.0 and 17.3 for the United States and France. Overall, the study revealed a fairly consistent pattern of epidemiological data across countries but several notable differences were also observed. As the authors emphasized, several of the subsamples were fairly small and the methods differed somewhat across sites. Moreover, although this study had coverage of 11 sites including Puerto Rico, Lebanon, Korea, and Taiwan, many of these were Western or high-income countries (e.g. the United States, Canada, Germany, France, Italy, New Zealand). The WMH Surveys Initiative draws from a wider range of countries and employs much greater standardization of methods, thus providing a unique opportunity to study the cross-national epidemiology of both PAs and PD.

## Method

The assessment of PD and PAs was included in 28 of the surveys included in this volume, originating from 25 countries and comprising 147,264 participants (Table 7.1). With respect to PD, a blinded



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clinical reappraisal study using the Structured Clinical Interview for DSM-IV (SCID) (First *et al.* 2002) found good diagnostic concordance between CIDI and SCID diagnoses, indicated by an area under the curve of 0.72 (Haro *et al.* 2006). In addition, while most of the available literature is on PD (and often in conjunction with or without agoraphobia), the WMH surveys have extensive data on PAs as well. Within those reporting PAs, we further distinguish between single and recurrent PAs, in order to evaluate the DSM-5 decision to use PAs as a generic specifier. For analyses examining whether PAs predict onset and course of psychiatric disorders, we used PAs *in the absence of PD*, as otherwise these would count as being part of a comorbid psychiatric disorder (i.e. PD).

# Results

## Prevalence

Significant differences in prevalence rates of PAs and PD can be observed between country groups based on income level (Table 7.1). Specifically, higher prevalence rates are found in the high-income countries. Overall lifetime prevalence of PAs for all countries combined is 13.2% (Table 7.1), but this figure varies from 2.1% to 18.5% for low/lower-middle-income countries, 6.0% to 20.1% for upper-middle-income countries, and 6.6% to 27.4% for high-income countries. Of the people with lifetime PA, only a minority of 12.8% have a lifetime PD diagnosis. Lifetime prevalence of PD is thus much lower: 1.7%. This percentage varies between 0.8% for the low/lower-middle-income countries to 1.1% for the upper-middle-income countries and 2.2% for the high-income countries. Of people with lifetime PA without PD, about two-thirds (66.5%) have recurrent PAs. This figure is fairly consistent for the three income groups of countries. Overall, differences between countries are driven more by income level than by geographical region.

Twelve-month prevalence rates for PAs and PD (Appendix Table 7A.1) are 4.9% and 1.0%, respectively. Slightly more than a third (34.5%) of people with lifetime PAs, but without lifetime PD, have PAs in the last 12 months. For PD, this figure is 57.1%, indicating a moderate level of disorder persistence. Prevalence rates for 30-day PAs and PD are 1.6% and 0.4% respectively (Appendix Table 7A.2). Of people with 12-month PAs without PD, 29.2% have 30-day PAs. For PD, this figure is 40.6%, which suggests that episode persistence is lower than disorder persistence. Median AOO of PD is 32 years (interquartile range (IQR) 20–47) (Appendix Table 7A.3). The AOO distribution results in a projected lifetime risk of PD at age 75 of 2.7%. Median AOO of PAs is 34 years (IQR 20–51), and for PAs without PD it is 35 years (IQR 20–52), resulting in a projected lifetime risk at age 75 of 23.0% for PAs and 20.6% for PAs without PD.

## Role Impairment and Treatment

Severe role impairment in the past 12 months is reported by 45.7% of people with 12-month PD (Table 7.2). Impairment is more or less equally reported for the home (26.9%), work (30.8%), relationship (26.9%), and social domains (30.5%) (Table 7.2). It is notable that relatively fewer respondents from low/lower-middle-income countries and from the African region report impairment.

Of people with 12-month PD with any impairment, 59.8% report seeking treatment, most often consisting of general medical care (44.1%) and specialty mental health care (30.3%) (data not shown). The proportion of treated cases increases as a function of level of impairment, with 74.6% of those reporting severe impairment indicating receipt of any treatment. In low/lower-middle-income countries, only about one-third of people with 12-month PD report seeking treatment, and this proportion is irrespective of the level of associated impairment. Higher treatment proportions are found in the higher-income countries, particularly at higher levels of associated impairment. As another indicator of functional impairment, people with 12-month PD report on average 43.8 days-out-of-role in the past year (data not shown). For those reporting severe impairment on any of the four domains, this figure is 72.9 days.

## Comorbidity and Correlates

Lifetime comorbidity with other mental disorders in people with lifetime PD is 80.4%. Comorbidity levels are particularly high for other anxiety disorders (63.1%) and mood disorders (53.7%), but considerably lower for substance-abuse disorders (26.2%) and disruptive behaviour/impulse-control disorders (10.4%). In people with lifetime comorbidity, onset of PD precedes the onset of the other disorders in a minority of cases (15.4%) (data not shown).

Being under the age of 60, having early AOO, being female, being unemployed or disabled ('other' employment status), being divorced/separated/widowed,



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**Table 7.1 Lifetime prevalence of panic attack (PA) and DSM-IV panic disorder (PD) in the World Mental Health Surveys**

| Country | Among total population | | | | | | Among lifetime PA without lifetime PD cases | | | | Part 1 sample sizes | Sample size used[b] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Lifetime PA | | Lifetime PA without lifetime PD cases | | Lifetime PD | | Proportion with single attack | | Proportion with recurrent attacks[a] | | | |
| | % | SE | % | SE | % | SE | % | SE | % | SE | | |
| **Low/lower-middle-income countries** | **6.9** | **0.2** | **6.1** | **0.2** | **0.8** | **0.1** | **29.8** | **1.4** | **61.5** | **1.4** | **36,498** | **36,395** |
| Colombia | 18.5 | 0.7 | 17.2 | 0.8 | 1.3 | 0.2 | 43.4 | 2.6 | 52.8 | 2.5 | 4,426 | 4,422 |
| Iraq | 7.5 | 0.6 | 6.2 | 0.6 | 1.4 | 0.3 | 27.6 | 4.8 | 47.4 | 5.5 | 4,332 | 4,295 |
| Nigeria | 2.6 | 0.3 | 2.4 | 0.3 | 0.2 | 0.1 | 25.0 | 4.9 | 67.3 | 5.3 | 6,752 | 6,713 |
| Peru | 7.1 | 0.4 | 6.7 | 0.4 | 0.5 | 0.1 | 31.2 | 2.9 | 62.7 | 2.6 | 3,930 | 3,929 |
| PRC (Beijing/Shanghai) | 2.1 | 0.3 | 1.7 | 0.2 | 0.4 | 0.1 | 17.2 | 4.5 | 79.5 | 4.9 | 5,201 | 5,197 |
| PRC (Shenzhen) | 2.5 | 0.3 | 2.2 | 0.3 | 0.3 | 0.1 | 20.9 | 5.0 | 79.1 | 5.0 | 7,132 | 7,129 |
| Ukraine | 13.4 | 0.6 | 11.2 | 0.6 | 2.2 | 0.3 | 16.8 | 1.7 | 70.4 | 2.0 | 4,725 | 4,710 |
| **Upper-middle-income countries** | **11.1** | **0.3** | **10.0** | **0.3** | **1.1** | **0.1** | **28.7** | **1.1** | **57.1** | **1.2** | **24,612** | **24,565** |
| Brazil | 11.7 | 0.6 | 10.0 | 0.6 | 1.7 | 0.2 | 26.1 | 1.7 | 56.8 | 2.2 | 5,037 | 5,023 |
| Bulgaria | 6.0 | 0.3 | 5.0 | 0.3 | 1.1 | 0.1 | 14.7 | 2.4 | 53.5 | 3.9 | 5,318 | 5,301 |
| Colombia (Medellin) | 20.1 | 1.3 | 18.8 | 1.2 | 1.3 | 0.3 | 39.5 | 2.4 | 48.7 | 2.5 | 3,261 | 3,260 |
| Lebanon | 13.9 | 0.9 | 13.4 | 0.9 | 0.5 | 0.1 | 32.2 | 2.9 | 55.9 | 2.6 | 2,857 | 2,851 |
| Mexico | 7.8 | 0.5 | 6.8 | 0.5 | 1.0 | 0.2 | 28.8 | 3.0 | 69.5 | 2.9 | 5,782 | 5,781 |
| Romania | 13.9 | 0.8 | 13.3 | 0.8 | 0.7 | 0.2 | 19.2 | 2.9 | 63.1 | 3.2 | 2,357 | 2,349 |
| **High-income countries** | **16.6** | **0.2** | **14.4** | **0.2** | **2.2** | **0.1** | **22.5** | **0.5** | **69.4** | **0.5** | **81,839** | **81,754** |
| Australia | 21.5 | 0.6 | 17.9 | 0.6 | 3.7 | 0.3 | 25.6 | 1.5 | 71.9 | 1.7 | 8,463 | 8,461 |
| Belgium | 10.1 | 1.0 | 8.5 | 0.8 | 1.6 | 0.3 | 27.6 | 3.2 | 58.2 | 3.2 | 2,419 | 2,417 |
| France | 11.1 | 0.9 | 9.0 | 0.8 | 2.1 | 0.3 | 37.5 | 3.5 | 58.9 | 3.6 | 2,894 | 2,894 |
| Germany | 10.1 | 0.6 | 8.5 | 0.6 | 1.6 | 0.2 | 29.5 | 3.9 | 66.5 | 3.9 | 3,555 | 3,555 |
| Israel | 10.0 | 0.5 | 9.1 | 0.5 | 0.9 | 0.1 | 24.3 | 2.2 | 55.6 | 2.5 | 4,859 | 4,853 |
| Italy | 8.0 | 0.5 | 6.4 | 0.4 | 1.6 | 0.2 | 14.9 | 2.2 | 70.0 | 2.7 | 4,712 | 4,708 |
| Japan | 6.6 | 0.4 | 5.9 | 0.4 | 0.8 | 0.1 | 28.2 | 3.2 | 65.8 | 3.7 | 4,129 | 4,126 |

**Table 7.1** (*cont.*)

| Country | Among total population | | | | | | Among lifetime PA without lifetime PD cases | | | | Part 1 sample sizes | Sample size used[b] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Lifetime PA | | Lifetime PA without lifetime PD cases | | Lifetime PD | | Proportion with single attack | | Proportion with recurrent attacks[a] | | | |
| | % | SE | % | SE | % | SE | % | SE | % | SE | | |
| New Zealand | 27.4 | 0.6 | 24.7 | 0.5 | 2.8 | 0.2 | 22.8 | 1.0 | 74.3 | 1.0 | 12,790 | 12,781 |
| Northern Ireland | 24.4 | 0.8 | 21.1 | 0.7 | 3.3 | 0.3 | 23.1 | 1.8 | 70.6 | 2.0 | 4,340 | 4,335 |
| Poland | 5.9 | 0.2 | 5.6 | 0.2 | 0.3 | 0.1 | 11.3 | 1.1 | 47.1 | 2.1 | 10,081 | 10,049 |
| Portugal | 19.6 | 0.7 | 17.9 | 0.6 | 1.7 | 0.3 | 21.9 | 1.9 | 64.4 | 2.1 | 3,849 | 3,841 |
| Spain | 9.6 | 0.5 | 8.4 | 0.5 | 1.2 | 0.2 | 33.5 | 3.0 | 54.1 | 3.2 | 5,473 | 5,472 |
| Spain (Murcia) | 16.3 | 1.0 | 14.7 | 1.0 | 1.6 | 0.4 | 27.1 | 2.3 | 54.5 | 4.1 | 2,621 | 2,617 |
| Netherlands | 14.0 | 0.8 | 11.0 | 0.7 | 3.0 | 0.4 | 24.3 | 3.7 | 72.3 | 3.7 | 2,372 | 2,370 |
| United States | 27.3 | 0.7 | 22.6 | 0.7 | 4.7 | 0.2 | 16.0 | 0.8 | 79.2 | 0.8 | 9,282 | 9,275 |
| **All countries combined** | **13.2** | **0.1** | **11.5** | **0.1** | **1.7** | **0.0** | **24.4** | **0.4** | **66.5** | **0.5** | **147,264** | **142,714** |
| **WHO regions**[c] | | | | | | | | | | | | |
| Region of the Americas | 16.8 | 0.4 | 14.6 | 0.4 | 2.2 | 0.1 | 26.7 | 0.9 | 66.6 | 0.9 | 31,718 | 31,690 |
| African region | 2.6 | 0.3 | 2.4 | 0.3 | 0.2 | 0.1 | 25.0 | 4.9 | 67.3 | 5.3 | 11,067 | 6,713 |
| Western Pacific region | 15.6 | 0.3 | 13.7 | 0.2 | 2.0 | 0.1 | 23.7 | 0.8 | 73.4 | 0.8 | 37,715 | 37,694 |
| Eastern Mediterranean region | 10.0 | 0.4 | 9.1 | 0.4 | 1.0 | 0.1 | 27.9 | 1.8 | 53.7 | 1.9 | 12,048 | 11,999 |
| Western European region | 13.6 | 0.2 | 11.7 | 0.2 | 1.9 | 0.1 | 25.7 | 0.9 | 64.1 | 1.0 | 32,235 | 32,209 |
| Eastern European region | 8.4 | 0.2 | 7.4 | 0.2 | 0.9 | 0.1 | 15.0 | 0.9 | 58.4 | 1.3 | 22,481 | 22,409 |
| **Comparison between countries**[d] | **$F_{27,v} = 164.6$*, $P < 0.001$** | | **$F_{27,v} = 143.0$*, $P < 0.001$** | | **$F_{27,v} = 32.4$*, $P < 0.001$** | | **$F_{27,v} = 12.7$*, $P < 0.001$** | | **$F_{27,v} = 16.9$*, $P < 0.001$** | | | |
| **Comparison between low-, middle-, and high-income country groups**[d] | **$F_{2,v} = 638.7$*, $P < 0.001$** | | **$F_{2,v} = 529.7$*, $P < 0.001$** | | **$F_{2,v} = 130.8$*, $P < 0.001$** | | **$F_{2,v} = 22.5$*, $P < 0.001$** | | **$F_{5,v} = 50.5$*, $P < 0.001$** | | | |
| **Comparison between WHO regions**[d] | **$F_{5,v} = 320.6$*, $P < 0.001$** | | **$F_{5,v} = 275.2$*, $P < 0.001$** | | **$F_{5,v} = 85.8$*, $P < 0.001$** | | **$F_{5,v} = 20.3$*, $P < 0.001$** | | **$F_{5,v} = 30.8$*, $P < 0.001$** | | | |

[a]Recurrent panic attacks = at least two panic attacks.
[b]Sample size used after excluding lifetime panic attack cases with missing age-of-onset.
[c]**Region of the Americas** (Colombia, Mexico, Brazil, United States, Colombia (Medellin)); **African region** (Nigeria); **Western Pacific region** (PRC (Shenzhen), PRC Beijing and Shanghai, Japan, Australia, New Zealand); **Eastern Mediterranean region** (Israel, Iraq, Lebanon); **Western European region** (Belgium, France, Germany, Italy, Netherlands, Spain, Northern Ireland, Portugal, Spain (Murcia); **Eastern European region** (Romania, Bulgaria, Poland, Ukraine).
[d]Wald design-corrected F-tests were used to determine if there is variation in prevalence estimates across countries. The denominator degree of freedom, v, is 5367.
PRC: People's Republic of China.

**Table 7.2 Severity of role impairment (Sheehan Disability Scale) associated with 12-month panic disorder, by country income groups and WHO region**

| Country | Proportion with severe role impairment (SDS score: 7–10) | | | | | | | | | | Number of 12-month panic disorder cases |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Home | | Work | | Relationship | | Social | | Any[a] | | |
| | % | SE | % | SE | % | SE | % | SE | % | SE | |
| **Country Income groups** | | | | | | | | | | | |
| Low/lower-middle-income countries | 21.7 | 3.8 | 19.0 | 3.8 | 17.1 | 4.0 | 17.2 | 3.9 | 29.9 | 4.3 | 204 |
| Upper-middle-income countries | 32.5 | 4.2 | 30.3 | 4.5 | 30.0 | 3.8 | 31.1 | 4.1 | 42.1 | 4.5 | 184 |
| High-income countries | 26.9 | 1.7 | 32.9 | 1.9 | 28.0 | 1.9 | 32.4 | 1.9 | 49.1 | 2.0 | 1,077 |
| **WHO regions** | | | | | | | | | | | |
| Region of the Americas | 27.9 | 2.6 | 28.4 | 2.6 | 26.9 | 2.7 | 31.7 | 2.9 | 46.5 | 3.0 | 446 |
| African region | 8.7 | 7.0 | 3.7 | 4.0 | 3.7 | 4.0 | 3.7 | 4.0 | 8.7 | 7.0 | 9 |
| Western Pacific region | 18.2 | 2.3 | 30.7 | 3.2 | 24.8 | 2.8 | 29.7 | 2.9 | 44.3 | 3.4 | 454 |
| Eastern Mediterranean region | 40.5 | 7.6 | 39.5 | 8.2 | 28.3 | 8.4 | 23.7 | 7.0 | 52.1 | 8.1 | 78 |
| Western European region | 33.7 | 3.3 | 35.6 | 3.4 | 29.8 | 3.2 | 33.7 | 3.2 | 48.6 | 3.4 | 339 |
| Eastern European region | 30.0 | 4.7 | 24.9 | 4.8 | 27.1 | 5.0 | 25.6 | 5.2 | 39.3 | 5.3 | 139 |
| All countries combined | 26.9 | 1.4 | 30.8 | 1.6 | 26.9 | 1.6 | 30.5 | 1.6 | 45.7 | 1.7 | 1,465 |
| **Comparison between low-, middle-, and high-income countries[b]** | **$F_{2,v} = 1.9$, $P = 0.154$** | | **$F_{2,v} = 5.1$*, $P = 0.006$** | | **$F_{2,v} = 3.4$*, $P = 0.035$** | | **$F_{2,v} = 5.4$*, $P = 0.004$** | | **$F_{2,v} = 7.5$*, $P < 0.001$** | | |
| **Comparison between WHO regions[b]** | **$F_{5,v} = 4.6$*, $P < 0.001$** | | **$F_{5,v} = 1.7$, $P = 0.130$** | | **$F_{5,v} = 0.9$, $P = 0.483$** | | **$F_{5,v} = 1.2$, $P = 0.287$** | | **$F_{5,v} = 1.2$, $P = 0.329$** | | |

[a]Highest severity category across four SDS role domains.
[b]Wald design-corrected F-tests were used to determine if there is variation in impairment severity across countries. The denominator degree of freedom, v, is 5367.

and having lower education or household income are all associated with both PAs without PD and with PD (data not shown). These correlates are largely comparable for the different country income groups, and largely in line with a recent systematic review (Moreno-Peral *et al.* 2014). Few differences are found when comparing risk factors for 30-day, lifetime, 12-month/lifetime, and 30-day/12-month cases, suggesting that similar risk factors may operate for onset and course of PAs and PD. However, as an exception, female gender is associated with increased odds of onset of PAs and PD (lifetime prevalence), but not with episode persistence (30-day/12-month).

## Number and Type of PAs

As noted earlier, there are two significant changes in DSM-5 regarding PD and PAs, namely that PD became unlinked from agoraphobia, and that the presence of PAs is a generic specifier that can apply to any mental disorders. This section explores the support for these changes.

In Table 7.3, we distinguish between single and recurrent PAs. Based on the AOO data we were able to determine the presence of a wide range of mental disorders that occurred after the first PA. To be on the safe side, we excluded the onset of a disorder that occurred in the same year as the PA. The findings are quite consistent in that single PAs are generally not associated with subsequent mental disorders. There are only a few exceptions to this general rule, namely that single PAs are associated with an increased risk of disruptive behaviour/impulse-control disorders and alcohol abuse and a decreased risk of specific phobia and any anxiety disorder. In contrast, recurrent PAs are associated with increased odds of all mental disorders. We also examined whether the course of a disorder varied as a function of the presence of single or recurrent PAs. Here we found that single PAs are generally slightly protective against the persistence of disorders while recurrent PAs are associated with a worse course. Specifically, the risk of any 12-month mental disorder given a lifetime disorder is significantly lower (OR 0.7) in the presence of a single PA and significantly higher (OR 1.3) in the presence of recurrent PAs.

In Table 7.4, we distinguish between several subgroups of individuals with combinations of anxiety disorders to evaluate the similarities and dissimilarities in terms of kinds and numbers of PAs. In respondents with a lifetime diagnosis of agoraphobia without PD, 52.4% experienced a PA. For social anxiety disorder and specific phobia without PD, rates of 42.2% and 32.5% are found. Thus even in the absence of PD, many people with anxiety disorders experience PAs. About half of the individuals who experience PAs report unexpected attacks. Remarkably, this ratio between expected and unexpected PAs is relatively stable across individual anxiety disorders, the exception being PD. The number of expected attacks among people experiencing expected attacks is higher than the number of unexpected attacks among those who experience unexpected attacks. This is the case for all groups, although the difference is smallest for individuals with PD. Median AOO of PAs is generally around 20 years, with the exception of people with a single PA in the absence of PD where the median AOO is later (29.5 years, IQR 20–41.6).

# Discussion

These analyses of the WMH surveys data on PD and PAs confirm the picture that PAs are a relatively common phenomenon (Von Korff *et al.* 1985; Eaton *et al.* 1994, 1998). In contrast, lifetime prevalence for PD is much lower. For PD, we found a lifetime prevalence of 1.7% and a projected lifetime risk at age 75 of 2.7%. These findings are largely in line with previous cross-national DSM-IV estimates of 1.4–2.9% (Weissman *et al.* 1997) but notably lower than prior estimates exclusively from high-income countries like the United States. Also comparable to previous reports, most PAs actually occur in the absence of PD. While 13.2% of respondents ever experienced one or more PAs, only 1.7% of respondents met criteria for lifetime PD. Similarly, while 23.0% of people are projected to ever experience one or more PAs, 89.6% of these individuals do not fulfil criteria for lifetime PD. Of interest, although there were substantial differences in the prevalence of PAs across countries, this ratio was very stable in that most people experiencing PAs did not develop PD.

Based on the association of PD with impairment, we conclude that this condition is a serious mental disorder with substantial consequences. Almost half of individuals with 12-month PD reported severe limitations in their functioning. It should be noted that this figure was even higher in a previous report on the NCS, namely 56% for PD without agoraphobia and 84.7% for PD with agoraphobia. We also calculated how many days in the past year that respondents with



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**Table 7.3 Comorbidity of single and recurrent panic attacks (with and without panic disorder) with DSM-IV disorders, all countries combined**

| Type of comorbid disorder | Panic attack without panic disorder as a predictor of comorbid disorder onset | | | | | | | | Panic attack with panic disorder as a predictor of comorbid disorder course | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Single attack | | | | Recurrent attacks | | | | Single attack | | | | Recurrent attacks | | | |
| | % with lifetime single PA onset prior to onset of lifetime disorder | | Lifetime single PA predicting lifetime disorder[a] | | % with lifetime recurrent PA onset prior to onset of lifetime disorder | | Lifetime recurrent PA predicting lifetime disorder[a] | | % with lifetime single PA prior to 12-month disorder episode among lifetime disorder cases[b] | | Lifetime single PA predicting 12-month disorder episode among lifetime disorder cases[c] | | % with lifetime recurrent PA prior to 12-month disorder episode among lifetime disorder cases[b] | | Lifetime recurrent PA predicting 12-month disorder episode among lifetime disorder cases[c] | |
| | % | (SE) | OR | (95% CI) | % | (SE) | OR | (95% CI) | % | (SE) | OR | (95% CI) | % | (SE) | OR | (95% CI) |
| **I. Mood disorder** | | | | | | | | | | | | | | | | |
| Major depressive episode/dysthymia | **17.8** | (1.5) | **1.1** | (0.9–1.3) | **39.2** | (1.0) | **2.0*** | (1.9–2.2) | **3.0** | (0.2) | **0.5*** | (0.4–0.6) | **22.5** | (0.6) | **1.2*** | (1.1–1.3) |
| Bipolar spectrum disorder | **21.0** | (4.1) | **0.9** | (0.6–1.3) | **54.7** | (2.4) | **2.9*** | (2.5–3.4) | **2.2** | (0.4) | **0.4*** | (0.2–0.7) | **29.0** | (1.4) | **1.1** | (0.8–1.3) |
| Any mood disorder | **18.0** | (1.4) | **1.1** | (0.9–1.3) | **39.1** | (1.0) | **2.1*** | (2.0–2.2) | **2.9** | (0.2) | **0.5*** | (0.4–0.6) | **22.8** | (0.6) | **1.2*** | (1.1–1.3) |
| **II. Anxiety disorder** | | | | | | | | | | | | | | | | |
| Generalized anxiety disorder | **17.3** | (2.4) | **0.9** | (0.6–1.2) | **42.7** | (1.6) | **2.3*** | (2.0–2.6) | **3.3** | (0.4) | **0.6*** | (0.5–0.9) | **25.8** | (1.1) | **0.9** | (0.8–1.1) |
| Social anxiety disorder | **5.9** | (1.6) | **0.6** | (0.4–1.1) | **19.5** | (1.3) | **2.1*** | (1.8–2.4) | **3.4** | (0.4) | **0.9** | (0.6–1.2) | **27.9** | (1.0) | **1.0** | (0.8–1.1) |
| Specific phobia | **1.9** | (0.7) | **0.5*** | (0.2–1.0) | **7.5** | (0.7) | **1.3*** | (1.1–1.6) | **3.5** | (0.3) | **0.9** | (0.7–1.2) | **21.5** | (0.6) | **1.0** | (0.8–1.1) |
| Agoraphobia without panic | **9.9** | (5.6) | **0.8** | (0.3–2.7) | **25.3** | (2.3) | **2.9*** | (2.3–3.7) | **4.2** | (1.0) | **1.0** | (0.4–2.4) | **37.1** | (2.3) | **1.2** | (0.8–1.6) |
| Post-traumatic stress disorder | **12.0** | (2.3) | **0.7** | (0.5–1.0) | **41.0** | (1.8) | **2.4*** | (2.1–2.7) | **4.0** | (0.6) | **0.6*** | (0.4–1.0) | **31.0** | (1.4) | **1.2** | (0.9–1.4) |
| Any anxiety disorder | **6.1** | (1.0) | **0.7*** | (0.5–1.0) | **18.1** | (0.8) | **1.9*** | (1.7–2.1) | **3.5** | (0.2) | **0.7*** | (0.5–0.9) | **24.2** | (0.6) | **1.0** | (0.9–1.2) |

**Table 7.3** (*cont.*)

| Type of comorbid disorder | Panic attack without panic disorder as a predictor of comorbid disorder onset | | | | | | | | Panic attack with panic disorder as a predictor of comorbid disorder course | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Single attack | | | | Recurrent attacks | | | | Single attack | | | | Recurrent attacks | | | |
| | % with lifetime single PA onset prior to onset of lifetime disorder | | Lifetime single PA predicting lifetime disorder[a] | | % with lifetime recurrent PA onset prior to onset of lifetime disorder | | Lifetime recurrent PA predicting lifetime disorder[a] | | % with lifetime single PA prior to 12-month disorder episode among lifetime disorder cases[b] | | Lifetime single PA predicting 12-month disorder episode among lifetime disorder cases[c] | | % with lifetime recurrent PA prior to 12-month disorder episode among lifetime disorder cases[b] | | Lifetime recurrent PA predicting 12-month disorder episode among lifetime disorder cases[c] | |
| | % | (SE) | OR | (95% CI) | % | (SE) | OR | (95% CI) | % | (SE) | OR | (95% CI) | % | (SE) | OR | (95% CI) |
| **III. Disruptive behaviour/impulse-control disorder** | | | | | | | | | | | | | | | | |
| Intermittent explosive disorder | **15.6** | (3.0) | **1.3** | (0.9–1.9) | **36.9** | (2.1) | **2.7*** | (2.3–3.2) | **2.7** | (0.5) | **0.8** | (0.5–1.4) | **20.9** | (1.2) | **1.1** | (0.8–1.4) |
| Binge-eating disorder | **35.1** | (9.4) | **1.5** | (0.7–3.1) | **62.8** | (4.2) | **2.8*** | (2.1–3.6) | **3.8** | (1.1) | **1.2** | (0.4–3.4) | **24.1** | (2.7) | **0.9** | (0.6–1.4) |
| Bulimia nervosa | **28.7** | (10.6) | **1.5** | (0.6–3.6) | **50.0** | (5.0) | **2.4*** | (1.7–3.5) | **6.0** | (2.2) | **2.3** | (0.9–6.1) | **24.8** | (4.4) | **1.0** | (0.6–1.8) |
| Any disruptive behaviour/impulse-control disorder | **23.1** | (3.9) | **1.5*** | (1.0–2.2) | **41.5** | (2.1) | **2.5*** | (2.1–2.9) | **3.2** | (0.5) | **1.0** | (0.6–1.6) | **22.2** | (1.2) | **1.0** | (0.8–1.3) |
| **IV. Substance-use disorder** | | | | | | | | | | | | | | | | |
| Alcohol abuse | **25.1** | (2.8) | **1.3*** | (1.0–1.8) | **55.6** | (1.6) | **2.3*** | (2.1–2.6) | **3.2** | (0.6) | **1.0** | (0.7–1.5) | **16.6** | (1.1) | **1.1** | (0.9–1.3) |
| Alcohol dependence | **20.0** | (4.3) | **0.9** | (0.6–1.4) | **56.9** | (2.4) | **2.7*** | (2.3–3.2) | **3.0** | (1.0) | **0.7** | (0.3–1.7) | **21.0** | (2.0) | **1.0** | (0.8–1.3) |
| Drug abuse | **22.9** | (4.0) | **1.3** | (0.9–1.9) | **53.1** | (2.4) | **2.6*** | (2.2–3.0) | **3.3** | (1.0) | **0.6** | (0.3–1.1) | **25.6** | (2.5) | **1.2** | (0.9–1.7) |
| Drug dependence | **23.8** | (6.3) | **1.1** | (0.6–2.1) | **57.0** | (3.3) | **3.0*** | (2.4–3.8) | **3.3** | (1.3) | **0.5** | (0.2–1.3) | **35.8** | (4.3) | **1.8*** | (1.1–2.8) |
| Any substance-use disorder | **20.8** | (2.4) | **1.2** | (0.9–1.6) | **51.1** | (1.5) | **2.3*** | (2.0–2.5) | **3.4** | (0.6) | **1.0** | (0.6–1.6) | **18.3** | (1.0) | **1.2** | (1.0–1.4) |
| **V. Any mental disorder** | **10.9** | **(0.9)** | **1.1** | **(0.9–1.3)** | **23.3** | **(0.7)** | **2.0*** | **(1.8–2.2)** | **3.4** | **(0.2)** | **0.7*** | **(0.6–0.8)** | **21.2** | **(0.4)** | **1.3*** | **(1.2–1.4)** |

*Significant at the 0.05 level, two-sided test.

[a]Each model was estimated using lifetime panic attack as predictor of lifetime comorbid disorder onset in a separate discrete-time survival model controlling for country, person-years, gender, and age-cohort. Person-years were restricted up to and including the first onset of lifetime comorbid disorder.

[b]Respondents with lifetime PA onset that occurred within 12 months of the age of interview were not included in the numerator.

[c]Each model was estimated using lifetime panic attack as predictor of 12-month comorbid episode among lifetime comorbid disorder cases in a separate logistic regression model controlling for country, gender, age-cohort, time since comorbid disorder onset, and age of comorbid disorder onset. Respondents with lifetime PA onset that occurred within 12 months of the age of interview were not counted among the predictor set.

**Table 7.4 Prevalence and age-of-onset of different types of panic attacks, all countries combined**

| | Any panic attacks | | Age-of-onset of attacks | Expected attacks only | | | | | | Unexpected attacks[b] | | Number of expected attacks[c] | Number of unexpected attacks[d] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Any[a] | | Real danger | | Strong fear | | | | | |
| | % | (SE) | Median (IQR) | % | (SE) | % | (SE) | % | (SE) | % | (SE) | Median (IQR) | Median (IQR) |
| Total sample | **13.2** | (0.1) | **21.5** (13.7–34.4) | **6.5** | (0.1) | **3.6** | (0.1) | **3.9** | (0.1) | **6.6** | (0.1) | **2.8** (1.0–8.3) | **1.9** (1.0–4.9) |
| Panic attack | – | – | **21.5** (13.7–34.4) | **49.5** | (0.5) | **27.2** | (0.4) | **29.4** | (0.4) | **49.6** | (0.5) | **2.8** (1.0–8.3) | **1.9** (1.0–4.9) |
| Panic attack without panic disorder | **100.0** | (0.0) | **21.5** (13.8–34.6) | **56.6** | (0.5) | **31.1** | (0.5) | **33.6** | (0.5) | **42.3** | (0.5) | **2.4** (1.0–5.9) | **1.2** (1.0–2.5) |
| Panic attack without panic disorder (single attack) | **100.0** | (0.0) | **29.5** (20.0–41.6) | **49.8** | (1.0) | **32.7** | (0.9) | **17.2** | (0.8) | **48.4** | (1.0) | – | – |
| Panic attack without panic disorder (recurrent attack) | **100.0** | (0.0) | **19.6** (12.8–31.5) | **49.0** | (0.6) | **24.8** | (0.5) | **32.4** | (0.5) | **50.6** | (0.6) | **3.8** (1.9–9.7) | **2.9** (1.5–7.9) |
| Panic disorder | **100.0** | (0.0) | **21.2** (13.0–32.3) | – | – | – | – | – | – | **100.0** | (0.0) | **9.6** (4.1–49.2) | **9.2** (4.7–19.8) |
| Agoraphobia with or without panic disorder | **64.6** | (1.5) | **19.3** (13.0–31.5) | **19.8** | (1.1) | **9.3** | (0.9) | **15.8** | (1.0) | **44.7** | (1.5) | **9.1** (3.0–42.1) | **4.9** (1.6–19.3) |
| Agoraphobia without panic disorder | **52.4** | (1.8) | **19.0** (12.8–31.5) | **25.9** | (1.4) | **12.0** | (1.1) | **20.5** | (1.3) | **26.4** | (1.6) | **5.4** (2.3–19.9) | **1.4** (1.0–2.6) |
| Social anxiety disorder | **48.5** | (0.8) | **18.1** (12.4–28.5) | **21.3** | (0.7) | **10.3** | (0.5) | **16.5** | (0.6) | **27.0** | (0.7) | **4.8** (2.1–18.14) | **3.1** (1.2–9.6) |
| Social anxiety disorder without panic disorder | **42.2** | (0.9) | **18.1** (12.2–28.5) | **23.9** | (0.7) | **11.5** | (0.5) | **18.6** | (0.7) | **17.9** | (0.7) | **4.1** (1.8–10.2) | **1.7** (1.0–2.8) |
| Specific phobia | **37.5** | (0.7) | **18.9** (12.4–30.4) | **17.1** | (0.5) | **8.5** | (0.4) | **12.3** | (0.4) | **20.2** | (0.5) | **4.1** (1.7–14.4) | **2.7** (1.0–7.3) |
| Specific phobia without panic disorder | **32.5** | (0.7) | **18.9** (12.5–31.0) | **18.4** | (0.5) | **9.1** | (0.4) | **13.3** | (0.5) | **13.7** | (0.5) | **3.3** (1.4–9.6) | **1.5** (1.0–2.6) |

"–" not applicable.
[a]Attacks that occurred in a situation of unreasonably strong fear or in a situation of real danger only.
[b]With or without expected attacks.
[c]Among cases with expected attacks.
[d]Among cases with unexpected attacks.

PD reporting severe impairment were unable to carry out their normal daily roles. We found this to amount to some two to three months in the year on average, suggesting quite substantial role limitations for some individuals with PD.

Comorbidity of PD with other mental disorders was found to be high (80.4% over the lifetime) and particularly so with regard to mood and anxiety disorders. Substantial differences were observed regarding treatment status, which is linearly related to the level of severity and country income level, ranging from 42.2% for individuals reporting no impairments to 74.6% for those reporting severe impairment, and from 35.6% for individuals in low/lower-middle-income countries to 66.9% for those in high-income countries.

Among respondents who ever had at least one PA, the majority had more than one PA. The ratio of recurrent attacks versus single attack was about 2:1 in all countries, apart from Nigeria, Poland, and Colombia (Medellin) where the majority of people experiencing PAs had more than one. Recurrent PAs were associated with a substantially lower AOO than single PAs (19.6 years versus 29.5 years). Remarkably, recurrent PAs were predictive of a broad range of subsequent mental disorders whereas single PAs were not. Significantly increased odds were found for all 14 included disorders, typically around 2. Highest odds were found for subsequent onset of drug dependence, bipolar disorder, agoraphobia (without panic) and binge-eating disorder, which were all about 3. Lowest odds (1.3) were found for specific phobia, which may be due to the low AOO of that disorder. Of interest, recurrent PAs were even associated with an increased odds (1.3) of reporting 12-month disorders among people with a lifetime mental disorder. This suggests that the presence of recurrent PAs may predict a poorer course of mental disorders. This finding therefore supports the DSM-5 decision to frame PAs as a generic severity marker, based on several indications from the literature (Klerman *et al.* 1991; Goodwin *et al.* 2001; Craske *et al.* 2010). Note however, that we found no increased odds of mental disorders for people with a single PA, nor any indication that the presence of single PAs are associated with a poor course of mental disorder among those with a lifetime mental disorder. The message should thus be that only recurrent PAs are a generic specifier for mental disorder severity.

In contrast, we found no support for a distinction between expected and unexpected PAs in the context of being generic specifiers for mental disorder severity. This finding is in line with several others (Craske *et al.* 1995; Bruce *et al.* 2005; Kessler *et al.* 2006). In the total sample, we found that about half of the respondents with lifetime PAs had unexpected PAs. This ratio between expected and unexpected PAs was relatively stable across specific groups of anxiety disorders, the exception, by definition, being individuals diagnosed with PD. Also in individuals with agoraphobia, 44.7% experienced unexpected attacks, and even in people with agoraphobia that did not qualify for PD, 26.4% experienced unexpected attacks. These findings challenge the notion that unexpected PAs are specific to PD, and suggest they are a common phenomenon across a range of mental disorders. We also observed that the numbers of expected and unexpected attacks differed in that expected PAs occurred about three to four times as often as unexpected PAs. This ratio was also relatively stable, although somewhat higher across subgroups of people with agoraphobia, specific phobia, and social anxiety disorder, and somewhat lower for panic disorder.

Returning to the start of this chapter and the definition of PAs and PD, it is clear that WMH data provide a valuable, new perspective. While many of the observations in the literature have been confirmed, there have also been several extensions. Notably, the distinction between expected and unexpected PAs may not be as informative as the distinction between single and recurrent PAs. The presence of recurrent PAs may well serve as a generic marker for psychopathology, associated not only with the presence of a range of other mental disorders but also with their course, an issue deserving more research in the future.

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