time data collection in the subject's own environment⁴. Additionally, users' interactions with their mobile devices and their respective sensors could provide passive, objective information about their behavior patterns⁵. In theory, this kind of information has the potential to help designing newer prophylactic strategies as well as allowing personalized treatments⁶. Moreover, integrating behavioral and biomedical data (i.e., genetics, biomarkers, neuroimaging, etc.) and analyzing these datasets could ultimately allow the development of new predictive models, and the identification of previously unsuspected etiopathogenic factors and possibly new treatment targets⁷.

However, in practice, big challenges lie ahead in the pathway of translating the above promises into reality alongside the expected barriers of age and education level. One problem affecting not only behavioral sciences, but all mobile technologies which could provide an essential component of Big Data, is that of fragmentation. The market fragmentation of current mobile operating systems (Android, iOS, Windows Phone, Blackberry, etc.) and smartphones ownership represents a still unaddressed and growing issue in the field. According to the International Telecommunications Union, in 2015, around 95% of the worldwide population had a subscription for a mobile-cellular telephone, but less than 50% of these devices were connected to the Internet⁸. Among smartphones users, Android and iOS together have 96.4% of market share according to the International Data Corporation, with 78% of this amount pertaining to Android⁹. The fragmentation in the market of wearable devices is much more problematic, with more than 20 companies offering these products, which are continuously feeding information to independent databases.

Hence, the promising future of the components of Big Data provided by mobile devices might be severely hampered by the companies' aim of selling their own products with data collected through non-open platforms. In other words, any smartphone or wearable provides relevant information to data-

bases owned by these companies, not available for being exported or integrated with clinical information¹⁰.

In order to obtain significant results from the promised potential of Big Data, it may seem that fragmentation is a small technical problem in comparison to other relevant issues, such as ethical and sociological aspects. However, keeping in mind that the ultimate goal of the Big Data promise is to integrate data from multiple sources and that mobile technologies play a key role in this process, fragmentation should not be underestimated. This problem can be overcome on the long run, providing there is a true effort of both public and private sectors to altruistically collaborate towards an open health science, which could ultimately improve health research and as a result have a significant impact on public health.

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D. Hidalgo-Mazzei is supported by an Emili Letang grant from the Hospital Clinic of Barcelona. F. Colom is funded by the Spanish Ministry of Economy and Competitiveness, Instituto Carlos III, through a "Miguel Servet II" post-doctoral contract and a FIS (PI 12/00910).

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DOI:10.1002/wps.20307

Specific anxiety disorders and subsequent risk for bipolar disorder: a nationwide study

Anxiety disorders are highly prevalent in people with bipolar disorder¹ and substantially worsen the course of the illness as well as treatment response²⁻⁴. Anxiety disorders typically precede the onset of bipolar disorder^{2,5,6} and might therefore represent markers of risk for subsequent bipolar disorder. However, anxiety disorders are heterogeneous, and large-scale studies delineating their relationship to bipolar disorder are scarce.

We conducted a large population-based study in order to determine which specific anxiety disorders increase the risk of developing bipolar disorder. We also assessed whether patients with anxiety disorders are more likely to transition from unipolar to bipolar disorder, and which specific anxiety disorders in parents increase their offspring's risk for bipolar disorder.

Using the Danish Civil Registration System⁷, we selected a cohort of 3,379,205 people born in Denmark between January 1, 1955 and November 31, 2006. We identified all patients diagnosed with bipolar disorder (ICD-8: 296.19 and 296.39; ICD-10: F30.00-F31.90) based on the Danish Psychiatric Central Register⁸ and the Danish National Hospital Registry⁹. Next we singled out individual and parental diagnoses of anxiety disorders leading to in- and outpatient contacts (ICD-10: F40.00-F40.20, F41.00-F41.10, F42.00-F42.99, F43.10; covering agoraphobia, generalized anxiety disorder (GAD), obsessive-compulsive disorder, panic disorder, post-traumatic stress disorder, specific phobia, and social phobia) and psychiatric case history in general (ICD-8 codes: 290-315; ICD-10 codes: F00-F99).

Data were examined by survival analysis following cohort members from their 5th birthday or January 1, 1995 until the onset of bipolar disorder, date of death, date of emigration from Denmark, or December 31, 2012, whichever occurred first. In incidence analyses, we determined the risk for bipolar disorder in patients with anxiety disorders compared to the general population, using a log linear Poisson regression model as implemented in SAS, version 9.3 (SAS Institute, Cary, NC, USA) and adjusted for calendar year, age, gender, place of residence at time of birth, and the interaction of age with gender. We subsequently tested whether anxiety disorders were also associated with a higher risk for bipolar disorder among persons with a psychiatric case history. Finally, we evaluated whether any specific anxiety disorder contributed to the risk for bipolar disorder over and above anxiety disorders in general.

In the analyses focusing on the risk of transition from unipolar depression to bipolar disorder, cohort members were followed from their first contact due to depression (ICD-8 code: 296.09, 269.29, 296.89, 269.99, 298.09, 298.19, 300.49 and 301.19; ICD-10 code: F32.00-F32.9, F33.00-F33.99, F34.10-F34.90 and F38.00-F39.99) or January 1, 1995 until first admission for bipolar disorder, date of death, date of emigration from Denmark, or December 31, 2012, whichever occurred first. We compared the transition rates for specific anxiety disorders to anxiety disorders in general. The effect of parental anxiety disorders was determined using a hierarchical model simultaneously adjusting for calendar year, age, gender, place of residence at time of birth, and the interaction of age with gender. The incidence rate ratio (IRR) was calculated using log-likelihood estimation. The p values and 95% confidence intervals (CIs) were based on likelihood ratio tests.

Among the 3,167,632 persons followed from 1995 to 2012, 9,283 were diagnosed with bipolar disorder during the 49,148,258 person-years at risk. Of those patients, 8.0% had been previously diagnosed with an anxiety disorder, corresponding to a crude IRR of 13.03 (95% CI: 12.10-13.78) and an adjusted IRR of 9.11 (95% CI: 8.44-9.82) for patients with anxiety disorders compared to the general population. All specific anxiety disorders increased the risk for bipolar disorder, with GAD (IRR=12.20, 95% CI: 10.47-14.11) and panic disorder (IRR=10.25, 95% CI: 9.01-11.59) increasing the risk more than anxiety disorders in general. In the subcohort restricted to persons with mental disorders, an anxiety disorder diagnosis was still associated with a higher risk for bipolar disorder (1.41, 95% CI: 1.31-1.53).

The parents of 180 patients diagnosed with bipolar disorder had contacts for anxiety disorders, resulting in an adjusted IRR of 2.72 (95% CI: 2.39-3.08) compared to the general population. The risk associated with parental anxiety disorders was significantly higher than that associated with a parental diagnosis of any mental disorder (IRR=2.16, 95% CI: 2.06-2.27) other than bipolar disorder (IRR=7.91, 95% CI: 7.23-8.64). Parental agoraphobia (IRR=3.80, 95% CI: 2.54-5.43) and social phobia (IRR=

3.52, 95% CI: 2.27-5.17) were the anxiety disorders increasing the risk more than any other parental mental disorders.

Of the people initially diagnosed with depression, 4.7% transitioned to bipolar disorder during the 548,370 person-years at risk, corresponding to a crude incidence rate of 69.61 per 10,000 person-years. Of those who transitioned, 14% had previously been diagnosed with an anxiety disorder, corresponding to an adjusted transition rate ratio of 1.22 (95% CI: 1.11-1.33). Among the specific anxiety disorders, only GAD (IRR=1.28, 95% CI: 1.06-1.52) and panic disorder (IRR=1.26, 95% CI: 1.07-1.46) were associated with increased transition risk. Parental bipolar disorder (IRR=2.64, 95% CI: 2.29-3.04) and parental anxiety disorder (IRR=1.20, 95% CI: 0.99-1.45) additionally increased the offspring's transition risk.

The results of this prospective study show a nine times higher risk of bipolar disorder among patients with anxiety disorders compared to the general population. The effect of specific anxiety disorders seemed differential, as GAD and panic disorder were found to increase the risk for bipolar disorder more than anxiety disorders in general. Patients with comorbid anxiety disorders were also more likely to transition from unipolar to bipolar disorder. Anxiety disorders were linked with a higher risk of bipolar disorder across generations: parental anxiety disorders were found to significantly increase the offspring's risk to be diagnosed with bipolar disorder and to transition from unipolar to bipolar disorder. Although a direct causal interpretation is not possible, these associations might have important implications for clinical practice. Screening for anxiety disorders could allow the identification of high-risk individuals who might benefit from careful mood monitoring and possibly targeted interventions (e.g., people with anxiety disorders whose parents have a bipolar disorder).

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DOI:10.1002/wps.20314