Personality disorder 2

Personality disorder across the life course

Giles Newton-Howes, Lee Anna Clark, Andrew Chanen

The pervasive effect of personality disorder is often overlooked in clinical practice, both as an important moderator of mental state and physical disorders, and as a disorder that should be recognised and managed in its own right. Contemporary research has shown that maladaptive personality (when personality traits are extreme and associated with clinical distress or psychosocial impairment) is common, can be recognised early in life, evolves continuously across the lifespan, and is more plastic than previously believed. These new insights offer opportunities to intervene to support more adaptive development than before, and research shows that such intervention can be effective. Further research is needed to improve classification, assessment, and diagnosis of personality disorder across the lifespan; to understand the complex interplay between changes in personality traits and clinical presentation over time; and to promote more effective intervention at the earliest possible stage of the disorder than is done at present. Recognition of how personality disorder relates to age and developmental stage can improve care of all patients.

Introduction

That personality develops from birth to adulthood seems obvious: individual differences in personality traits are recognised from birth and these differences are understood to arise from genetic endowment, changing with maturation and environmental factors until adulthood. What is not so obvious is the continuous change and development that occurs with experience across the entire life course in both the healthy and pathological ranges, as inherited characteristics interact with environmental factors. The pervasive effect of personality disorder—when personality traits are extreme, and personality development is arrested, delayed, or derailed—is often overlooked in clinical practice. However, recognition of this disorder has the potential to deepen understanding of individual patients and to enhance the ability to help them manage their lives. The role of this Lancet Series paper is to review evidence that shows the growing understanding that personality disorder is clinically significant throughout life, with potential effects on all mental state and physical disorders. Disorders of mental state were referred to as Axis I disorders; a term now made obsolete by the elimination of Disorders of mental state and physical disorders, and as a disorder that should be recognised and managed in its own right. The pervasive effect of personality disorder is clinically significant throughout life, with potential effects on all mental state and physical disorders. Disorders of mental state were referred to as Axis I disorders; a term now made obsolete by the elimination of Disorders of mental state and physical disorders, and as a disorder that should be recognised and managed in its own right. The pervasive effect of personality disorder is often overlooked in clinical practice, both as an important moderator of mental state and physical disorders, and as a disorder that should be recognised and managed in its own right. Contemporary research has shown that maladaptive personality (when personality traits are extreme and associated with clinical distress or psychosocial impairment) is common, can be recognised early in life, evolves continuously across the lifespan, and is more plastic than previously believed. These new insights offer opportunities to intervene to support more adaptive development than before, and research shows that such intervention can be effective. Further research is needed to improve classification, assessment, and diagnosis of personality disorder across the lifespan; to understand the complex interplay between changes in personality traits and clinical presentation over time; and to promote more effective intervention at the earliest possible stage of the disorder than is done at present. Recognition of how personality disorder relates to age and developmental stage can improve care of all patients.

Dimensions versus categories

Personality disorder is classified in both section II of DSM-5 (the main body of the manual) and in the 10th edition of the International Classification of Diseases (ICD-10) as a categorical construct. This approach has been criticised because it arbitrarily separates normal from abnormal personality and ignores the developmental course of personality traits across the lifespan. The categorical construct yields substantial comorbidity between purportedly distinct diagnoses, and substantial heterogeneity within specific personality trait dimensions. Rather than being very stable, we now know that both normal and abnormal personality can change trajectory across the lifespan. We also now know that personality disorder is treatable and has acute manifestations that are amenable to intervention. Even characteristic traits can change with time, especially when helped with effective evidence-based treatments that might work, in part, by catalysing delayed maturational processes.

Search strategy and selection criteria

We searched Medline from inception, PsycINFO from Jan 1, 1967 onwards, and Embase from inception until Aug 1, 2014 on the Ovid platform. We did free text searches for “personality” or “personality disorder” or “personality pathology” and “lifespan” or “life course” or “longitudinal” to provide the initial broad scientific literature base. Additionally we examined the scientific literature related to the McLean Study of Adult Development, the Collaborative Longitudinal Personality Disorders Study, and the Children in the Community study. We critically reviewed scientific literature related to personality disorder across the lifespan in a narrative style to provide a broad-based overview. We only reviewed articles written in English.
The construct also has poor coverage of presenting cases, and very poor agreement between diagnostic assessments. The full DSM-5 and ICD-10 systems have not been widely adopted in either routine clinical practice or clinical research, with the focus largely restricted to borderline and antisocial personality disorders. Although experts agree that categorical approaches to personality disorder are inadequate, consensus on a more scientifically robust and clinically useful dimensional system has been difficult to attain. One alternative personality disorder model is represented in section III of DSM-5, which uses as its basis for diagnosis the identification of core personality dysfunction and pathological personality traits within a hierarchical model that can be identified across the lifespan. A core construct of personality disorder is also proposed for ICD-11.

Assessment and its effect on a lifespan view of personality

Progress in the understanding of personality and its relation to personality disorder across the lifespan has come largely through research that is directly or indirectly focused on personality assessment. Soon after personality disorder was placed on a separate axis from other clinical syndromes in DSM-III, with specific criteria defining each personality disorder, researchers developed structured interviews and self-report questionnaires to assess the newly defined categories. Through the widespread use of these measures, several things quickly became apparent. First, convergent validity was poor between clinical and structured interviews, between structured interviews, between interviews and self-report questionnaires, and, to a lesser extent, between questionnaires. Notably, convergence was poor, even regarding merely the presence or absence of personality disorder. Thus, personality disorder researchers disagreed on how to operationalise the disorder and as a result study results were difficult to compare. Second, although joint-interview reliability was generally good to excellent, temporal reliability of personality disorder assessment was low, even across periods as brief as 1 week. In these cases, true change could not explain the findings, and 6 month or 12 month retest coefficients were similar to those obtained in the short term. Third, irrespective of method, personality disorder disorder assessments yielded many comorbid diagnoses, both between the different personality disorder types and between personality disorder and mental state syndromes. Additionally, many personality disorder cases fell outside the narrow focus of the ten categorical personality disorders, which, along with the polythetic method of diagnosis (eg, five of nine criteria met), created substantial heterogeneity within personality disorder categories. Fourth, despite high comorbidity, the system provided poor coverage of the personality disorder domain, such that the clinical picture of only about half of all individuals with diagnosable personality disorder met criteria for a specific DSM-IV personality disorder, and thus were best diagnosed with personality disorder not otherwise specified. Taken together, these results clearly showed that the fundamental issue was with the categorical conceptualisation of personality disorder, not the assessments per se.

Personality disorder as a genetically trait-based unitary construct

For many years, the scientific literature examining normal personality development and that examining personality disorder evolved in parallel, rather than in concert. This separation hindered the consideration of the clinical implications of personality from a lifespan-developmental perspective. In the past 20 years, substantial research has been done within a joint framework, although it has yet to be fully integrated. A notable finding is that personality traits evident in childhood stabilise throughout life beyond age 30 years. Such traits are roughly 50% heritable, with little variance accounted for by shared environmental factors, the remainder being attributable to individuals’ unique experiences and how their genetic make-up interacts with the environment. Genetic factors and environmental constancies probably underpin the continuity of personality, whereas changing environmental effects imply plasticity and thereby the opportunity for clinical intervention.

Heritability studies from the Norwegian Institute of Public Health Twin Panel using DSM-IV clusters identified common genetic variables for cluster A and C personality disorder, and common genetic and environmental factors associated with cluster B personality disorder (particularly antisocial personality disorder). One genetic factor might predispose to personality disorder, with other genetic factors causing predisposition for the dimensional traits of low agreeableness or so-called pathological introversion. Candidate genes have been investigated, largely within the serotonin system, although no clear causal gene or group has been identified. Early-life epigenetic variability as a result of early-childhood adversity might account for differential gene expression, with genetic features congruent across cultures.

Clinical attention is skewed heavily towards borderline personality disorder, narrowing research and treatment to the extreme end of a particular range and neglecting other important and clinically relevant aspects of adaptive and maladaptive personality. By contrast, consideration of personality and related disorder as a unitary construct affords improved clinical recognition of a broad range of personality disorder, in part because individual differences are relevant to management of all health disorders, and in part because research has documented that personality factors underpin most, if not all, psychopathological abnormalities.
important point to recognise is that, as elements of personality change over time, related psychopathological abnormalities change too, affecting the evolving clinical picture.\textsuperscript{6,7} We recommend that the medical community takes a broad, life-course perspective on adaptive and maladaptive personality traits. This perspective allows for comprehensive clinical assessment that can identify potential targets for treatment at different life stages.

Convergence between normal and abnormal range personality models
With the closing of the research gap between normal and abnormal personality, the study of normal-range personality has produced a hierarchical five factor model of personality traits,\textsuperscript{8} known also as the Big Five. Measures of these factors, by contrast with the drawbacks of personality disorder assessment, have strong psychometric properties and account for substantial variance in both normal-range personality and personality disorder.\textsuperscript{9} Results of studies in children and adolescents have shown a similar higher-order structure to the personality dimensions seen in adulthood,\textsuperscript{10} and specific measures of personality disorder in children, adolescents, and adults\textsuperscript{11} yield equivalent results. Table 1 shows the relations between the Big Five factors and the models in DSM-5 section III and proposed for ICD-11.

Stability and change
Prospective longitudinal data\textsuperscript{12} suggest that individual differences are preserved from as young as 3 years of age through to 18 years of age in the general population, although the strength of associations between individual differences in early childhood and adulthood are only weak to moderate. Personality traits become consistent through exposure to a consistent environment, genetic effects, psychological make-up, the goodness of fit between individuals and their environment, and a strong sense of identity.\textsuperscript{13}

Until the 1980s, William James’ view of personality, originally published in 1890, was widely accepted: “By the age of 30, the character has set like plaster, and will never soften again.”\textsuperscript{14} However, results from several longitudinal, meta-analytic, and large-scale cross-sectional studies show this view is only partly correct. In terms of the relative extent of individuals’ personality traits, consistency, beginning in infancy, increases monotonically. Meta-analytic data from 2000 onwards show that personality across the normal–abnormal range is moderately stable during childhood, increases in stability from adolescence to emerging adulthood, and then changes more slowly from age 30 years. Specifically, the Big Five dimensions of personality already show substantial stability across community\textsuperscript{15} and clinical\textsuperscript{16} samples of children and adolescents. Importantly for the assessment of personality disorder in adolescence, no sudden increase in trait stability happens in the transition from the second to the third decade of life.\textsuperscript{17} Rather, evidence suggests that personality continues to stabilise until at least age 60 years.\textsuperscript{18} Rather than setting like plaster, personality’s rate of change merely slows over time,\textsuperscript{18} but does not cease. The causes of these changes are not clearly understood, but the direction of change is outlined (table 2). Longitudinal clinical samples\textsuperscript{19} show these trends of personality disorder status changing over time without specific intervention. Odd or avoidant personality disorder tends to increase over time, juxtaposing the so-called burnout often cited in antisocial and borderline personality disorder.\textsuperscript{20}

The Children in the Community Study\textsuperscript{4} reported that personality disorder seems to change from childhood through to adulthood in similar ways to normal-range personality; however, these findings need replication. Methodological drawbacks related to personality disorder assessment in the early phases of this study recommend cautious interpretation. No robust studies have followed the course of personality traits or personality disorder from childhood to later life, leaving a major gap in knowledge. The Children in the Community Study\textsuperscript{21} identified that features of personality disorder peak at about age 13–14 years and reduce monotonically from age 14 years to 28 years.\textsuperscript{22} Some of this reduction is due to decreases in impulsivity, attention seeking, and dependency, and increases in social competence and

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<th>Table 1: Five-factor model of personality compared with trait domains in DSM-5, section III, and proposed for ICD-11</th>
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<td><strong>DSM-5, section III</strong></td>
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<tr>
<td>Neuroticism</td>
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<td>Extraversion\textsuperscript{1}</td>
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<td>Openness</td>
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\textsuperscript{1} DSM-5=Diagnostic and Statistical Manual of Mental Disorders, fifth edition. ICD-11=International Classification of Disease, revision 11. *Or absence of.

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<th>Table 2: Life-course trends in absolute (mean level) personality trait domains in DSM-5, section III</th>
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<tr>
<td><strong>Change</strong></td>
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<td>Negative affectivity</td>
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<td>Positive affectivity or extraversion</td>
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<td>Disinhibition</td>
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<td>Detachment</td>
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\textsuperscript{1} DSM-5=Diagnostic and Statistical Manual of Mental Disorders, fifth edition.
self-control that suggest normative change. The features of personality disorder in this study were moderately stable, mirroring findings reported in studies of adults assessed over similar time intervals. Adolescents with diagnosed personality disorder tended to have a higher frequency of personality disorder features during early adulthood than adolescents not diagnosed with personality disorder, suggesting continuity of personality disorder from adolescence to adulthood, and 21% of participants had increases in the frequency of their personality disorder features during this period. Overall, this study’s findings suggest that child and adolescent personality disorder is the strongest predictor, even more than common mental state disorders, of young adult personality disorder.

Although personality traits are largely consistent across time, they also remain dynamic throughout life; individuals with personality disorder tend to change more over time than those without it, typically, but not always, in the direction of improvement. Personality disorder in mid-adulthood (age 30–45 years) particularly represents a combination of relatively stable maladaptive traits and acute disturbances (e.g., suicidality or hyper-aggression) that increase and decrease over time (again mostly improving) compared with personality disorder in younger or older people. These acute disturbances are what often lead to clinical presentations and perhaps propagate the mistaken clinical belief that personality disorder is solely an externalising disorder of adulthood. Despite these variable disturbances, general psychosocial functioning (e.g., interpersonal relationships and occupational functioning) in individuals with personality disorder tends to be poor but stable, compared with the more rapid changes seen with more severely dysfunctional, acute personality disorder manifestations (e.g., suicidality). This stability of poor functioning can give rise to the misleading clinical impression that personality disorder itself is stable. Importantly, change in personality traits predicts change in personality disorder, but not vice versa, meaning personality traits probably more closely resemble the actuality of personality than categories of the disorder.

**Personality disorder begins in childhood and adolescence**

Experts generally agree that personality disorder has its roots in childhood and adolescence, and this view was made explicit in the operational definitions of the categorical personality disorders that were introduced in DSM-III. Nonetheless, the sections on disorders of childhood and adolescence in the DSM-5 and ICD-10 still do not mention personality disorder, although ICD-11 will acknowledge this (see paper 1 in this Series).

Specific data on prospectively assessed risk factors for personality disorder are still meagre. A series of publications from the Children in the Community Study (summarised by Cohen and colleagues) reported that adverse childhood experiences and maternal reports of anxiety, depressive symptoms, and conduct difficulties predicted personality disorder 10 years later, suggesting that similar or identical psychopathology is labelled as mental state disorder in children and relabelled as personality disorder in adult life. Personality disorder usually becomes clinically apparent during the transition between childhood and adulthood and has the potential to disrupt the complex developmental tasks associated with this phase of life and the achievement of adult role functioning. However, should personality disorder be diagnosed before age 18 years? Although the DSM-5 and ICD-10 advocate caution in doing so, they do not preclude personality disorder diagnosis in adolescence, except for antisocial personality disorder. DSM-5 stipulates only that the features of a personality disorder be present for 1 year, which seems too short a period to accurately distinguish a mental state disorder from a personality trait disorder. ICD-10 states that personality disorder is highly unlikely to be diagnosed before age 16–17 years, but offers no scientific justification for this. Nonetheless, accurate diagnosis is hindered in both systems by the absence of developmentally appropriate personality disorder criteria or examples of criteria consistent with adolescent behaviour.

Until the late 1990s, most so-called developmental studies of personality disorder focused on early childhood experiences and how they affect later (adult) psychopathology. Such childhood effects are important, but they might be mediated and even reversed by later experiences. An exclusive focus on distal factors is arguably non-developmental because it assumes that the determinants of mental health are invariant across the lifespan. The results of several studies have shown similar associations between normal and pathological personality traits from adolescence through to adulthood, supporting an overarching structural framework across the lifespan.

**Diagnosis of personality disorder in young people**

Despite the scientific evidence for the validity of personality disorder in childhood and adolescence, the diagnosis remains taboo in these age groups. The evidence presented in this Series paper suggests that such views are no longer justified. Many clinicians avoid the diagnosis on the grounds that they are protecting patients from the stigma associated with the label. Notably, this stigma is common and is reinforced by some health professionals. Crucially, however, in view of present knowledge, clinicians should be provided with information that will help them to make clinically appropriate diagnoses of personality disorder without fear of stigmatising patients, because failure to recognise or diagnose the disorder curtails appropriate intervention and risks inappropriate or harmful intervention. The DSM-5, section III, describes an alternative personality disorder system that has incorporated the
evidence for the disorder in young people, removing age-related caveats for its diagnosis, and the same is proposed for ICD-11. Both classifications recognise the dimensional nature of personality disorder across the lifespan and, further, ICD-11 provides a category of personality difficulty, which represents so-called sub-threshold personality disorder. When clinicians are unsure of or hesitant to use a personality disorder diagnosis with young people, use of the personality difficulty category will support prevention, early identification, and treatment of such problems.

**Personality disorder in later life**

The medical community’s understanding of the specific implications of personality disorder in later life (age >65 years) is hindered by a scarcity of longitudinal research and a reliance on cross-sectional data. The high-quality community and clinical longitudinal studies of personality disorder have not followed up participants older than 50 years, limiting knowledge of the effects of personality disorder in this age group. Assessment difficulties further hinder research that is in progress.

Many of the personality descriptors in the present diagnostic systems for personality disorder imply middle-age adult functioning, rather than the roles more common in later life. For example, an individual’s ability to maintain employment is of little relevance if they are retired. Similarly, constriction of social connectedness might be due to a move into alternative accommodation away from friends, or death of a partner or friends, rather than interpersonal difficulties. Present personality disorder classification also needs almost continuous abnormality from adolescence onwards, and therefore the prevalence of personality disorder would be expected to decrease uniformly, which is not the case and has little empirical justification. Cases of personality disorder possibly arise de novo in adulthood or later life because of environmental or interpersonal changes interacting with personality traits, and these patients might be misclassified by present taxonomies. As described previously, normal personality becomes increasingly stable and increasingly adaptive in later life. Personality disorders related to neuroticism or negative affectivity diminish over time with increased representation of schizoid, paranoid, and schizotypal presentations. Individuals in later life will encounter different types of environments and have different roles from those in middle adulthood, and these differences might exacerbate or ameliorate maladaptive personality-trait manifestations. For example, transition from independent living to a nursing home for a patient with detachment-domain personality traits (eg, social avoidance) might lead to substantial difficulties related to the interaction between these personality traits and the communal environment. However, the types of interactions and their most common or most troublesome effects are unknown. Furthermore, the stability of personality in older adults tends to be overestimated and those in later life are more generally ascribed a positive profile, with negative attributions tending to relate to physical, as opposed to psychological, characteristics. Observers tend to rate maladaptive personality traits less highly in older samples of patients compared with younger samples, suggesting this bias towards minimisation of personality problems in later life is not restricted to clinicians. Observer bias might also preclude clinicians and researchers from examining older adults’ personality profiles in psychiatric and medical settings. This bias towards minimisation of personality problems ignores the effects that personality traits, particularly neuroticism and negative affectivity, have on psychological functioning and social outcomes in later life.

Evidence from the past 3 years points to a range of negative effects of personality disorder in later life that might account for a high proportion of mortality, functional loss, and ill health. Substantial evidence exists that high neuroticism or negative affectivity detrimentally affects a range of health outcomes, and that borderline personality disorder (a diagnosis characterised by high amounts of neuroticism or negative affectivity) might have a particular association with poor health in late life. Cognitive decline and Alzheimer’s disease are also related to changes, not only in neuroanatomy, but also in personality. Personality profiles characterised by high neuroticism or negative affectivity and low conscientiousness are also related to cognitive decline in later life. Cohort studies of psychiatric patients have identified that those with co-occurring personality disorders generally have poorer outcomes than those without co-occurring disorders, but particularly in elderly people. Similar negative relations exist for non-suicidal self-injury, substance-use disorders, and depressive disorders. The little recognition that personality disorder in later life receives might be concealing a substantial public health burden that will become increasingly important in countries with ageing populations.

**Treatment implications of a life-course perspective**

In view of the advances in the understanding of personality disorder in the past 15–20 years, its treatment can no longer be viewed as futile. This view is important because data suggest that long-lasting outcomes are more likely to be achieved through changes in personality traits over time, as opposed to treatments solely targeting psycho-pathological abnormalities. Treatment development needs to focus on individuals’ personality traits that cause the most difficulty and poor functional outcomes. Studies need to acknowledge the changing course of personality, and the need for active comparison interventions and adequately powered, long-term follow-up. For example, emotion dysregulation is a hallmark of raised neuroticism or negative affectivity, and in 2010 it was proposed
as a possible change mechanism in acceptance and mindfulness-based treatments. Similarly, disinhibitory personality disorder probably underlies impulse-control difficulties in both personality disorder and substance-use disorder; thus, treatments should target symptomatic manifestations of disinhibition. Maladaptive detachment-domain traits have been shown to be reduced after successful treatment of social anxiety disorder, suggesting the possibility of adaptation of such interventions to treat personality disorder. These three domains of maladaptive personality, emotion dysregulation, disinhibition, and detached traits are all targets for clinical investigation of personality change.

A lifespan perspective on personality disorder is helpful when considering not only personality disorder treatment per se, but also physical disorders. However, this topic is beyond the scope of this Series paper.

The intersection of mental state disorder and personality disorder
Almost all referrals to mental health-care providers, and the usual focus of clinical attention, concerns the treatment of mental state disorder. However, personality disorder can be diagnosed in up to half of patients with mental state disorder, making it one of the most common psychiatric disorders. The published work generally reports poorer outcomes for mental state disorder in the presence of personality disorder than in its absence. These findings emphasise the need to assess for personality disorder and raise the possibility that personality disorder might underlie many instances of so-called treatment-resistant mental state disorder, which might occur because clinicians mistakenly interpret traits of personality disorder to be persistent symptoms or because the great malleability of personality in young patients helps improvement in mental state disorder. Assessment of personality traits shows consistent themes across an individual’s lifespan that might warrant specific intervention in addition to the management of acute mental state disorder. For example, identification of substantial neuroticism or negative affectivity in a patient presenting with treatment-resistant depression might suggest the need for structured psychotherapy as the primary intervention, as opposed to combination pharmacotherapy. Similarly, trait detachment in a late adolescent individual presenting with reality distortion might identify the need for social skills training as opposed to pharmacotherapy for so-called ultra-high-risk psychosis. A major clinical difficulty is the relative absence of randomised controlled trials for interventions aimed at personality trait domains and functional outcomes, as opposed to specific personality disorder types such as borderline personality disorder. A re-conceptualisation of personality as an enduring, dimensional concept underpinning the phenomenology of mental state disorders allows for a more comprehensive and targeted intervention to address longitudinal, rather than only cross-sectional, disturbance than was possible before.

A life-course perspective on future challenges for personality disorder research
Possibly the greatest scientific and clinical challenge for a lifespan perspective on personality disorder is the need to adopt a classification system that is both clinically useful and scientifically robust. From a scientific viewpoint, such a system will need to show the dimensional nature of the traits that underlie both adaptive and maladaptive personality, and the changing nature of personality across the lifespan. At the same time, scientific research findings need to be translated into clinically useful formats that take a lifespan perspective to enable consideration of personality disorder at all ages. Recognition of personality disorder in childhood and adolescence will enable prevention, earlier detection, and implementation of evidence-based interventions aimed at changing the life-course trajectory of personality disorder. For example, substantial information exists about childhood-onset and adolescent-onset conduct disorder and the developmental pathways leading to adult personality disorder, along with associated outcomes such as substance misuse, mental state disorders, and poor physical health. However, health practitioners’ concerns about early labelling interfere with adoption of an appropriate lifespan perspective that would allow for continuity of treatment across developmental periods. Relatedly, identification of trait-based disorder in adulthood eases recognition of targets for more enduring change than merely the management of acute disturbances in personality disorder. Furthermore, identification of personality disorder in elderly people provides the opportunity to develop interventions to improve both their physical and psychological health.

The reciprocal effects of personality and mental state disorder are challenging. A great change in clinical thinking is needed to recognise not only the importance of personality disorder in so-called stand-alone personality disorder, but also the effects of adaptive and maladaptive personality on mental state and physical disorders. This argument falls outside the scope of this Series paper, but recognition of the need for a more comprehensive, dimensional approach to all mental disorder than is used at present, carries the promise of improved outcomes for individuals, decreasing the public burden of mental disorder. A lifespan approach might also lead to decreased stigma and discrimination, including that perpetrated by mental health workers, who continue to think of personality disorder as untreatable, and equate it with difficult or disagreeable patients. In summary, the medical community’s recognition and understanding of personality disorder has flourished in the past three decades, but substantial areas in which to expand knowledge, and ample opportunities to apply understanding to improve clinical care, remain.

Contributors
All authors contributed equally to the preparation of this Series paper.