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ORIGINAL ARTICLE

The association between childhood adversities and subsequent first onset of psychotic experiences: a cross-national analysis of 23 998 respondents from 17 countries

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Background. Although there is robust evidence linking childhood adversities (CAs) and an increased risk for psychotic experiences (PEs), little is known about whether these associations vary across the life-course and whether mental disorders that emerge prior to PEs explain these associations.

Method. We assessed CAs, PEs and DSM-IV mental disorders in 23 998 adults in the WHO World Mental Health Surveys. Discrete-time survival analysis was used to investigate the associations between CAs and PEs, and the influence of mental disorders on these associations using multivariate logistic models.

Results. Exposure to CAs was common, and those who experienced any CAs had increased odds of later PEs [odds ratio (OR) 2.3, 95% confidence interval (CI) 1.9–2.6]. CAs reflecting maladaptive family functioning (MFF), including abuse, neglect, and parent maladjustment, exhibited the strongest associations with PE onset in all life-course stages. Sexual abuse exhibited a strong association with PE onset during childhood (OR 8.5, 95% CI 3.6–20.2), whereas Other CA types were associated with PE onset in adolescence. Associations of other CAs with PEs disappeared in adolescence after adjustment for prior-onset mental disorders. The population attributable risk proportion (PARP) for PEs associated with all CAs was 31% (24% for MFF).

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Conclusions. Exposure to CAs is associated with PE onset throughout the life-course, although sexual abuse is most strongly associated with childhood-onset PEs. The presence of mental disorders prior to the onset of PEs does not fully explain these associations. The large PARPs suggest that preventing CAs could lead to a meaningful reduction in PEs in the population.

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Key words: Childhood adversity, discrete-time survival analysis, maladaptive family functioning, population attributable risk proportion, psychotic experiences, World Mental Health survey.

Introduction

Psychotic experiences (PEs), including hallucinations and delusions, are common among the general population with a lifetime prevalence of 5.8–12.5% (Nuevo *et al.* 2010; Linscott & van Os, 2013; McGrath *et al.* 2015). Recent evidence indicates that exposure to childhood adversities (CAs) is associated with elevated risk of later PEs (Varese *et al.* 2012; Trotta *et al.* 2015; Morgan & Gayer-Anderson, 2016), with a meta-analysis reporting that CAs are associated with a 76% increased risk of PEs (Trotta *et al.* 2015).

Existing research on CAs and PEs is limited by a focus on specific types of CAs rather than a comprehensive set of CAs. For example, studies have reported mainly on the following types of CAs and risk of PEs: (*a*) sexual abuse (Read *et al.* 2003; Shevlin *et al.* 2007; Kilcommons *et al.* 2008; Bentall *et al.* 2012; Murphy *et al.* 2014; van Dam *et al.* 2015), (*b*) child abuse and neglect (Janssen *et al.* 2004; Arseneault *et al.* 2011; Kelleher *et al.* 2013; van Dam *et al.* 2015), and (*c*) bullying and peer victimisation (van Dam *et al.* 2012; Kelleher *et al.* 2013; Wolke *et al.* 2014; Cristobal-Narvaez *et al.* 2016).

CAs rarely occur in isolation (Green *et al.* 2010; Kessler *et al.* 2010; McLaughlin *et al.* 2010*b*). The pathways linking CAs and subsequent mental health are also complex and inter-correlated. For example, an association between parental mental illness and psychopathology in the offspring may be influenced by parenting ability (an 'environmental' exposure) as well as a range of confounding factors including shared genetic effects. CAs, like many traditional measures of environmental adversity, are modestly to moderately heritable (Kendler & Baker, 2007). Thus, more complex models that account for both the *type* and *number* of CAs are needed to determine whether the associations of CAs with PEs are specific to certain types of experiences but not others, and how increasing levels of exposure influence the risk for PEs. Indeed, several prior studies have documented a dose-response relationship between *number* of CAs and lifetime prevalence of PEs (Janssen *et al.* 2004; Shevlin *et al.* 2007; Wigman *et al.* 2011*a*, *b*; Bentall *et al.* 2012; Murphy *et al.* 2013; Muenzenmaier *et al.* 2015).

Moreover, while the evidence linking CAs and lifetime PEs is robust (Morgan & Gayer-Anderson, 2016), little is known about the patterning of these associations at different stages of development. In particular, we are unaware of studies that have examined whether PEs tend to occur in close proximity to CA exposure, or whether CAs are associated with the onset of PEs at later periods in the life-course. PEs that emerge soon after CAs would suggest more direct and proximal mechanisms, consistent with stress-related mechanisms (CAs lead to a sensitization process that renders exposed individuals more reactive to subsequent stressors) (Cristobal-Narvaez *et al.* 2016). On the other hand, PEs that emerge many decades later might suggest indirect pathways, perhaps mediated by the occurrence of mental disorders. With regard to the latter possibility, extensive evidence suggests that CAs are associated with elevated risk of first onset of a wide range of mental disorders (Green *et al.* 2010; Kessler *et al.* 2010; McLaughlin *et al.* 2010*b*; 2012). We recently demonstrated that most mental disorders are also associated with increased odds of subsequent PE onset (McGrath *et al.* 2016*b*). Thus, it seems reasonable to assume that the association between CAs and PEs may be mediated, at least in part, by the onset of mental disorders following exposure to CAs. A recent analysis of the National Comorbidity Survey found that the associations of CAs with PEs were mediated partly by depression and/or anxiety (Sitko *et al.* 2014), although the temporal sequence of the association was not ascertained. Other research suggests that symptoms related to affective or emotional instability partially mediate the association between CAs and PEs (Bak *et al.* 2005; Kramer *et al.* 2012; Marwaha *et al.* 2014). Based on this initial work, there is a need for studies that explore the influence of mental disorders on the relationship between CAs and PEs. Ideally, these studies should explore a range of mental disorders, and ensure that the variables of interest are temporally ordered (i.e. that CAs occur prior to onset of mental disorders, which occur prior to the onset of PEs), a necessary but not sufficient condition to infer causality.

Finally, prior work has estimated the population attributable risk proportions (PARPs) of mental disorders that are associated with CAs, and found sizable

PARPs both in the United States and cross-nationally (e.g. 38–45% of childhood-onset mental disorders; and 28–29% of early-adult onset mental disorders) (Green *et al.* 2010; Kessler *et al.* 2010). Estimates of PARPs related to psychotic experiences have also been derived from meta-analysis (33%) (Varese *et al.* 2012), but the relative importance of different types of CAs in contributing to the onset of PEs in the population remains unknown.

The aims of the present study were to examine the associations between CAs and first-onset of PEs, determine whether those associations vary at different stages of the life-course, and investigate the degree to which temporally-prior mental disorders explain the association between CAs and subsequent PE onset. We also estimated the population attributable risk proportion of PEs related to CA exposure. We used a large sample of adults drawn from a cross-national population-based study – the WHO World Mental Health (WMH) surveys.

Method

Samples

The WMH surveys are a coordinated set of community surveys administered in probability samples of the general population in countries throughout the world (www.hcp.med.harvard.edu/WMH; Kessler & Ustun, 2004). We examined 17 WMH surveys that included both the CIDI Psychosis Module and items related to CAs. These 17 countries are distributed across North and South America (Colombia, Mexico, Peru, Sao Paulo in Brazil, USA); Africa (Nigeria); the Middle East (Iraq, Lebanon); Asia (Shenzhen in the People's Republic of China); and Europe (Belgium, France, Germany, Italy, The Netherlands, Portugal, Romania, Spain). All 17 surveys were based on multi-stage, clustered area probability sampling designs (Supplementary Table S1). The weighted average response rate across all 17 countries was 71.9%.

In keeping with previous studies of PEs (Saha *et al.* 2011*a*, *b*; McGrath *et al.* 2015, 2016*a*, *b*), we made the *a priori* decision to exclude individuals with PEs who screened positive for possible schizophrenia/psychosis, and manic-depression/mania. Thus, we excluded respondents who (*a*) reported (1) *schizophrenia/psychosis* or (2) *manic-depression/mania* in response to the question '*What did the doctor say was causing* (*this/these*) *experiences?*'; or (*b*) reported lifetime use of an antipsychotic medication for these symptoms. This resulted in the exclusion of 91 respondents (0.4% of all respondents), leaving 23998 respondents for this study (see Supplementary Table S1).

Procedures

All surveys were conducted in the homes of respondents by trained lay interviewers. Informed consent was obtained before beginning interviews in all countries. Procedures for obtaining informed consent and protecting individuals (ethical approvals) were approved and monitored for compliance by the institutional review boards of the collaborating organizations in each country (Kessler & Ustun, 2008*a*). Standardized interviewer training and quality control procedures were used consistently in the surveys. Full details of these procedures are described elsewhere (Kessler *et al.* 2006; Kessler & Üstün, 2008*b*).

Interviews were administered in two parts to reduce respondent burden. Part 1 was administered to all participants and included the core diagnostic assessment of DSM-IV mental disorders. Part 2 of the interview included additional questions about PEs, correlates and other disorders was administered to respondents who met lifetime criteria for any Part 1 disorder and a random proportion of other respondents without any mental disorders. Part 2 individuals were weighted by the inverse of their probability of selection to adjust for differential sampling, and therefore provide representative data on the target adult general population. Additional weights were used to adjust for differential probabilities of selection within households, non-response, and to match the samples to population socio-demographic distributions.

Data collection and data items

The instrument used in the WMH surveys was the WHO Composite International Diagnostic Interview (CIDI) (Kessler & Üstün, 2008*b*), a validated fully-structured diagnostic interview (http://www.hcp.med.harvard.edu/wmhcidi/instruments_download.php) designed to assess the prevalence and correlates of a wide range of mental disorders according to the definitions and criteria of both the DSM-IV and ICD-10 diagnostic systems. WHO translation, back-translation, and harmonisation protocols were used to adapt the CIDI for use in each participating country.

Psychotic experiences

The CIDI Psychosis Module included questions about six PE types – two related to hallucinatory experiences (visual hallucinations, auditory hallucinations) and four related to delusional experiences (thought insertion/withdrawal, mind control/passivity, ideas of reference, plot to harm/follow) (Supplementary Tables S2a, S2b). The respondents were asked if they ever experienced each PE (e.g. '*Have you ever seen something that wasn't there that other people could not see?*'; '*Have you ever heard any voices that other people said did not exist?*' etc.). Only PEs occurring when the person was '*not dreaming, not half-asleep, or not under the influence of alcohol or drugs*' were included. Respondents who reported

PEs were then asked a probe question about the age of onset of PEs (i.e. '*How old were you the very first time* (*this/either of these things/any of these things*) *happened to you?'*).

Childhood adversity

The WMH surveys assessed a range of family-related CAs (see Kessler *et al.* 2010). Eleven dichotomously scored CAs occurring before age 18 were assessed (full details are provided in Supplementary material S3). Age-of-exposure data were collected for other parental loss, parental divorce, parental death in the CIDI childhood section (e.g. '*How old were you when your father/ mother died*'), while the data on sexual abuse were collected using questions in the post-traumatic stress disorder section. As with previous analyses of CAs in the WMH surveys (Green *et al.* 2010; Kessler *et al.* 2010), we undertook an exploratory factor analysis via promax rotation (Supplementary Table S4), and confirmed that two meaningful groups of CAs were identified: (*a*) 'Maladaptive Family Functioning' (MFF) CAs, and (*b*) 'Other CAs'. Seven CAs loaded onto the MFF factor (parental mental illness, substance disorder and criminal behaviour, family violence, physical abuse, sexual abuse and neglect) and four CAs (parental death, parental divorce, other parental loss and economic adversity) loaded onto the Other CA factor. All subsequent analyses examined CAs grouped by MFF and Other CAs.

Mental disorders

The WMHS CIDI assessed lifetime history of 21 mental disorders including *mood disorders* (major depressive disorder, bipolar disorders); *anxiety disorders* [panic disorder, generalized anxiety disorder (GAD), specific phobia, social phobia, agoraphobia without panic, post-traumatic stress disorder (PTSD), separation anxiety disorder (SAD) further divided into childhood SAD and adult separation anxiety disorder]; *behaviour disorders* (intermittent explosive disorder, attention deficit disorder, oppositional defiant disorder, conduct disorder); *eating disorder* (anorexia nervosa, bulimia nervosa, and binge eating disorder); and *substance use disorders* (alcohol abuse, alcohol dependence, drug abuse, and drug dependence). The disorders that require childhood onset (e.g. attention deficit disorder, oppositional defiant disorder, conduct disorder, separation anxiety disorder) were included in Part 2 and are limited to respondents in the age range 18–39 or 18–44 years (depending on site) because of concerns about recall bias among older respondents (Kessler *et al.* 2007). All other disorders were assessed for the full sample age range. Clinical reappraisal studies indicate that lifetime diagnoses based on the CIDI have good concordance with diagnoses based on blinded clinical interviews (Haro *et al.* 2006). In keeping with our previous research, standardized diagnostic hierarchy rules among the disorders assessed were applied where appropriate (Kessler *et al.* 2005; McGrath *et al.* 2016*a*).

Statistical analysis

Discrete-time survival analyses with person-year as the unit of analysis was used to investigate the associations between CAs and PEs. A person-year dataset was created such that each year in the life of each respondent (up to and including the age of onset of PE or in those without PE, their age at interview) was treated as a separate observational record. Age-of-exposure dates were available for sexual abuse, other parental loss, parental divorce and parental death, otherwise age 4 years was set as a default age-of-exposure, in keeping with previous analyses for CAs used in the WMH studies (Bruffaerts *et al.* 2010; Green *et al.* 2010). In all analyses, the temporal order required the onset of CAs to precede that of PEs. We first estimated bivariate associations of CAs with PEs followed by a series of multivariate models: (*a*) M1 included all CAs simultaneously into the models without considering number of CAs (type model), (*b*) M2 used only number of CAs based on MFF and/or Other CAs (number model), and (*c*) M3 based on both *type and number* of CAs (multivariate interactive model). We also examined if there were gender differences in the associations between CAs and PEs. In order to choose a model for subsequent analyses, we examined both (*a*) model fitting measures [Bayesian Information Criterion (BIC), Akaike's Information Criterion (AIC); Akaike, 1974; Schwarz, 1978], and (*b*) χ^2 tests in order to compare the odds ratios between CA types and/or number indicators as predictors of PEs.

Next, we re-estimated associations based on the most informative model for PE onsets occurring in four life-course stages: childhood (4–12 years); adolescence (13–19 years); young adulthood (20–29 years); and later adulthood ($\geqslant$30 years). This allowed us to examine whether the associations of CAs with PE onset varied across the life-course. Then, we examined the strength and pattern of association between CAs and PEs when adjusted for 21 temporally ordered mental disorders (i.e. the mental disorder occurred after the CA age-of-exposure but prior to the onset of PEs).

Finally, the PARPs were calculated based on the proportion of PE associated with the CA in the bivariate models. PARPs can be interpreted as the expected proportion of reduction in the outcome prevalence if CAs were eradicated (Cole & MacMahon, 1971; Rothman & Greenland, 2005). In order to assess the differential

Table 1. *Prevalence of childhood adversities (CA) among those with and without psychotic experiences*

Type of childhood adversity	Without psychotic experience ($n = 22\,337$)		With psychotic experience ($n = 1661$)		Total ($n = 23\,998$)	
	%[a]	S.E.	%[a]	S.E.	%[a]	S.E.
I. Maladaptive family functioning CAs						
Parental mental illness	6.5	0.2	17.3	1.2	7.1	0.2
Parental substance disorder	3.6	0.2	9.0	1.1	3.9	0.2
Parental criminal behaviour	2.4	0.1	7.3	0.9	2.7	0.1
Family violence	6.1	0.2	15.9	1.2	6.7	0.2
Physical abuse	7.5	0.2	21.7	1.4	8.3	0.2
Sexual abuse	1.2	0.1	5.8	1.0	1.5	0.1
Neglect	4.3	0.2	14.0	1.3	4.8	0.2
Any maladaptive family functioning CAs	20.3	0.4	45.9	2.0	21.7	0.4
II. Other CAs						
Parental death	13.4	0.3	14.3	1.1	13.5	0.3
Parental divorce	5.1	0.2	11.6	1.2	5.5	0.2
Other parental loss	5.9	0.2	11.2	1.1	6.2	0.2
Economic adversity	2.9	0.1	5.7	0.8	3.0	0.1
Any other CAs	22.8	0.4	32.3	1.7	23.4	0.4
III. Any childhood adversities	36.6	0.5	59.8	1.8	37.9	0.5
IV. Total number of childhood adversities						
Exactly 1 adversity	13.4	0.4	21.6	1.5	13.8	0.3
Exactly 2 adversities	13.4	0.3	14.6	1.3	13.5	0.3
$\geqslant$3 adversities	6.9	0.2	19.7	1.4	7.6	0.2

[a]Estimates were based on weighted data.

impact of three country level strata on PE risk, we conducted *post-hoc* analyses by including interaction terms between CAs and country income strata. Details of the country strata classification have been published elsewhere (McGrath *et al.* 2015).

As the WMH data are both clustered and weighted, the design-based Taylor series linearization implemented in SUDAAN software was used to estimate standard errors and evaluate the statistical significance of coefficients. Survival coefficients were exponentiated and are reported as odds ratios (ORs). Significance tests were evaluated using 0.05-level two-sided tests.

Results

Prevalence of CAs in those with and without PEs

More than one-third of respondents ($n = 10{,}015$, 37.9%) reported exposure to at least one CA before age 18 years (Table 1). The prevalence of CA exposure among respondents with PEs was 59.8% compared to 36.6% in those with no PEs. Among respondents with PEs, there was wide variation in the frequency of exposure to specific types of CAs, with the highest prevalence reported for physical abuse (21.7%) followed by parental mental illness (17.3%). Among those with PEs, 19.7% had been exposed to three or more CAs, whereas the comparable proportion in those without PEs was 6.9%.

The influence of type and number of CAs

Table 2 summarizes the associations between CAs and subsequent first onset of PEs using type and/or number of CAs in both bivariate and multivariate models. In the bivariate model, all CAs with the exception of parental death were significantly associated with increased odds of subsequent PEs. Respondents with exposure to any CA had twice the odds of subsequent onset PEs compared to respondents with no CAs (OR 2.3, 95% CI 1.9–2.6). The ORs ranged from 1.7–4.0 for MFF CAs and 1.4–1.9 for Other CAs, with the highest ORs associated with sexual abuse (OR 4.0, 95% CI 2.6–6.3) physical abuse (OR 2.8, 95% CI 2.3–3.3), and parental criminal behaviour (OR 2.7, 95% CI 2.0–3.7).

In general, the ORs in the multivariate model that controlled for all CA types were smaller than in the bivariate model, due to the high co-occurrence of CAs (see M1 multivariate model, Table 2). In the multivariate model, the ORs for PEs associated with specific

Table 2. *Bivariate and multivariate associations between childhood adversities (CA) and the subsequent first onset of psychotic experiences*

	Bivariate[a] OR (95% CI)	M1 Multivariate type[b] OR (95% CI)	M2 Multivariate number[c] OR (95% CI)	M3 Multivariate type + number[d] OR (95% CI)
I. MFF CAs				
Parental mental illness	2.5* (2.1–3.0)	2.0* (1.6–2.3)	–	2.2* (1.8–2.7)
Parental substance disorder	1.7* (1.3–2.1)	0.9 (0.7–1.2)	–	1.1 (0.8–1.5)
Parental criminal behaviour	2.7* (2.0–3.7)	1.7* (1.3–2.3)	–	2.0* (1.4–2.8)
Family violence	2.1* (1.7–2.5)	1.2 (0.9–1.5)	–	1.4* (1.0–1.8)
Physical abuse	2.8* (2.3–3.3)	2.0* (1.6–2.4)	–	2.2* (1.8–2.7)
Sexual abuse	4.0* (2.6–6.3)	2.7* (1.7–4.2)	–	3.0* (1.9–4.8)
Neglect	2.2* (1.8–2.8)	1.1 (0.9–1.5)	–	1.4* (1.0–1.8)
Any MFF	2.7* (2.3–3.2)	–	–	–
Joint significance of all seven MFF CA indicators	–	$\chi^2_7 = 213.3$*	–	$\chi^2_7 = 114.2$*
Differences in the ORs of the seven MFF CA indicators		$\chi^2_6 = 41.7$*		
Number of MFF CA indicators				
1	–	–	2.2* (1.8–2.6)	–
2	–	–	2.8* (2.2–3.6)	0.9 (0.6–1.2)
⩾3	–	–	4.0* (3.1–5.2)	0.6* (0.3–1.0)
Joint significance of the three number of MFF CA measures	–	–	$\chi^2_3 = 135.3$*	$\chi^2_2 = 5.1$
II. Other CAs				
Parental death	1.2 (1.0–1.4)	1.1 (0.9–1.3)	–	1.1 (0.9–1.3)
Parental divorce	1.5* (1.2–1.9)	1.3* (1.0–1.7)	–	1.3* (1.0–1.7)
Other parental loss	1.7* (1.3–2.1)	1.3 (1.0–1.6)	–	1.3 (0.9–1.7)
Economic adversity	1.9* (1.4–2.5)	1.4* (1.0–1.9)	–	1.4 (0.9–2.1)
Any Other CAs	1.4*(1.2–1.7)	–	–	–
Joint significance of all four Other CA indicators	–	$\chi^2_4 = 18.6$*	–	$\chi^2_4 = 7.2$
Differences in the ORs of the four Other CA indicators		$\chi^2_3 = 3.0$		
Number of Other CA indicators				
1	–	–	1.2 (1.0–1.4)	–
2	–	–	1.5* (1.2–2.1)	1.0 (0.6–1.5)
⩾3	–	–	1.8 (1.0–3.4)	0.9 (0.4–2.2)
Joint significance of the three number of Other CA measures	–	–	$\chi^2_3 = 11.9$*	$\chi^2_2 = 0.0$
III. Total CAs				
Any childhood adversities	2.3* (1.9–2.6)	–	–	–
Joint significance of all 11 CA indicators	–	$\chi^2_{11} = 326.6$*	–	$\chi^2_{11} = 133.3$*
Differences in the ORs of the 11 CA indicators		$\chi^2_{10} = 52.8$*		
AIC	–	18954.9	18987.3	18954.0
BIC	–	19355.8	19329.3	19402.0

OR, Odds ratio; CI, confidence interval; MFF, maladaptive family functioning; AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion.

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

[a] Each model was estimated with one childhood adversity entered at a time as predictor of psychotic experiences onset controlling for country, person-year dummies, age cohort and sex.

[b] M1: Model was estimated with dummy variables for all childhood adversities entered simultaneously as predictors of psychotic experiences onset including the controls specified in note a.

[c] M2: Model was estimated with dummy variables for number of MFF CAs (exactly 1 MFF, exactly 2 MFF and ⩾3 MFF) and number of Other CAs (exactly 1 Other CA, exactly 2 Other CAs and ⩾3 Other CAs) entered simultaneously as predictors of psychotic experiences onset including the controls specified in note a.

[d] M3: Model was estimated with dummy variables for type and number of childhood adversities (starting at exactly 2 MFF and ⩾3 MFF, exactly 2 Other CA and ⩾3 Other CAs) entered simultaneously as predictors of psychotic experiences onset including the controls specified in note a.

Total number of person-years used across all models = 9 75 199.

types of CAs varied significantly ($\chi^2_{10} = 52.8$, $p < 0.001$). The CAs that remained significantly associated with PEs in this model were parental mental illness, parent criminal behaviour, physical and sexual abuse, parent divorce, and economic adversity. For these CAs, the adjusted ORs ranged from 1.7–2.7 for MFF CAs and 1.3–1.4 for Other CAs. The highest adjusted ORs ($\geqslant 2$) were found for sexual abuse (OR 2.7, 95% CI 1.7–4.2), physical abuse (OR 2.0, 95% CI 1.6–2.4), and parental mental illness (OR 2.0, 95% CI 1.6–2.3). We further examined whether there were gender differences in the associations of the latter three CAs with subsequent PE onset (data not shown). The sex-specific associations were similar for parental mental illness (females: OR 1.9, 95% CI 1.5–2.4; males: OR 2.0, 95% CI 1.4–2.9). For physical abuse, the OR (95% CI) was somewhat higher for males (2.3, 1.7–3.0) compared to females (1.7, 1.3–2.3), whereas for sexual abuse, the OR was higher and significant for females (2.7, 1.7–4.4) and lower and non-significant for males (1.7, 0.8–3.6).

In the model examining *number* of CAs only (i.e. exactly 1, exactly 2, $\geqslant 3$ CAs), there was a monotonic increase in the odds of PEs in respondents exposed to a greater number MFF CAs, indicating a dose-response relationship between number of CAs and PEs. A similar pattern of increasing odds of PEs was observed as the number of Other CAs increased (see M2 multivariate model, Table 2).

When we examined more complex models using type and number simultaneously in the multivariate models (M3), the OR associated with number of MFF and Other CAs were for the most part lower than 1.0, indicating a pattern of sub-additive interactions, whereby the incremental association of each additional CAs lessens in magnitude as the number of CAs increases. Taking into account the BIC and AIC as well as the pattern of findings across the models, we chose indicators only for *type* of MFF and Other CAs as the most informative model for subsequent analyses (Table 2, model M1).

In summary, we observed that exposure to CAs is associated with an increased odds of subsequent onset of PEs, that different CA types vary in their association with subsequent PEs, and that there was a dose-response relationship between higher numbers of CA types and increased risk of subsequent PEs.

Associations between CAs and subsequent onset of PEs across four life-course stages

Table 3 shows the associations between CAs and subsequent onset of PEs in four life-course stages (see M1). MFF CAs, as a set (i.e. when all MFF types were considered together), were associated with onset of PEs in all four life-course stages (childhood, adolescence, early adulthood, later adulthood), whereas Other CAs, as a set, were associated with PE onset only during adolescence. A test for variation in the ORs across life-course stages was significant for MFF CAs ($\chi^2_{21} = 39.8$, $p = 0.008$), but not in Other CAs, ($\chi^2_{12} = 9.4$, $p = 0.66$). When examining the associations of particular CA types with PE onset across the life-course, only two MFF CAs (parental mental illness, physical abuse) were significantly associated with increased odds of subsequent PE onset across each of the four life-course stages. Across particular CA types, only sexual abuse showed significant variation across life-course stages with respect to subsequent PE onset ($\chi^2_3 = 15.2$, $p = 0.002$). The highest OR for sexual abuse and PE onset was during childhood (4–12 years) (OR 8.5, 95% CI 3.6–20.2), and further analyses confirmed that respondents exposed to sexual abuse were more likely to have their PE onset during childhood (4–12 years) compared to older years ($\geqslant 13$; $\chi^2_1 = 5.5$, $p = 0.019$).

In summary, MFF CAs are associated with PEs in all life-course stages, whereas Other CAs are associated with PEs only in adolescence. Moreover, while MFF CAs are associated with PEs across all life-course stages, sexual abuse was more strongly associated with PEs that emerge during childhood (4–12 years).

Associations between CAs and PEs adjusting for mental disorders

Next, we examined the associations of CAs with PEs adjusting for mental disorders that were temporally prior to the onset of PEs (Table 4). There were slight reductions in the ORs associated with particular CA types after adjusting for mental disorders (M4) compared to the unadjusted model (M1). However, the associations of both MFF CAs and Other CAs with PEs remained significant as a set after adjusting for mental disorders. We also examined the association of CAs with PEs within the subgroup of respondents without any mental disorders that were temporally prior to the onset of PEs (M5). As a set, associations for MFF CAs remained significant with PEs, but the relationship became non-significant for Other CAs. Of interest, the OR (95% CI) for the relationship between sexual abuse and PEs was 6.7 (2.5–18.0).

Finally, we examined the role of temporally-prior mental disorders in the associations of CAs and PEs across life-course stages (Table 5). The pattern of findings was similar to the unadjusted life-course models, with one exception. As a set, MFF and Other CAs were no longer associated with PE onsets during adolescence after adjustment for temporally prior mental disorders. The association between sexual abuse and PEs during childhood persisted.

Table 3. *Multivariate associations between childhood adversities (CA) and the subsequent first onset of psychotic experiences in each of four life-course stages*[a]

	Childhood, age 4–12[b] (*p*-years = 2 86 818) OR (95% CI)	Adolescence, age 13–19[c] (*p*-years = 1 64 230) OR (95% CI)	Young adulthood, age 20–29[d] (*p*-years = 1 98 248) OR (95% CI)	Later adulthood, age ⩾30[e] (*p*-years = 3 25 903) OR (95% CI)	Test for significance difference: (childhood *v.* other 3 life-course stages) χ^2 (*p*-value)	Test for the significance of the slope differences across 4 life course stages	
						χ^2 (*p*-value)	χ^2 (*p*-value)
I. MFF CAs							
Parental mental illness	2.1* (1.4–3.0)	2.3* (1.5–3.5)	1.6* (1.2–2.1)	1.8* (1.2–2.8)	$\chi^2_1 = 0.0$ (0.937)	$\chi^2_3 = 1.5$ (0.674)	$\chi^2_{21} = 39.8$* (0.008)
Parental substance disorder	0.9 (0.5–1.5)	1.0 (0.6–1.7)	0.9 (0.6–1.4)	1.0 (0.5–2.0)	$\chi^2_1 = 0.1$ (0.776)	$\chi^2_3 = 0.1$ (0.992)	
Parental criminal behaviour	2.3* (1.2–4.4)	1.6 (0.9–2.8)	1.7 (0.9–3.2)	1.2 (0.7–2.0)	$\chi^2_1 = 2.3$ (0.130)	$\chi^2_3 = 2.5$ (0.481)	
Family violence	1.5 (0.9–2.7)	1.4 (0.9–2.1)	1.1 (0.7–1.6)	0.9 (0.6–1.4)	$\chi^2_1 = 1.9$ (0.171)	$\chi^2_3 = 3.1$ (0.373)	
Physical abuse	2.1* (1.4–3.3)	1.5* (1.0–2.2)	1.9* (1.3–2.8)	2.2* (1.5–3.2)	$\chi^2_1 = 0.0$ (0.959)	$\chi^2_3 = 3.7$ (0.300)	
Sexual abuse	8.5* (3.6–20.2)	1.8* (1.0–3.1)	1.1 (0.6–2.0)	2.8* (1.5–5.1)	$\chi^2_1 = 5.5$* (0.019)	$\chi^2_3 = 15.2$* (0.002)	
Neglect	1.4 (0.9–2.3)	0.9 (0.6–1.4)	1.2 (0.8–1.8	1.1 (0.7–1.7)	$\chi^2_1 = 0.6$ (0.423)	$\chi^2_3 = 2.5$ (0.472)	
Joint significance of all seven MFF CA indicators	$\chi^2_7 = 131.3$*	$\chi^2_7 = 41.2$*	$\chi^2_7 = 53.4$*	$\chi^2_7 = 65.8$*			
II. Other CAs							
Parental death	1.4 (0.8–2.4)	0.9 (0.6–1.3)	1.4 (0.9–2.0)	0.9 (0.6–1.3)	$\chi^2_1 = 2.4$ (0.122)	$\chi^2_3 = 5.7$ (0.129)	$\chi^2_{12} = 9.4$ (0.665)
Parental divorce	1.2 (0.7–2.3)	1.3 (0.9–1.9)	1.2 (0.8–1.8)	1.4 (0.9–2.0)	$\chi^2_1 = 0.0$ (0.855)	$\chi^2_3 = 0.0$ (0.998)	
Other parental loss	1.4 (0.8–2.6)	1.2 (0.7–1.8)	1.2 (0.7–1.9)	1.4 (0.9–2.2)	$\chi^2_1 = 0.1$ (0.717)	$\chi^2_3 = 1.0$ (0.792)	
Economic adversity	1.2 (0.6–2.3)	1.9* (1.2–3.2)	1.1 (0.5–2.3)	1.2 (0.7–2.1)	$\chi^2_1 = 0.2$ (0.651)	$\chi^2_3 = 2.6$ (0.455)	
Joint significance of all four Other CA indicators	$\chi^2_4 = 4.3$	$\chi^2_4 = 12.6$*	$\chi^2_4 = 3.2$	$\chi^2_4 = 6.6$			

OR, Odds ratio; CI, confidence interval; MFF, maladaptive family functioning.

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

[a] Model was estimated with dummy variables for all childhood adversities entered simultaneously as predictors of psychotic experiences onset controlling for country, person-years, age cohort and sex.

[b] Model is restricted to person-years between 4 and 12.

[c] Model is restricted to person-years between 13 and 19.

[d] Model is restricted to person-years between 20 and 29.

[e] Model is restricted to person-years > 29.

Table 4. *Multivariate associations between childhood adversities (CA) and the subsequent first onset of psychotic experiences*

	Base model from Table 2[a] (py = 9 75 199) OR (95% CI)	Base model and additionally control for mental disorders[b] (py = 9 75 199) OR (95% CI)	Base model but restricted to those with no mental disorder[c] (py = 5 95 792) OR (95% CI)
I. MFF CAs			
Parental mental illness	2.0* (1.6–2.3)	1.5* (1.3–1.8)	1.9* (1.2–3.1)
Parental substance disorder	0.9 (0.7–1.2)	0.9 (0.7–1.2)	1.5 (0.9–2.7)
Parental criminal behaviour	1.7* (1.3–2.3)	1.7* (1.2–2.3)	1.9 (1.0–3.7)
Family violence	1.2 (0.9–1.5)	1.0 (0.8–1.3)	1.0 (0.6–1.7)
Physical abuse	2.0* (1.6–2.4)	1.8* (1.4–2.1)	2.5* (1.7–3.8)
Sexual abuse	2.7* (1.7–4.2)	2.2* (1.4–3.5)	6.7* (2.5–18.0)
Neglect	1.1 (0.9–1.5)	1.1 (0.9–1.4)	1.2 (0.6–2.1)
Joint significance of all seven MFF CA indicators	$\chi^2_7 = 213.3$*	$\chi^2_7 = 97.6$*	$\chi^2_7 = 79.3$*
II. Other CAs			
Parental death	1.1 (0.9–1.3)	1.1 (0.9–1.3)	0.9 (0.6–1.3)
Parental divorce	1.3* (1.0–1.7)	1.3 (1.0–1.6)	0.9 (0.5–1.5)
Other parental loss	1.3 (1.0–1.6)	1.2 (1.0–1.6)	1.3 (0.8–2.1)
Economic adversity	1.4* (1.0–1.9)	1.3 (1.0–1.8)	1.6 (0.9–3.1)
Joint significance of all four Other CA indicators	$\chi^2_4 = 18.6$*	$\chi^2_4 = 13.5$*	$\chi^2_4 = 4.8$

py, Person-years; OR, odds ratio; CI, confidence interval; MFF, maladaptive family functioning.

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

[a] See note b in Table 2 for a description of model 1.

[b] Model specification is as above and additionally control for 21 DSM-IV mental disorders and exactly 2 and $\geqslant$3 DSM-IV mental disorders.

[c] Base model but restricted to those without prior history of mental disorder temporally prior to the onset of PEs.

In summary, the pattern of associations between CAs and subsequent PEs remained similar in models adjusted for mental disorders, apart from weakening of the association between MFF or Other CAs and PE onset in adolescence after accounting for temporally prior mental disorders.

PARPs between CAs and PEs

The overall PARP for PEs associated with CAs was 30.9% (Supplementary Table S5) with most of this proportion attributable to MFF CAs (24%). With regard to individual CAs, physical abuse had the highest PARP (8.2%), followed by parental mental illness (6.9%).

Post-hoc *analysis*

We conducted an additional analysis to assess the differential impact of three country-level strata on PEs risk using interaction terms between CAs and country strata. While the overall joint effect was significant ($\chi^2_{22} = 40.4$, $p = 0.001$), we found that the pairwise estimates for individual CAs on PEs were all non-significant except for 'economic adversity' (data not shown). This particular CA was rarely reported in low income countries, leading to unstable and imprecise estimates. Otherwise, this exposure was also associated with comparable estimates in middle and high income strata countries.

Discussion

Based on the largest study of PEs and CAs to date, we confirmed that CAs are associated with a more than two-fold increased odds of subsequent first onset of PEs, which is similar but slightly higher than the pooled estimate from a recent systematic review (Trotta *et al.* 2015). We also confirmed a dose-response relationship between higher numbers of CA types and odds of subsequent PEs, consistent with previous literature (Janssen *et al.* 2004; Wigman *et al.* 2011*b*; Kelleher *et al.* 2013; Muenzenmaier *et al.* 2015; van Dam *et al.* 2015). Additionally, we contributed four novel findings: first, that CAs involving MFF were more strongly related to PEs than Other CAs; second, that CAs involving MFF were associated with onset of PEs across all stages of the life-course; third, that temporally prior mental disorders appeared to explain the association of CAs with PE onset in adolescence, but not other life-course stages; and finally, that CAs involving MFF may account for nearly one-quarter

Table 5. *Multivariate associations between childhood adversities (CA) and the subsequent first onset of psychotic experiences in each of four life-course stages with adjustment for mental disorders*[a]

	Childhood, age 4–12[b] (py = 2 86 818) OR (95% CI)	Adolescence, age 13–19[c] (py = 1 64 230) OR (95% CI)	Young adulthood, age 20–29[d] (py = 1 98 248) OR (95% CI)	Later adulthood, age 30+[e] (py = 3 25 903) OR (95% CI)	Test for significance difference: (childhood *v.* other 3 life-course stages) χ^2 (*p* value)	Test for the significance of the slope differences across 4 life-course stages	
						χ^2 (*p* value)	χ^2 (*p*-value)
I. MFF CAs							
Parental mental illness	2.0* (1.4–2.8)	1.7* (1.1–2.7)	1.2 (0.9–1.6)	1.6* (1.0–2.4)	$\chi^2_1 = 0.7$ (0.415)	$\chi^2_3 = 3.3$ (0.345)	$\chi^2_{21} = 53.6$* (0.000)
Parental substance disorder	0.9 (0.5–1.5)	1.0 (0.6–1.7)	0.9 (0.6–1.5)	1.0 (0.5–2.0)	$\chi^2_1 = 0.0$ (0.847)	$\chi^2_3 = 0.1$ (0.990)	
Parental criminal behaviour	2.4* (1.3–4.5)	1.5 (0.8–2.7)	1.8 (0.9–3.3)	1.2 (0.7–1.9)	$\chi^2_1 = 2.8$ (0.095)	$\chi^2_3 = 2.8$ (0.417)	
Family violence	1.5 (0.9–2.7)	1.2 (0.8–1.8)	1.0 (0.6–1.5)	0.7 (0.5–1.1)	$\chi^2_1 = 3.4$ (0.064)	$\chi^2_3 = 5.4$ (0.146)	
Physical abuse	2.1* (1.3–3.3)	1.3 (0.9–1.9)	1.7* (1.2–2.5)	2.0* (1.3–2.9)	$\chi^2_1 = 0.1$ (0.830)	$\chi^2_3 = 4.0$ (0.260)	
Sexual abuse	9.3* (3.7–23.8)	1.5 (0.9–2.7)	0.9 (0.5–1.8)	2.1* (1.1–4.1)	$\chi^2_1 = 7.4$* (0.007)	$\chi^2_3 = 15.7$* (0.001)	
Neglect	1.4 (0.9–2.3)	0.9 (0.5–1.4)	1.1 (0.7–1.8)	1.0 (0.7–1.6)	$\chi^2_1 = 0.8$ (0.364)	$\chi^2_3 = 2.3$ (0.514)	
Joint significance of all 7 MFF CA indicators	$\chi^2_7 = 109.0$*	$\chi^2_7 = 13.0$	$\chi^2_7 = 19.7$*	$\chi^2_7 = 32.3$*			
II. Other CAs							
Parental death	1.4 (0.7–2.4)	0.9 (0.6–1.3)	1.3 (0.9–2.0)	0.8 (0.6–1.2)	$\chi^2_1 = 2.3$ (0.126)	$\chi^2_3 = 6.0$ (0.111)	$\chi^2_{12} = 10.0$ (0.612)
Parental divorce	1.2 (0.7–2.2)	1.3 (0.9–1.9)	1.2 (0.8–1.8)	1.3 (0.9–1.9)	$\chi^2_1 = 0.0$ (0.981)	$\chi^2_3 = 0.0$ (0.999)	
Other parental loss	1.4 (0.8–2.6)	1.1 (0.7–1.8)	1.2 (0.7–1.9)	1.3 (0.9–2.0)	$\chi^2_1 = 0.2$ (0.638)	$\chi^2_3 = 1.0$ (0.806)	
Economic adversity	1.3 (0.7–2.5)	1.7* (1.1–2.8)	1.0 (0.5–2.3)	1.1 (0.6–2.0)	$\chi^2_1 = 0.3$ (0.597)	$\chi^2_3 = 2.8$ (0.424)	
Joint significance of all 4 Other CA indicators	$\chi^2_4 = 4.4$	$\chi^2_4 = 9.3$	$\chi^2_4 = 2.7$	$\chi^2_4 = 4.8$			

py, Person-years; OR, odds ratio; CI, confidence interval; MFF, maladaptive family functioning.

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

[a] Model was estimated with dummy variables for all childhood adversities entered simultaneously as predictors of psychotic experiences onset controlling for country, person-years, age cohort, sex and 21 DSM-IV mental disorders.

[b] Model is restricted to person-years between 4 and 12.

[c] Model is restricted to person-years between 13 and 19.

[d] Model is restricted to person-years between 20 and 29.

[e] Model is restricted to person-years >29.

of all PE onsets in the population. We discuss each of these in turn.

First, we examined whether the association of CAs with PEs varied according to CA types. To date, prior research has neither included a wide range of CA types, nor used statistical models that acknowledged the inter-correlated nature of CAs. Although all CAs were associated with PEs when examined one-at-a-time, when examined together, only four CAs reflecting MFF (parental mental illness, parental criminal behaviour, physical abuse, and sexual abuse) and two Other CAs (parental divorce, economic adversity) remained associated with subsequent PEs.

Second, CAs involving MFF were associated with PE onsets in every stage of the life-course, whereas Other CAs were associated only with PEs in adolescence.

We have recently presented the age-of-onset curve for PEs – the median (interquartile range; IQR) was 26 (17–41) years, indicating that PEs commence across a surprisingly wide age range (McGrath *et al.* 2016*b*). Our findings suggest that Other CAs might increase the risk for PEs through mechanisms that have proximal consequences (Bentall *et al.* 2014; Morgan & Gayer-Anderson, 2016). In contrast, MFF CAs appear to create a generalized diathesis for PEs that persists across the life-course. This diathesis could involve a variety of emotional, neurobiological, and cognitive processes that are influenced by CAs, including heightened vulnerability to stress (McLaughlin *et al.* 2010*c*), elevated emotional reactivity and poor emotion regulation skills (McLaughlin *et al.* 2010*a*; 2015; McCrory *et al.* 2011; Heleniak *et al.* 2016), and deficits in cognitive control (DePrince *et al.* 2009). Each of these domains, in turn, has been proposed as mechanisms that may underlie PEs (Freeman *et al.* 2007; Bentall *et al.* 2009, 2014; Morgan & Gayer-Anderson, 2016). CAs related to MFF may differentially lead to social differentiation and social defeat (at the individual and/or family level), which has been linked to risk of PEs (Morgan & Gayer-Anderson, 2016). Identifying the precise mechanisms through which MFF CAs influence risk for PEs and determining why this vulnerability persists throughout the life-course are key areas for future research.

Third, associations between CAs and PEs were largely unchanged in childhood and adulthood after adjustment for mental disorders that began prior to the onset of PEs. In contrast, CAs were no longer associated with PE onset in adolescence after accounting for prior-onset mental disorders. We have previously identified an association between mental disorder and PEs (McGrath *et al.* 2016*a*). Our findings suggest that prior mental disorders might be particularly important as a pathway to PEs in adolescence among youths with exposure to CAs. It is possible that the vulnerability factors that predispose to adolescent-onset PEs also contribute to other early-onset mental disorders that emerge following exposure to CAs. With respect to vulnerability factors, we found that parental mental illness was associated with an increased odds of PEs. This finding, which could reflect shared genetic vulnerabilities and/or adverse environmental exposures (e.g. suboptimal parenting), is consistent with other studies that have reported an association between family history of mental disorder and lifetime prevalence of PEs (Kelleher & Cannon, 2011; Varghese *et al.* 2011; Jeppesen *et al.* 2015). Alternatively, CAs might increase risk for this early-life variant of PEs only among individuals who developed psychopathology following CA exposure as has been shown in other disorders such as PTSD (Breslau *et al.* 2008; Koenen *et al.* 2008).

Sexual abuse exhibited a particularly strong association with PEs that emerge during childhood (4–12 years), with an 8.5 fold increased odds of PE emergence among respondents who were sexually abused. Clinicians and researchers have long been aware of the association between childhood sexual abuse and clinical psychotic disorders (e.g. schizophrenia) (Read *et al.* 2005; Cutajar *et al.* 2010), and thus the link between this exposure and PEs has been of interest (Morgan & Gayer-Anderson, 2016). Many studies have previously reported links between sexual abuse and PEs (Read *et al.* 2003; Shevlin *et al.* 2007; Bentall *et al.* 2012; Murphy *et al.* 2014; van Dam *et al.* 2015; Cristobal-Narvaez *et al.* 2016). Identifying mechanisms that explain this association is important for targeting interventions to prevent the onset of PEs in children who have been sexually abused (e.g. psychotherapy aimed at reducing psychological vulnerabilities). Our findings suggest that intervening mental disorders do not play a meaningful role in this pathway.

Fourth, CAs were associated with a substantial proportion of PE onsets in the population, and the bulk of the population attributable risk involves MFF CAs. This suggests that – assuming the association of CAs with PEs is causal – nearly one-third of PEs could be prevented if exposure to CAs was eliminated or if interventions were developed that could mitigate the risk pathways linking CAs to PEs. Similarly high PARPs have been observed for other mental disorders associated with CAs (Green *et al.* 2010; Kessler *et al.* 2010; McLaughlin *et al.* 2012), underscoring the significance of CAs in shaping the distribution of psychopathology in the population.

The current study has several limitations which deserve comment. We excluded those who were screen-positive for possible psychotic disorders (based on self-report, use of antipsychotic medications to treat PEs). However, we did not have access to valid measures of clinical psychotic disorders in our sample, and thus it is feasible that a small proportion of

respondents with clinical psychosis were included in the analyses. We also relied on retrospective reports about age of onset, which might have led to a recall bias. For some CAs, we were not able to determine an age of onset, and used a default of age 4 which is the standard earliest age of onset for disorders and exposures within the WMH studies. However, we note that several prospective studies have confirmed the association between CAs and subsequent PEs (Arseneault *et al.* 2011; Fisher *et al.* 2013; Kelleher *et al.* 2013; Rossler *et al.* 2014; Wolke *et al.* 2014). While we were able to explore a much wider range of CAs than previous studies, we focused on family-related exposures and we lacked information on childhood bullying. In light of the growing body of evidence linking this particular type of CA with PEs, this would be an important exposure to include in future studies (Kelleher *et al.* 2008; van Dam *et al.* 2012; Fisher *et al.* 2013; Wolke *et al.* 2014). We did not adjust for multiple comparisons in this study which may lead to inflation of Type I errors. In the current analyses we have focused on PEs as a class only, however there is evidence to suggest that certain types of CAs (e.g. sexual abuse) may be linked to hallucinations more than delusions (Bentall *et al.* 2014). We plan to explore this research question in future studies.

Conclusions

Based on the largest single study to date, our cross-national study confirms the association between CAs and the subsequent onset of PEs. CAs related to MFF are associated with PEs that emerge across the life span, and intervening mental disorders do not account for this finding. Childhood sexual abuse was strongly associated with PEs that emerged during childhood. While we have more than enough evidence linking CAs with adverse mental and physical health outcomes (Scott *et al.* 2010), the robust literature now linking CAs and PEs can provide important clues to aetiopathogenesis of PEs and mental disorders (Heleniak *et al.* 2016). These, in turn, can inform clinically-targeted interventions designed to reduce the burden of mental disorders in those exposed to CAs (Bentall *et al.* 2014; Morgan & Gayer-Anderson, 2016).

Appendix. WMH Survey Collaborators

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Supplementary material

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