Age of Onset of Mental Disorders

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Etiopathogenetic and Treatment Implications

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Foreword

This is an important book. It presents the first in-depth investigation of the age of onset (AOO) distributions of common mental disorders, a critical and, until recently, neglected aspect of mental disorder population dynamics. As the editors of this fascinating compilation point out in their introduction, AOO distributions have profound implications, not the least of which are the far greater importance of mental disorders than physical disorders in influencing the life trajectories of children, adolescents, and young adults due to the typically earlier AOOs of mental than physical disorders and the fact that early-onset disorders seldom are treated until after they have persisted for a number of years.

The editors note in their introductory chapter that research over the past two decades has shown that timely interventions with prodromal or incident cases of early-onset mental disorders can be effective in delaying, and sometimes even preventing, onset as well as in reducing lifetime persistence and severity once onset occurs. The editors expand on this theme in the concluding chapter, where they describe innovative early-intervention programmes that have been proven effective in reducing the burden of mental disorders. The monograph would have been enhanced if these innovative early intervention studies had been a more central focus on the disorder-specific chapters (e.g. Correll et al. 2018; Donaldson et al. 2015; Hawkins et al. 2008; van der Gaag et al. 2013).

The chapters in this volume focused much more on three broad areas of more basic research that have expanded in response to the successes of early intervention research: improving estimation of AOO distributions; discovering reliable prodromal patterns that provide targets for preventive intervention; and investigating potentially modifiable pathways that link early-onset to persistence-severity.

With regard to estimating AOO, the material reviewed in the chapters makes it clear that even though broad consistencies exist in basic epidemiological data on AOO distributions for the mental disorders considered here, considerable uncertainty exists beyond these basics. This is true in large part because mental disorders are accretion disorders, that is, disorders in which early signs and symptoms are often present for many years before the disorders declare themselves. This makes it difficult to know exactly what we mean by an "onset." In addition, and possibly as a result of the fact that so many early-onset mental disorders have an insidious onset, it is uncommon for people with mental disorders to seek treatment for incident episodes unless these episodes are either very severe or persist for a number of years (Wang et al. 2007). As a result of this fact, information about AOO distributions

comes largely, although not entirely (e.g. Fogel et al. 2006), from retrospective reports based on epidemiological samples. Recall bias in these reports can distort estimates. Although innovative methods exist to reduce this bias to some extent by splicing together synthetic AOO curves in ways that reduce length of recall (Eaton et al. 2012), these methods were not used in any of the chapters in the volume.

So much uncertainty exists about AOO due to these limitations that several of the chapters in this volume were devoted almost entirely to reviewing and evaluating the descriptive evidence on AOO distributions (e.g. the Dagani et al. chapter on bipolar disorder and the Legerstee et al. chapter on anxiety disorders). In one case, the Chanen et al. chapter on personality disorders, the authors went so far as to abandon hope of determining AOO in any serious way, noting that clinically significant paediatric manifestations of personality pathology are the norm among people with personality disorders and that these early manifestations are typically so nonspecific and intertwined with Axis I disorders that it is possible to define clear disorder onsets only as end points that typically occur in the transition to adulthood.

Interestingly, most of the chapters that focused on describing AOO distributions were concerned more with central tendency (i.e. mean or median AOO) than dispersion (i.e. the breadth of the age range in which onsets occur), although the few chapters that considered dispersion found it to be as striking as central tendency in differentiating among mental disorders. This is made clear in the Chanen et al. chapter on personality disorders, which, as noted in the last paragraph, distinguished between a prodromal paediatric phase and a syndromal phase that typically begins in the transition to adulthood; the Legerstee et al. chapter on anxiety disorders, which emphasised the importance of an early childhood risk window for the fear disorders as compared to a later and broader risk window for other anxiety disorders; the Kelly et al. and Connor et al. chapters, which noted that a relatively narrow risk window in adolescence and young adulthood exists for onset of substance use disorders; and the Coghill et al. chapter on attention deficit hyperactivity disorder (ADHD), where the authors noted new evidence suggesting that there might be a wider risk window than was previously thought to be the case.

The second of the three areas of research noted above, on the discovery of reliable prodromal signs and symptoms that could provide targets for preventive intervention, is hampered by the fact that it is often unclear which of these signs and symptoms are causal risk factors. This, in turn, leads to uncertainties about how to intervene to prevent progression even after reliable predictors of onset are found. A number of chapters in this volume note these uncertainties. Yet, surprisingly little emphasis was placed in these chapters on the investigations of researchers in developmental psychopathology (Lewis 2014), youth mental health (Rice et al. 2018), and early high-risk (Hartmann et al. 2018) who address these uncertainties by carrying out fine-grained longitudinal studies and interventions during the years prior to typical AOO to document reliable markers of incipient psychopathology and to evaluate causal hypotheses. In recent years, this type of research has become increasingly interdisciplinary and focused on biomarkers. Although as-yet of uncertain clinical value, epigenetics has been a focus of much of the latter work, given that mental disorders are known to cluster in families and environmental risk factors are thought to interact with genetic predispositions (Hyde 2015).

It is sometimes possible to make inferences about causal pathways by inspecting subgroup AOO distributions, as in the hypothesis described by Häfner in his chapter on schizophrenia about the role of oestrogen in explaining sex differences in schizophrenia, a hypothesis that was originally proposed based on observed sex differences in AOO distributions of schizophrenia related to ages of menarche and menopause. A similar kind of work has been carried out to investigate the extent to which sex hormones explain the well-known higher prevalence of major depression among women than men (Angold and Costello 2006). Implications of this work for preventive intervention have also been considered (Adam et al. 2008).

An important exception to the lack of focus on pre-onset interventions was found in the chapters on substance use disorders (SUDs), where a good deal of attention was focused on pre-disorder precursors and preventive interventions. This is, in some ways, not surprising, though, as there are clear behavioural characteristics of precursors to SUDs, such as early first use, rapid progression from first use to regular use, and binge use (in the case of alcohol), all of which have long been known to predict SUD onset. As reviewed in the SUD chapters, interventions designed to influence these earlier stages have been carried out and have been found to predict the subsequent onset and progression of SUDs. These studies are also unique among those considered in this volume to consider restricted access to means as a focus of preventive intervention, although this is also a focus, and the subject of considerable controversy in the USA with regard to firearms, in research on risk factors for suicide (Yip et al. 2012).

The third of the three areas of investigation I noted earlier involves pathways that link early-onset with later disorder persistence-severity. A number of chapters comment on studies of this sort. A major interest of researchers working in this area is in sorting out the relative importance of several different pathways that could all plausibly be involved as causes of these predictive associations. Speaking broadly, these include the possibility that early-onset disorders themselves have biological effects, possibly related to critical periods in brain development, that account for the associations of early AOO with persistence-severity (see the discussion of "susceptibility windows" in the chapter by Fiorito et al.); that comorbid condition either cause and/or are caused by early-onset disorders and account for the associations of early onset of these disorders with subsequent persistence-severity; and that the more extreme negative effects of early-onset than later-onset disorders cases on developmental trajectories account for the associations of early-onset with persistence-severity (see the discussion of the earlier AOO of schizophrenia among men than women leading to great disruption in developmental trajectories described in the chapter by Häfner).

The possibility of early-onset disorders having unique biological effects was discussed by Miettunen et al. in their chapter on schizophrenia spectrum disorder, where they suggested that early AOO is associated with increased cognitive deficits and brain alterations that lead to subsequent persistence-severity. Yet the evidence reviewed in that chapter focused more on documenting predictive mediation than evaluating the extent to which these biomarkers might be causal mediators. This is a challenging area of investigation, but one that needs to be tackled to make progress in understanding the translational implications of information about biological determinants of the effects of early onset.

One of the most interesting programmes of research on this topic was initiated by Post (2015), who suggested that major depressive episode recurrence creates increased reactivity via epigenetic mechanisms that, in turn, promote further severity-persistence. This work highlights the importance of distinguishing between the effects of AOO and the effects of duration of untreated disorder. The two are related, of course, due to the fact that the treatment rate is lower for early-onset than later-onset disorders, leading to early-onset cases having a longer duration of untreated prevalence. The clinical importance of the distinction can be seen by noting that efforts to reduce episode duration would imply that the kinds of treatments developed to promote rapid episode remission, which currently are used mostly for severe cases, might also make sense to consider as first-line treatments for incident episodes (e.g. Canuso et al. 2018). If episode recurrence is more important, in comparison, then maintenance medications, which currently are recommended primarily for patients with recurrent or chronic disorders (e.g. Gelenberg et al. 2010), might be considered as preventive interventions against recurrence among incident cases. Or, given concerns about negative effects of long-term medication administered after incident episodes, non-pharmacologic treatments focused on preventing recurrence might be investigated as treatments-of-choice for early-onset incident cases (e.g. Huijbers and Speckens 2015).

Another potentially important set of pathways involves the mediating effects of secondary comorbid mental disorders of the associations of early-onset primary mental disorders with persistence-severity of those disorders and with other negative life course outcomes associated with these early-onset primary disorders. Although most of the chapters in this volume commented on the fact that early-onset disorders are associated with high comorbidity, few of them discussed the possibility that this comorbidity could account for the associations of early-onset with subsequent persistence-severity of the primary disorders or with negative life course outcomes associated with these disorders. Furthermore, none of the chapters discussed the value of developing preventive interventions for patients with refractory early-onset disorders to prevent the onset of secondary disorders in the hopes that such preventive interventions, if successful, might influence the persistence-severity of the primary disorders. For example, we know that youngsters with ADHD are at increased risk of numerous negative life course outcomes because of secondary comorbid disorders that intervene between temporally primary ADHD and these outcomes and that often persist even after the ADHD remits (Kessler et al. 2014). The investigation of these mediating associations and the implementation-evaluation of interventions designed to prevent onset of the secondary disorders that mediate the effects of early-onset primary disorders on these outcomes could have great clinical significance. This is especially true given that very high proportions of mental disorders, and especially severe-persistent mental disorders, are secondary comorbid disorders associated with early-onset primary disorders (Kessler and Price 1993).

A related possibility is that early-onset disorders are more persistent-severe than later-onset disorders because they have more negative life course consequences that lead to subsequent disorder persistence-severity. This could occur either because early-onset disorders occur during critical periods of life course development or because their longer durations, partially influenced by their low rates of treatment, put

people with early onsets at risk for longer periods of time than if their disorders had later AOOs. In either of these cases, interventions aimed at preventing these negative life course consequences might be effective in reducing persistence-severity of early-onset disorders even if these disorders were refractory. Given that research exists on secondary preventive interventions designed to avert these effects, this focus needs much more serious attention in a monograph on AOO. A good example is clinical research on paediatric-onset anxiety disorders, which are known to be associated with a wide range of later-life impairments due to the fact that anxious youth are at increased risk of using alcohol and illicit drugs for self-medication (Menary et al. 2011). This maladaptive coping style, in turn, leads to other negative outcomes that can exacerbate anxiety. So strong is this pattern that some psychological interventions for adolescent anxiety disorder include a component to prevent self-medication by promoting the use of more productive coping strategies (Kendall et al. 2004).

One gets the impression from the reviews in this volume that the natural history of research in a number of disorder-specific areas is poised to begin launch initiatives aimed at tracing out mediating processes of the sort sketched out in the last three paragraphs. The closing chapter by the editors is especially exciting in pointing to translational implications of doing this. The next generation of AOO research will likely use AOO as a point of departure for investigating other key characteristics of mental disorder population dynamics by developing, implementing, and refining coordinated interventions that begin much earlier in the life course than current treatments and lead to a dramatic reduction in the global burden of mental disorders. Although the next part of the script is yet to be clearly specified, the current volume at least provides a solid foundation for this next generation of research.

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