Psychological Medicine

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The impact of schizophrenia and mood disorder risk alleles on emotional problems: investigating change from childhood to middle age

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Original Article

Cite this article: Riglin L, Collishaw S, Richards A, Thapar AK, Rice F, Maughan B, O'Donovan MC, Thapar A (2018). The impact of schizophrenia and mood disorder risk alleles on emotional problems: investigating change from childhood to middle age. *Psychological Medicine* **48**, 2153–2158. https://doi.org/10.1017/S0033291717003634

Received: 12 September 2017
Revised: 10 November 2017
Accepted: 15 November 2017
First published online: 14 December 2017

Key words:
Anxiety; depression; emotional problems; genetic; longitudinal; NCDS; polygenic risk scores; schizophrenia

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Abstract

Background. Previous studies find that both schizophrenia and mood disorder risk alleles contribute to adult depression and anxiety. Emotional problems (depression or anxiety) begin in childhood and show strong continuities into adult life; this suggests that symptoms are the manifestation of the same underlying liability across different ages. However, other findings suggest that there are developmental differences in the etiology of emotional problems at different ages. To our knowledge, no study has prospectively examined the impact of psychiatric risk alleles on emotional problems at different ages in the same individuals.

Methods. Data were analyzed using regression-based analyses in a prospective, population-based UK cohort (the National Child Development Study). Schizophrenia and major depressive disorder (MDD) polygenic risk scores (PRS) were derived from published Psychiatric Genomics Consortium genome-wide association studies. Emotional problems were assessed prospectively at six time points from age 7 to 42 years.

Results. Schizophrenia PRS were associated with emotional problems from childhood [age 7, OR 1.09 (1.03–1.15), $p = 0.003$] to mid-life [age 42, OR 1.10 (1.05–1.17), $p < 0.001$], while MDD PRS were associated with emotional problems only in adulthood [age 42, OR 1.06 (1.00–1.11), $p = 0.034$; age 7, OR 1.03 (0.98–1.09), $p = 0.228$].

Conclusions. Our prospective investigation suggests that early (childhood) emotional problems in the general population share genetic risk with schizophrenia, while later (adult) emotional problems also share genetic risk with MDD. The results suggest that the genetic architecture of depression/anxiety is not static across development.

Introduction

Emotional problems – depression and anxiety – are the most common adult mental health problems (Kessler *et al.* 2005). When defined as categorical diagnoses, they affect around 16% of the population at any one time and are a leading cause of disability (Murray & Lopez, 1997; McManus *et al.* 2009; Murray & Lopez, 2013). Emotional problems present throughout the life span but often are considered as originating in childhood and adolescence (Rutter *et al.* 2006). Findings from longitudinal, high-risk and cross-generational studies show strong links between emotional problems in childhood/adolescence and adult life (Rutter *et al.* 2006; Thapar *et al.* 2012; Maughan & Collishaw, 2015). This has led to the prevailing belief that symptoms index the same underlying liability across different ages, regardless of whether they manifest in childhood, adolescence, or adulthood. However, there are some observations that argue against a developmental continuity hypothesis that assumes that the same liability underlies the manifestation of symptoms at different ages. Epidemiological research suggests that gender ratios of emotional problems differ across the lifespan – in childhood, males are as commonly affected as females but an increasingly strong female preponderance emerges in adolescence (Lewinsohn *et al.* 1998; Kessler *et al.* 2001; Green *et al.* 2005; Beesdo *et al.* 2009). This raises the possibility of etiological differences between very early emotional problems and those that emerge later. There is also evidence that treatment response may differ with age, with some types of effective adult antidepressant medications having either no therapeutic effects in childhood and adolescence (e.g. tricyclics) or being less effective in this age group: the reasons for this remain a puzzle (Hazell *et al.* 1995; Thapar *et al.* 2012; Brent & Maalouf, 2015).

Molecular genetic studies may provide insight into etiological differences between emotional problems at different stages of the life span. For complex disorders, large genome-wide

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association studies of patients and controls suggest that individual common risk alleles have small effects. However, findings from these studies can be used to generate an individual's estimated total burden of risk alleles (indexed by polygenic risk scores, PRS) for a particular disorder (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013). These scores, although weakly predictive at present, do provide a biological indicator of genetic loading for an illness (see Kendler, 2016). Previous studies find that both schizophrenia and mood disorder risk alleles contribute to adult major depressive disorder (MDD) and anxiety disorders (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Okbay *et al.* 2016; Verduijn *et al.* 2017; Docherty *et al.* 2017) and that schizophrenia PRS contribute to childhood emotional problems (Nivard *et al.* 2017; Riglin *et al.* 2017*a*). However, findings from a recent genetic study of adult MDD suggested a heterogeneous genetic architecture that was indexed by age-of-onset (Power *et al.* 2017); while a genome-wide significant locus was identified to be specifically associated with 'later-onset' depression (after a median age of 27 years), depression that began earlier was associated with schizophrenia risk alleles. To date, as far as we know, there have been no systematic attempts at examining whether the molecular genetic architecture of emotional problems in the general population changes with age – from childhood to adulthood. A prospective cohort design would enable investigation of the same individuals at different ages.

We set out to investigate the contribution of schizophrenia and MDD risk alleles to emotional problems during childhood, adolescence, young adulthood and mid-life that were assessed in a longitudinal UK population-based cohort – the National Child Development Study (NCDS). Based on previous cross-sectional findings for patients with MDD (Power *et al.* 2017), we hypothesized that 'early' emotional problems in childhood and adolescence would be indexed by schizophrenia risk alleles identified in GWA case–control studies of patients with schizophrenia but that 'later' emotional problems in adulthood would be predicted by MDD risk alleles.

Methods

Sample

The NCDS is a well-established prospective UK birth cohort. The study recruited 18 558 children from England, Wales, and Scotland born during 1 week in 1958. In 2002, when participants were aged 44 years, a biomedical survey was conducted which included the collection of genetic data. Participants who took part in the biomedical survey ($N = 9377$) were broadly representative of the full cohort with regards to childhood social class, maternal and physical characteristics, and key adult characteristics although non-participation (and dropout across the study follow-up periods more broadly) was associated with being born to a single parent family, early social care, non-white ethnicity, and childhood cognitive and behavioral problems (Atherton *et al.* 2008). Participants for the present study are those with genotype data: $N = 5257$ individuals following quality control (see below). These individuals were broadly representative of the full biomedical participants in terms of childhood sociodemographic factors and emotional problems, but had lower levels of emotional problems in adulthood than those without genotype data (online Supplementary Table S1). Full details of the study are described elsewhere (Power & Elliott, 2006). Ethical approval for the biomedical survey from which genetic data were available was obtained from the South East Multicentre Research Ethics Committee.

Emotional problems

Emotional problems were assessed six times: in childhood (age 7 years), late childhood (age 11), adolescence (age 16 years), young adulthood (age 23 years), adulthood (age 33 years), and mid-life (age 42 years).

In childhood, late childhood and adolescence, data were collected using parent reports of two depression/anxiety items (miserable or tearful; worries about many things) from an abbreviated version of the Rutter A scale for children (Rutter *et al.* 1970) (individuals item range 0–2; possible range for total score 0–4). At ages 7 and 11 years, this used 'modified' response options (never, sometimes, frequently), while at age 16 years, this used the 'standard' Rutter response options (does not apply, applies somewhat, certainly applies). In adulthood (including mid-life), data were collected using self-reports of 11 depression/anxiety items from the Malaise Inventory (Rodgers *et al.* 1999) (individuals item response yes/no; possible range for total score 0–11; individuals items are included in online Supplementary Table S2).

The primary outcome measures were total Rutter A scale emotional scores and total depression/anxiety Malaise scores. Sensitivity analyses were conducted using outcomes defined by the total score for a 'restricted' set of two items that were common to the Rutter A and Malaise scales (miserable, worries; see online Supplementary Table S3). For descriptive purposes, emotional symptom scores were also dichotomized whereby the top 10% of individuals were considered to have emotional problems; these were used to generate groups based on the presence of 'early' symptoms (age 7 or 11 years) and 'later' symptoms (age 33 or 42 years).

Polygenic risk scores

PRS were generated as the weighted mean number of disorder risk alleles in approximate linkage equilibrium ($R^2 < 0{\cdot}25$), using standard procedures (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013); full details of these methods are given elsewhere (Riglin *et al.* 2017*b*). Schizophrenia and MDD risk alleles were identified as those associated with case status in the Psychiatric Genetic Consortium (PGC) analyses (schizophrenia 35 476 cases and 46 839 controls; MDD 9240 cases and 9519 controls) at a threshold of $p < 0.05$ for schizophrenia and $p < 0.5$ MDD. For schizophrenia, the threshold was both the modal and median threshold that in PRS analyses of the samples contributing to that meta-analysis, captured the maximum phenotype variance (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). For MDD, this threshold maximally captures phenotypic variance in the MDD GWAS study (Ripke *et al.* 2013). Associations across a range of *p*-thresholds are shown in Supplementary Fig. S1. Individuals were genotyped at age 44 years; roughly half of the sample on the Infinium HumanHap 550 K v3 and half on the Illumina 1.2 M ($N = 2519$ and 2738 respectively). PRS were derived from the overlapping 510 982 single nucleotide polymorphisms which passed quality control. In line with previous work, platform and 10 population stratification principal components were included as covariates in all analyses (Riglin *et al.* 2017*b*). Individuals with genetic data were included in this study: $N = 5257$.

https://doi.org/10.1017/S0033291717003634 Published online by Cambridge University Press

Statistical analyses

Associations between schizophrenia PRS and MDD PRS and emotional problems at each age were primarily investigated using ordinal regressions in Stata version 13 (StataCorp, 2013). All analyses controlled for sex. Sensitivity checks were conducted to investigate alternative explanations for age differences in associations between emotional problems and PRS findings. First, we assessed whether any age-related differences in association were driven by measurement differences. We generated outcomes derived from the 'restricted set' of two items (miserable; worries) which were the same across the child and adult scales – see online Supplementary Table S3 for details. Second, to check whether associations were driven by persistent *v.* later-onset symptoms, we generated four groups: those with elevated symptoms (top decile) in childhood only (age 7 or 11 years, but not later: $N = 269$), in adult life only (ages 33 or 42, but not earlier: $N = 168$), and those who showed persistently elevated scores (age 7 or 11 and age 33 or 42: $N = 145$). These were compared to those that never had elevated levels of symptoms (age 7, 11, 16, 23, 33, or 42: $N = 1604$). Finally, the potential impact of missing data (which ranged from 3.5% to 23.3%) was investigated by running analyses using non-response weights (see online Supplementary Material).

Results

Frequencies for total emotional problem scores at each age are shown in Fig. 1; emotional problems were associated with female gender at every age (see Fig. 1). Correlations between measures are given in online Supplementary Table S4.

Associations with schizophrenia and MDD risk alleles

Associations between PRS and emotional problems are shown in Table 1 and Fig. 2. Schizophrenia PRS were associated with emotional problems from childhood to mid-life (ages 7, 16, 23, 33, and 42 years – although not at age 11 years), while MDD PRS were associated with emotional problems only in adulthood (including mid-life: ages 33 and 42 years).

Sensitivity checks

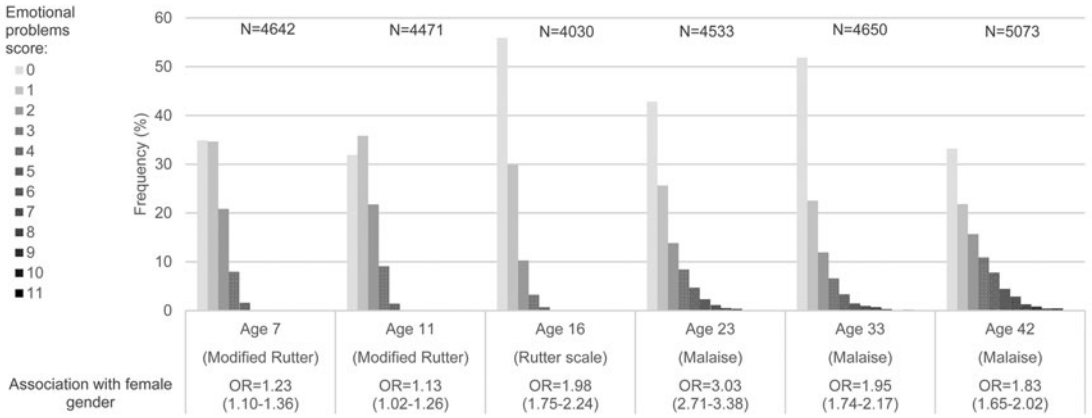
Running analyses on the restricted set of depression/anxiety items found associations between schizophrenia PRS and emotional problems from childhood to mid-life and between MDD PRS and emotional problems in adulthood only, suggesting age-related differences in associations between PRS and emotional problems are not driven by item differences between the child and adult scales (see online Supplementary Table S5). Frequencies for the restricted set of total emotional problems are shown in online Supplementary Fig. S2.

Assessing persistent and later-onset emotional problems found no clear pattern of associations between PRS and specific age-at-onset/persistence groups, although there was some indication that associations between schizophrenia PRS and childhood emotional problems may be driven by persistent problems and that associations between MDD PRS and adult emotional problems may be driven by later-onset emotional problems. However, these analyses were underpowered due to small sample sizes (see online Supplementary Fig. S3).

Investigating the potential impact of missing data using non-response weights did not change the pattern of associations (online Supplementary Table S6).

Discussion

We set out to investigate the contribution of psychiatric disorder risk alleles to emotional problems across childhood, adolescence, young adulthood, and mid-life. Similar associations across the life span would suggest that the same liability underlies the manifestation of emotional problems at different ages – as implied by strong links between emotional problems in childhood/adolescence and depression/anxiety in adult life (Rutter *et al.* 2006; Thapar *et al.* 2012; Maughan & Collishaw, 2015). Our findings suggest that associations with mood disorder and schizophrenia risk alleles differ across ages, implying possible age-related heterogeneity in the genetic architecture of emotional problems in the general population. Specifically, in keeping with a previous study of patients with MDD, schizophrenia risk alleles – indexed by PRS – were associated with emotional problems across the life span from childhood (age 7 years) to mid-life (age 42 years)



NB. Ages 7 and 11 (Modified Rutter items) and 16 years (Rutter items) are scored 0-4; ages 23, 33 and 42 years (Malaise items) are scored 0-11. OR=odds ratios (with 95% confidence intervals).

Fig. 1. Frequencies for total emotional problems (depression/anxiety) at different ages.

https://doi.org/10.1017/S0033291717003634 Published online by Cambridge University Press

Table 1. Associations between schizophrenia and major depressive disorder polygenic risk scores (PRS) and emotional problems

Emotional problems	Schizophrenia risk alleles			MDD risk alleles		
	OR	(95% CI)	*p* value	OR	(95% CI)	*p* value
Age 7	1.09	(1.03–1.15)	0.003	1.03	(0.98–1.09)	0.228
Age 11	1.00	(0.95–1.06)	0.925	0.98	(0.93–1.04)	0.551
Age 16	1.09	(1.02–1.16)	0.012	0.98	(0.92–1.04)	0.450
Age 23	1.08	(1.01–1.13)	0.021	1.02	(0.97–1.08)	0.420
Age 33	1.07	(1.01–1.35)	0.027	1.06	(1.00–1.12)	0.048
Age 42	1.10	(1.05–1.17)	<0.001	1.06	(1.00–1.11)	0.034

*Emotional problems measured by depression/anxiety items from the Rutter A scale at ages 7, 11, and 16 years and from the Malaise Inventory at ages 23, 33, and 42 years.

(apart from age 11 years), while MDD risk alleles were associated with emotional problems in adulthood (ages 33 and 42) but not in younger individuals.

Our hypothesis that schizophrenia PRS would impact 'early' emotional problems in childhood and adolescence was driven by recent genetic work which found 'earlier-onset' depression (before a median age of 27 years) had greater genetic overlap with schizophrenia compared with 'later-onset' depression (Power *et al.* 2017). This is the third sample in which associations between schizophrenia risk alleles and anxiety symptoms/emotional problems have been observed during childhood/adolescence (Jones *et al.* 2016; Nivard *et al.* 2017; Riglin *et al.* 2017*a*). Sensitivity checks suggested that associations between schizophrenia PRS and emotional problems in childhood might be driven, at least partly, by early-onset, persistent emotional problems which are still present in adulthood – although this hypothesis requires replication.

Our second hypothesis, that MDD risk alleles would impact 'later' emotional problems, was supported by findings that MDD PRS were associated with emotional problems in adulthood (ages 33 and 42) but not before – during childhood, adolescence, or early 20s (ages 7, 11, 16, and 23). The findings suggest that later emotional problems are genetically more similar to MDD than are early or childhood/adolescent onset emotional problems. Our finding that adult emotional problems are associated with both MDD and schizophrenia PRS is consistent with previous work using similar outcomes in population samples (Gale *et al.* 2016; Hyde *et al.* 2016; Okbay *et al.* 2016). Our results at age 23 years were similar to those found in adolescence and we observed association with MDD PRS only after the age of 30. Similarly, stratification by age-at-onset of a GWAS of patients with MDD suggested 'adult-onset' MDD emerged around 27 years of age. These findings suggest that whether focusing on patients or the general population, the early 20s might not be as clearly distinct from adolescence and as similar to later adulthood as assumed by the cut-point of age 18 years that is typically used to compare 'children' and 'adults' and divide clinical services.

The present study is the first, to our knowledge, to examine prospectively the impact of schizophrenia and MDD risk alleles on emotional problems at different ages in the same individuals. This work adds to findings from MDD patient studies in suggesting that early-onset emotional problems may share more genetic risk with schizophrenia, while adult emotional problems share genetic risk with both schizophrenia and MDD. This could be viewed as arguing against a straightforward developmental continuity hypothesis, at least in terms of genetic architecture. The findings instead suggest the possibility that different liabilities may underlie the manifestation of symptoms at different ages,

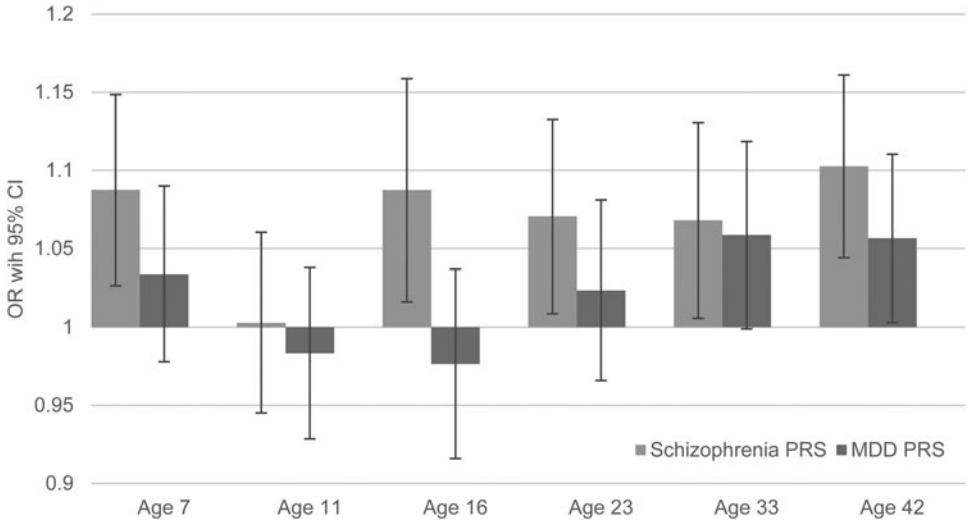


Fig. 2. Associations between schizophrenia and major depressive disorder (MDD) polygenic risk scores (PRS) and emotional problems.

https://doi.org/10.1017/S0033291717003634 Published online by Cambridge University Press

which may explain why gender ratios and treatment responses for depression have been found to differ by age and developmental stage (Hazell *et al.* 1995; Thapar *et al.* 2012; Brent & Maalouf, 2015). This suggestion – that genetic architecture is not static across development – would also have implications for initiatives such as R-doc as it implies that the biological correlates of the same symptoms or psychiatric construct could be dissimilar at different ages (Insel *et al.* 2010; Cuthbert & Insel, 2013).

This study should be considered in light of a number of limitations. One issue of particular importance is the use of different measures and reporters of emotional problems. As is typical of longitudinal studies, different measures and informants were used in childhood and adult life, which creates challenges for longitudinal research. To assess developmental continuities and change robustly, the use of the same measures (with the same informant, wording, response options, etc.) is required across each wave of data collection (Goodman *et al.* 2007; Collishaw *et al.* 2009). This is an issue for historical cohorts such as NCDS and we urge cohort investigators with ongoing data collection in different countries to give this serious consideration, especially when participants are transitioning between childhood/adulthood. While we were able to observe age-related differences in associations when using the same measure and reporter (MDD PRS were associated with Malaise scores at ages 33 and 42 but not at age 23 years) and sensitivity analyses restricting our outcomes to the same depression/anxiety items at each age revealed a similar pattern of results, we cannot rule out that some differences are driven by measurement differences rather than age.

Additional limitations include that, while our sample benefits from prospective data collected from childhood to mid-life, it does not yet cover the entire life span: emotional problems with onset in older age may differ from those with earlier onset (Alexopoulos, 2005). Further, our sample is a longitudinal study that suffers from non-random attrition: individuals with higher neuropsychiatric PRS and emotional problems are less likely to remain in studies until adulthood which may have reduced power to detect associations between PRS and emotional problems (Wolke *et al.* 2009; Martin *et al.* 2016). Another consideration is that NCDS was included as a control sample in the PGC GWAS (Ripke *et al.* 2013; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Although this does not threaten the validity of the current investigation because it is a *within-* rather than between-sample analysis, statistical power will have been reduced because NCDS was included as a control group in the original discovery investigation. Finally, although PRS are useful indicators of genetic liability (see Kendler, 2016), at present they explain very little phenotype variance in population traits – and are especially weak for MDD so the small effect sizes that we observe are typical for this kind of work (e.g. Riglin *et al.* 2016). For example – adopting the approach used by Kendler (2016) individuals in the top 2.5% for schizophrenia PRS would have a roughly 20% increased risk of having an additional emotional problem symptom in mid-life, while individuals in the top 2.5% for MDD PRS would have a roughly 12% increased risk. This means PRS should be regarded as indicators of genetic liability rather than as predictors. These limitations highlight the need for further replications in population-based and patient studies but ones that assess developmental differences.

The present study indicates that emotional problems in the general population show genetic overlap with schizophrenia and MDD but that childhood emotional problems may share more genetic risk with schizophrenia, while later emotional problems may also share genetic risk with MDD. These findings suggest that the genetic architecture of emotional problems may not be static across development, and that different liabilities could contribute to the manifestation of symptoms at different ages.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291717003634

Acknowledgements. The authors are grateful to the Centre for Longitudinal Studies (CLS), UCL Institute of Education for the use of the NCDS data and to the UK Data Service for making them available. However, neither CLS nor the UK Data Service bear any responsibility for the analysis or interpretation of these data. Data governance was provided by the METADAC data access committee, funded by ESRC, Wellcome, and MRC (grant number: MR/N01104X/1). This work made use of data and samples generated by the 1958 Birth Cohort (NCDS), which is managed by the Centre for Longitudinal Studies at the UCL Institute of Education, funded by the Economic and Social Research Council (grant number ES/M001660/1). Access to these resources was enabled via the Wellcome Trust & MRC: 58FORWARDS grant (108439/Z/15/Z) (The 1958 Birth Cohort: Fostering new Opportunities for Research via Wider Access to Reliable Data and Samples). Before 2015 biomedical resources were maintained under the Wellcome Trust and Medical Research Council 58READIE Project (grant numbers WT095219MA and G1001799). Genotyping was undertaken as part of the Wellcome Trust Case-Control Consortium (WTCCC) under Wellcome Trust award 076113, and a full list of the investigators who contributed to the generation of the data is available at http://www.wtccc.org.uk. This work was supported by the Medical Research Council (MR/M012964/1).

Declaration of interest. None.

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https://doi.org/10.1017/S0033291717003634 Published online by Cambridge University Press