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Psychotic experiences and general medical conditions: a cross-national analysis based on 28,002 respondents from 16 countries in the WHO World Mental Health Surveys

Kate M. Scott[1], **Sukanta Saha**[2], **Carmen C.W. Lim**[2], **Sergio Aguilar-Gaxiola**[3], **Ali Al-Hamzawi**[4], **Jordi Alonso**[5], **Corina Benjet**[6], **Evelyn J. Bromet**[7], **Ronny Bruffaerts**[8], **José Miguel Caldas-de-Almeida**[9], **Giovanni de Girolamo**[10], **Peter de Jonge**[11], **Louisa Degenhardt**[12], **Silvia Florescu**[13], **Oye Gureje**[14], **Josep M. Haro**[15], **Chiyi Hu**[16], **Elie G. Karam**[17], **Viviane Kovess-Masfety**[18], **Sing Lee**[19], **Jean-Pierre Lepine**[20], **Zeina Mneimneh**[21], **Fernando Navarro-Mateu**[22], **Marina Piazza**[23], **José Posada-Villa**[24], **Nancy A. Sampson**[25], **Juan Carlos Stagnaro**[26], **Ronald C. Kessler**[25], and **John J. McGrath**[27,*] **on behalf of the WHO World Mental Health Survey Collaborators**[+]

[1]Department of Psychological Medicine, University of Otago, Dunedin, New Zealand [2]Queensland Centre for Mental Health Research and Queensland Brain Institute, The University of Queensland, St. Lucia, Queensland, Australia [3]Center for Reducing Health Disparities, UC Davis Health System, Sacramento, California, USA [4]College of Medicine, Al-Qadisiya University, Diwaniya governorate, Iraq [5]Health Services Research Unit, IMIM-Hospital del Mar Medical Research Institute, Barcelona, Spain; Pompeu Fabra University (UPF), Barcelona, Spain; and CIBER en Epidemiología y Salud Pública (CIBERESP), Barcelona, Spain [6]Department of Epidemiologic and Psychosocial Research, National Institute of Psychiatry Ramón de la Fuente, Mexico City, Mexico [7]Department of Psychiatry, Stony Brook University School of Medicine, Stony Brook, New York, USA [8]Universitair Psychiatrisch Centrum - Katholieke Universiteit Leuven (UPC-KUL), Campus Gasthuisberg, Leuven, Belgium [9]Lisbon Institute of Global Mental Health and Chronic Diseases Research Center (CEDOC), NOVA Medical School | Faculdade de Ciências Médicas, Universidade Nova de Lisboa, Lisbon, Portugal [10]Unit of Epidemiological and Evaluation Psychiatry, Istituti di Ricovero e Cura a Carattere Scientifico (IRCCS)-St. John of God Clinical Research Centre, Via Pilastroni 4, Brescia, Italy [11]Developmental Psychology, Department of Psychology, Rijksuniversiteit Groningen, Groningen, NL; Interdisciplinary Center Psychopathology and Emotion Regulation, Department of Psychiatry, University Medical Center Groningen, Groningen, NL [12]National Drug and Alcohol Research Centre, University of New South Wales, Sydney, Australia [13]National School of Public Health, Management and

Address for correspondence: Prof John McGrath j.mcgrath@uq.edu.au.
[+]WHO World Mental Health Survey Collaborators are listed in the Appendix

ROLE OF THE FUNDER/SPONSOR

The funders had no role in the design and 15 conduct of the study; collection, management, analysis, and interpretation of 16 the data; preparation, review, or approval of the manuscript; and decision to 17 submit the manuscript for publication.

CONFLICT OF INTEREST

Competing interests: In the past 3 years, Dr. Kessler received support for his epidemiological studies from Sanofi Aventis; was a consultant for Johnson & Johnson Wellness and Prevention, Shire, Takeda; and served on an advisory board for the Johnson & Johnson Services Inc. Lake Nona Life Project. Kessler is a co-owner of DataStat, Inc., a market research firm that carries out healthcare research.

Development, Bucharest, Romania [14]Department of Psychiatry, University College Hospital, Ibadan, Nigeria [15]Parc Sanitari Sant Joan de Déu, CIBERSAM, Universitat de Barcelona, Sant Boi de Llobregat, Barcelona, Spain [16]Shenzhen Institute of Mental Health & Shenzhen Kangning Hospital, Shenzhen, China [17]Department of Psychiatry and Clinical Psychology, Faculty of Medicine, Balamand University, Beirut, Lebanon; Department of Psychiatry and Clinical Psychology, St George Hospital University Medical Center, Beirut, Lebanon; Institute for Development Research Advocacy and Applied Care (IDRAAC), Beirut, Lebanon [18]Ecole des Hautes Etudes en Santé Publique (EHESP), EA 4057, Paris Descartes University, Paris, France [19]Department of Psychiatry, Chinese University of Hong Kong, Tai Po, Hong Kong [20]Hôpital Lariboisière- Fernand Widal, Assistance Publique Hôpitaux de Paris; Universités Paris Descartes-Paris Diderot; INSERM UMR-S 1144, Paris, France [21]Survey Research Center, Institute for Social Research, University of Michigan, Ann Arbor, Michigan, USA [22]UDIF-SM, Subdirección General de Planificación, Innovación y Cronicidad, Servicio Murciano de Salud. IMIB-Arrixaca. CIBERESP-Murcia, Murcia, Spain [23]Universidad Cayetano Heredia, Lima, Peru; National Institute of Health, Lima, Peru [24]Colegio Mayor de Cundinamarca University, Faculty of Social Sciences, Bogota, Colombia [25]Department of Health Care Policy, Harvard Medical School, Boston, Massachusetts, USA [26]Departamento de Psiquiatría y Salud Mental, Facultad de Medicina, Universidad de Buenos Aires, Argentina [27]Queensland Centre for Mental Health Research, and Queensland Brain Institute, University of Queensland, St. Lucia, Queensland, Australia; and National Centre for Register-based Research, Aarhus BSS, Aarhus University, Aarhus, Denmark

Abstract

Background—Previous work has identified associations between psychotic experiences (PEs) and general medical conditions (GMCs) but their temporal direction remains unclear as does the extent to which they are independent of comorbid mental disorders.

Methods—28,002 adults in 16 countries from the WHO World Mental Health Surveys were assessed for PEs, GMCs, and 21 DSM-IV mental disorders. Discrete-time survival analyses were used to estimate the associations between PEs and GMCs with various adjustments.

Results—After adjustment for comorbid mental disorders, temporally prior PEs were significantly associated with subsequent onset of 8/12 GMCs (arthritis, back or neck pain, frequent or severe headache, other chronic pain, heart disease, high blood pressure, diabetes, and peptic ulcer) with odds ratios ranging from 1.3 (95% CI=1.1–1.5) to 1.9 (95% CI=1.4–2.4). In contrast, only three GMCs (frequent or severe headache, other chronic pain, and asthma) were significantly associated with subsequent onset of PEs after adjustment for comorbid GMCs and mental disorders, with odds ratios ranging from 1.5 (95% CI = 1.2–1.9) to 1.7 (95% CI = 1.2–2.4).

Conclusions—PEs were associated with the subsequent onset of a wide range of general medical conditions, independent of comorbid mental disorders. There were also associations between some medical conditions (particularly those involving chronic pain) and subsequent PEs. Although these findings will need to be confirmed in prospective studies, clinicians should be aware that psychotic symptoms may be risk markers for a wide range of adverse health outcomes. Whether PEs are causal risk factors will require further research.

Keywords

Psychotic experiences; general medical conditions; physical disorders; mental disorders; asthma; arthritis; pain; headache; heart disease; diabetes

Introduction

There is now clear evidence demonstrating that psychotic experiences (PEs) in the absence of psychotic disorders are common in the general population (Linscott and van Os, 2013, McGrath *et al.*, 2015). Recent research showing that those with PEs are at increased risk of premature mortality (Sharifi *et al.*, 2015) heightens interest in the relationship between PEs and general medical conditions (GMCs). Although this is a relatively new topic of investigation, evidence is accruing that PEs are associated with a range of GMCs such as heart disease, diabetes, arthritis, asthma, dental problems, hearing loss, and chronic pain conditions (Saha *et al.*, 2011a, Moreno *et al.*, 2013, Koyanagi and Stickley, 2015a, Oh and DeVylder, 2015, Koyanagi *et al.*, 2016b, Stubbs *et al.*, 2016, Koyanagi *et al.*, 2017). Several studies have also found associations between PEs and sleep problems (Koyanagi and Stickley, 2015b, Thompson *et al.*, 2015, DeVylder and Kelleher, 2016, Oh *et al.*, 2016, Andorko *et al.*, 2017), and a recent randomized controlled trial found that treatment of insomnia reduced the prevalence of PEs (Freeman *et al.*, 2017).

Two questions arise in relation to these PE-GMC associations. The first question is whether they are independent of comorbid common mental disorders given that (i) PEs are associated with common mental disorders (DeVylder *et al.*, 2014, McGrath *et al.*, 2016b) and (ii) that common mental disorders are associated with GMCs (Lawrence *et al.*, 2013, Scott *et al.*, 2016). Only a very small number of studies have examined this question and the results are equivocal. In general, these studies find that associations between PEs and GMCs are attenuated after adjustment for comorbid mental disorders but that some associations do persist (Saha *et al.*, 2011a, Moreno *et al.*, 2013, Oh and DeVylder, 2015). In a study of PEs and pain conditions, however, the associations lost significance after adjustment for comorbid mental disorders (Koyanagi *et al.*, 2016b).

The second important question concerns the temporal direction of associations. Prior studies have not been able to consider the temporal sequencing of PEs and GMCs; that is, whether temporally prior PEs are associated with subsequent onset of GMCs, and/or whether GMCs are associated with subsequent first onset of PEs. Mindful that certain GMCs typically have an early onset (e.g. asthma) while many have later onset (e.g. heart disease, cancer), understanding the extent to which these PEs and GMCs associations follow a specific temporal sequence has important theoretical, clinical and public health significance. Ideally, this kind of investigation of temporal sequence should be undertaken in prospective studies. However, this would require very large cohorts with information on PEs, mental disorders and GMCs followed for decades (given the typically early onset of PEs and mental disorders, and later onset of most GMCs). To our knowledge, no such data are presently available. Therefore, in order to examine the temporal direction of PEs and GMCs, we have

used retrospectively collected data from the World Mental Health Surveys (Kessler and Üstün, 2004) on age-at onset of PEs, mental disorders and GMCs.

The specific aims of this study were to examine: (a) whether PEs are associated with subsequent onset/diagnosis of GMCs; (b) whether GMCs are associated with subsequent onset of PEs; c) whether these associations are independent of a wide range of antecedent mental disorders; and d) the role of severity of PEs (number of PE types, annualized frequency of PEs) in the association with GMCs.

Method

Samples

The WHO World Mental Health (WMH) surveys are a coordinated set of community surveys generally administered to adult respondents (18 years and over) in countries throughout the world (Kessler and Üstün, 2004). Data for this study were drawn from the 16 WMH surveys that included both the Psychosis Module and items related to GMCs (N=28,002). These 16 surveys are distributed across North and South America (Argentina, Colombia, Mexico, Peru, USA); the Middle East (Iraq); Asia (Shenzhen in the People's Republic of China); the South Pacific (New Zealand); and Europe (Belgium, France, Germany, Italy, the Netherlands, Portugal, Romania, Spain). The majority of these surveys were based on multi-stage, clustered area probability household sampling designs, the exceptions being Belgium, Germany and Italy, which used municipal resident registries to select respondents (Supplementary table S1). The weighted (by sample size) average response rate across the 16 surveys was 71.3%.

In order to focus on the correlates of PEs in those without psychotic disorders, we made the *a priori* decision to exclude individuals who had PEs but who also screened positive for possible schizophrenia/psychosis and manic-depression/mania. Thus, in keeping with previous studies of PEs (Saha *et al.*, 2011b, McGrath *et al.*, 2015, McGrath *et al.*, 2016a, McGrath *et al.*, 2016b), 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?"* (respondents with these disorders who did not report PEs were not excluded); and (b) those who ever took an antipsychotic medication for these symptoms. This resulted in the exclusion of 124 respondents (0.4%), leaving 28,002 respondents for this study.

Procedures

WMH interviews 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 organisations in each country. Standardised 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 and Üstün, 2008).

Interviews were administered face to face in two parts. Part 1, which assessed a core set of mental disorders was administered to all respondents. Part 2 of the interview which assessed additional mental disorders, questions about PEs, and GMCs, was administered to respondents who met lifetime criteria for any Part I disorder, and a random proportion of the remaining sample of those without any Part 1 disorders. Part 2 respondents 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. Details about sampling methods are available elsewhere (Kessler and Üstün, 2004). Additional weights were used to adjust for differential probabilities of selection within households, nonresponse, and to match the samples to population socio-demographic distributions in each country.

Measures

The WMH surveys administered the WHO Composite International Diagnostic Interview (CIDI)(Kessler and Üstün, 2008), a validated fully-structured diagnostic interview 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. Translation, back-translation, and harmonisation protocols were used to adapt the CIDI for use in each participating country.

General medical conditions (GMCs)—General medical conditions were assessed based on a series of questions adapted from the US National Health Interview Survey. Twelve conditions were assessed in this study. Respondents were asked if they had a lifetime history of symptom-based conditions (i.e., arthritis or rheumatism, chronic back or neck pain, frequent or severe headaches, any other chronic pain or stroke) and whether they were ever told by a doctor or other health professional that they had a series of medical conditions (e.g. heart disease, cancer, diabetes mellitus, hypertension, asthma, other chronic lung diseases or peptic ulcer). For all of these conditions reported, respondents were also asked how old they were when they were first diagnosed with the condition or first experienced the symptomatic condition. Prior research has demonstrated good concordance between self-reported illness and medical records (Baumeister *et al.*, 2010).

Psychotic experiences (PEs)—The CIDI Psychosis Module included questions about six PE types – two related to hallucinatory experiences and four related to delusional experiences. We excluded PEs experienced while dreaming, half-asleep or under the influence of alcohols or drugs (Supplementary tables S2a, S2b). In this paper, we present estimates of GMCs for “Any PEs” only (i.e. not individual types of PEs). In addition, we included two key PE variables: (a) number of PE types; and (b) an annualized frequency metric based on the frequency of PE episodes per year. We derived the latter by dividing the total number of PE episodes by the time since onset of the first PE (age at interview minus age-at onset plus 1 in order to avoid zero as a denominator). We used the median threshold to dichotomize this metric. Age-at-onset of respondents with PEs was also assessed.

Mental disorders—The WMH version of the CIDI assessed lifetime history of 21 mental disorders broadly classified into *mood disorders; anxiety disorders; behavior disorders;*

eating disorders and *substance use disorders* (see Supplementary table S2c). Full details are given in several WMH publications including two of our recent papers (McGrath *et al.*, 2016b, McGrath *et al.*, 2017). 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, standardised diagnostic hierarchy rules among the disorders assessed were applied where appropriate (McGrath *et al.*, 2016b).

Statistical Analysis

Descriptive statistics were used for the lifetime prevalence of PEs, GMCs, and GMCs among respondents with and without PEs. Respondents with GMCs that developed after PEs, and GMCs that developed before PEs were compared using weighted Rao-Scott Chi-Square test. Discrete-time survival models with person-year as the unit of analysis were used to investigate the temporal sequencing of associations between PEs and GMCs. When examining the predictive relationship between temporally prior PEs and the subsequent onset of GMCs, PEs that occurred in the same year as GMCs or following GMCs were excluded. Those without GMCs were censored at their age at interview. We used any PEs, number of PE types, and annualized frequency of PEs in base models as predictors of subsequent GMCs adjusting for; (a) age at interview, sex, person-year, and country; (b) in multivariate models we additionally adjusted for 21 antecedent mental disorders (i.e. disorders occurring antecedent or intervening between PEs and GMCs). Likewise, when examining the relationship between temporally prior GMCs and subsequent onset of PEs, we excluded GMCs that occurred in the same year as PEs onset or following PEs. Those without PEs were censored at their age at interview. To examine the associations between GMCs and subsequent onset of PEs, a series of base and multivariate models (M1 – M5) was developed. For the base models, we incorporated one GMC at a time to predict for subsequent PEs adjusting for age at interview, gender, person-year and country. For multivariate models, we incorporated: (a) all GMCs types simultaneously (Model M1), (b) number of GMCs without any information about type (Model M2), (c) type and number of GMCs (Model M3), and (d) type and number of GMCs with adjustments for antecedent mental disorders (Model M4) in predicting subsequent PE onset. Models M3 and M4 allow for non-additive relationships between type and number such that the effect of number of GMCs may vary across types. Finally, as there are associations between smoking and both (a) GMCs (Doll, 1998, Keto *et al.*, 2016) and (b) PEs (Koyanagi *et al.*, 2016a), we undertook post-hoc analyses where we adjusted for lifetime occurrence of tobacco use (yes/no) as an additional variable with all other adjustments.

As the WMH data are both clustered and weighted, the design based Taylor series linearization implemented in SUDAAN software (RTI International, 1999) was used to estimate the standard errors and evaluate the statistical significance of the coefficients. Survival coefficients and their standard errors were exponentiated to generate ORs and 95% confidence intervals. All significance tests were evaluated using 0.05-level two-sided tests.

Results

Characteristics of the sample

The age range of the combined cross-national sample was 18–99 (supplementary Table 1), with a weighted mean age of 41.9 years (SE=0.2) and median age of 38.2 years (IQR= 26.5–53.3). Females accounted for 51.6% of the sample (SE=0.4).

Prevalence of general medical conditions (GMCs)

The weighted prevalence of PEs in this sample was 5.0% (SE=0.2). The lifetime prevalence of GMCs ranged from 1.3% (SE = 0.1) for other chronic lung diseases to 24.3% (SE = 0.4) for back or neck pain (Table 1). When divided into those with or without PEs, the prevalence of GMCs was consistently higher for those with lifetime PEs compared to those without. Among the subset of respondents with both lifetime GMC and PEs, a large proportion of respondents experienced PEs prior to GMCs, consistent with the later age of onset of most of the GMCs examined in this study (Table 1; see also supplementary table S4).

Associations between PEs and subsequent onset of general medical conditions

We first examined the associations between PEs and subsequent onset of GMCs (Table 2). Temporally prior PEs were significantly associated with subsequent first onset of 8 of the 12 GMCs (i.e., arthritis, back or neck pain, other chronic pain, frequent or severe headache, heart disease, high blood pressure, diabetes, and peptic ulcer). The odds ratios (ORs) ranged from 1.4 (95% CI=1.2–1.7) for high blood pressure to 2.3 (95% CI=1.8–3.0) for other chronic pain. There was a significant dose-response relationship between number of PE types and all the eight GMCs indicating increasing odds of GMCs with increasing number of PE types (χ^2 ranged between 10.5 and 73.3). Those with more frequent annualized PEs (> 0.3 episodes per year) compared to those with ≤ 0.3 episodes per year had approximately two-fold increased odds of developing subsequent GMCs. After adjusting for antecedent mental disorders, the majority of the associations between PEs and these eight GMCs lessened in magnitude but remained statistically significant.

Associations between temporally prior general medical conditions and subsequent onset of PEs

Next, we examined the associations between temporally prior GMCs and the subsequent onset of PEs (Table 3). In the base model, 7 of the 12 GMCs (arthritis, back or neck pain, frequent or severe headache, other chronic pain, high blood pressure, asthma, and peptic ulcer) were significantly associated with increased odds of any PEs. The ORs ranged between 1.7 and 2.7 with the highest OR for other chronic pain (OR = 2.7, 95% CI = 2.1–3.5) followed by frequent or severe headache (OR = 2.1, 95% CI = 1.7–2.5). When we adjusted for comorbidity of other GMCs (M1), five of the GMCs (arthritis, back or neck pain, frequent or severe headache, other chronic pain, and asthma) remained statistically significant. Next, after fitting the model that included number as well as type of GMCs (M3), the significant associations of these conditions with PE onset persisted. Finally, when we adjusted for antecedent mental disorders (M4), only three of the five GMCs previously associated with PEs (frequent or severe headache, other chronic pain, and asthma) remained

statistically significant (OR = 1.5, 95% CI = 1.2–1.9; OR = 1.7, 95% CI = 1.2–2.4; OR = 1.6, 95% CI = 1.2–2.1 respectively).

When we repeated the main analyses using additional adjustment for smoking, there was no substantial change in the results except for other chronic lung diseases (as expected) in which the odds ratios attenuated substantially in both analyses (supplementary tables S3a & S3b). However, in the final adjusted models, the associations between PEs and other chronic lung diseases (whether PEs as the predictor for GMCs or vice versa) were not significant.

There was a significant dose-response relationship between the number of GMCs and subsequent first onset PEs, with ORs monotonically increasing with increasing number of GMCs ($\chi^2_4 = 117.9$, $P < .001$) indicating that multimorbidity of GMCs predicts first onset PEs (M2, Table 3). This model, however, assumes an additive relationship between the number of GMCs and onset of PEs. In the next models (M3 and M4) that take type of GMCs into account and remove the additive assumption about the effect of number of GMCs, the ORs for the association of GMCs with odds of subsequent PEs became progressively smaller with each additional GMC. These sub-additive interactions need to be interpreted with caution however as number-of-general medical conditions as a set fell short of significance.

Discussion

In this large, population-based dataset from 16 countries we found that temporally prior PEs were significantly associated with subsequent first onset of 8 of the 12 GMCs studied (i.e., arthritis, back or neck pain, other chronic pain, frequent or severe headache, heart disease, high blood pressure, diabetes, and peptic ulcer). PEs were not significantly associated with subsequent onset of asthma, cancer, other chronic lung disease or stroke. After adjustment for mental disorders antecedent to the GMCs, all previously significant associations remained significant, although all were somewhat attenuated which suggests that a portion of these PE-GMC associations are explained by comorbid mental disorders. These results extend findings from prior studies (Saha *et al.*, 2011a, Moreno *et al.*, 2013, Oh and DeVylder, 2015) by providing description of associations between PEs and a range of GMCs in the general population independent of comorbid mental disorders. In addition, our temporally ordered survival analyses based on a large cross-national sample provide new insights into the temporal direction of associations between PEs and GMCs. For while we found that prior onset PEs were predictive of 8 of the 12 GMCs, conversely, we also found that 3 of the 12 GMCs (i.e., frequent or severe headache, other chronic pain, and asthma) were significantly associated with subsequent first onset of PEs.

We were also able to undertake examination of how associations between PEs and GMCs varied by PE severity, as indicated by number of PE types and frequency of annualized PEs. For the associations of PEs with subsequent GMCs, we observed a dose-response pattern for many (although not all) of the associations whereby those with a higher number of PEs types and higher frequency of annualized PEs were more likely to develop subsequent GMCs. For many associations though, especially for those of PEs with subsequent pain conditions (with the exception of headache), this pattern was no longer evident after adjustment for mental

disorders, suggesting that some of the increased risk of GMCs associated with a higher burden of prior PEs may be mediated by comorbid mental disorders. In considering the reverse direction of associations of GMCs with subsequent PEs, we similarly observed a dose response pattern whereby a higher count of temporally prior GMCs was associated with higher odds of subsequent first onset of PEs, although the added risk became smaller with each additional GMC. While it is widely accepted that people with psychotic disorders are more likely to develop a range of chronic GMCs (Stubbs *et al.*, 2016) and have reduced life expectancy (Laursen *et al.*, 2014, Hjorthoj *et al.*, 2017), our findings suggest that those with PEs, even in the absence of known psychotic disorders, also warrant close scrutiny in relation to physical health.

The observational nature of this study precludes any firm conclusions about whether these associations reflect causal mechanisms. That said, there are plausible mechanisms that could be involved. The fact that the strongest temporal sequence observed in this study was from prior PEs to subsequent onset of GMCs is consistent with the now substantial evidence for associations between antecedent common mental disorders and subsequent onset of GMCs (Thurston *et al.*, 2013, Whooley and Wong, 2013, Scott, 2014, Scott *et al.*, 2016). This raises the possibility that some of the same mechanisms that mediate the relationship between the common mental disorders and GMCs may be contributing to the associations between PEs and GMCs, and one such mechanism may be deleterious health behaviours associated with PEs such as smoking (Moreno *et al.*, 2013). However, when we repeated the main analysis controlling for smoking, there was no substantial change in the results indicating that the association between PEs and GMCs was not affected substantially by smoking history. It may also be relevant that PEs have a well-established relationship with sleep disturbance (Koyanagi and Stickley, 2015b, Thompson *et al.*, 2015, DeVylder and Kelleher, 2016, Oh *et al.*, 2016, Andorko *et al.*, 2017); poor sleep could therefore be part of a nexus of adverse health behaviours associated with PEs that mediates associations with poor health outcomes, but this requires further study before any conclusions can be drawn. To the extent that PEs serve as a marker of general psychological distress (Yung *et al.*, 2006, Saha *et al.*, 2011c), it is also theoretically conceivable that PEs could be associated with subsequent GMCs via chronic elevation or dysregulation of the physiological stress response pathways given that considerable evidence has accrued for these biological mechanisms in the associations of depression and anxiety with subsequent cardio-metabolic conditions (Davies *et al.*, 2010, Stetler and Miller, 2011). However, this suggestion remains speculative in the absence of any known evidence for such biological perturbations in people with PEs; this is an important area for future research. In addition to these potential causal explanations, it should also be noted that there are also several potential shared determinants of PEs and GMCs such as genetics, low birth weight and adverse early circumstances, and indeed, sleep disturbances. On the basis of this study, therefore, we can say that PEs appear to be risk markers for a range of subsequent poor health outcomes, but determining whether they are causal risk factors will require more definitive study designs that can control for a range of potential confounds.

After adjustment for comorbid mental disorders, the only GMCs that were associated with subsequent onset of PEs were asthma and two of the pain-related conditions (frequent/severe headaches and other chronic pain). This suggests the possibility that inflammatory

mechanisms related to GMCs could contribute to the subsequent emergence of PEs. For example, a birth cohort study reported an association between childhood asthma and/or eczema and the onset of PEs by age 13 years (Khandaker *et al.*, 2014). The fact that frequent/severe headaches and other chronic pain conditions were significantly associated with PEs in both temporal directions is interesting in light of the robust evidence from prior studies of the relationship between PEs and pain conditions (Koyanagi and Stickley, 2015a, 2016b). Of note is that while one of those prior studies (2016b) found that the significant association between PEs and pain was fully accounted for by depression and anxiety disorders, the present study found these associations between PEs and pain conditions (in both temporal directions) to persist despite comprehensive adjustment for 21 comorbid mental disorders. The well-established connections between chronic pain and sleep disturbance (Smith and Haythornthwaite, 2004), taken together with the several reports cited above of sleep disturbance in association with PEs, suggest that the present study's findings may reflect complex reciprocal relationships between chronic pain, sleep disturbance and psychological distress, particularly in the context of multimorbidity. It should also be noted that people with sleep disturbance may take hypnotic medications, which may influence the association between sleep disturbance and PEs – this topic warrants additional research.

While the current study has many strengths (e.g., range of PE types, large sample size, range of countries, uniform methodology for data collection), the methodological limitations are also considerable. Perhaps chief amongst these is the fact that the analyses were dependent on retrospective recall of the occurrence of mental disorders and PEs. Lifetime recall of mental disorders is unreliable and recall of the onset timing of mental disorders is known to be subject to bias (Simon and Von Korff, 1995, Moffitt *et al.*, 2010). Although the probing strategy employed in the WMH surveys has been shown to reduce this bias to some extent (Knäuper *et al.*, 1999), it is likely that some inaccuracy in onset timing remains and that mild disorders in particular will be under-recalled (Wells and Horwood, 2004). Recall of AOO of the GMCs is generally more reliable (Pattaro *et al.*, 2007), but the assessment of GMCs in this study was less rigorous than the assessment of mental health problems and self-report of physician-assigned diagnoses will miss some conditions that are asymptomatic in early stages. These limitations will undoubtedly have resulted in some individuals with a true history of PE, mental disorder and/or general medical condition being misclassified as non-cases. It is important to note though that this kind of misclassification tends to bias associations towards the null, making the results conservative. Survival bias may also contribute to the conservative nature of these findings. We excluded those who screened positive for possible psychotic disorders but it is possible that some respondents who reported PEs had an untreated psychotic disorder. Finally, it should be noted that many of the GMCs examined in this study are chronic conditions of aging (e.g., heart disease, arthritis, cancer, stroke). While the median age of onset for PEs is 26 years (McGrath *et al.*, 2016c), later-onset PEs have also been noted. It is feasible that the mechanisms underlying later-onset PEs may be influenced by the neurobiological correlates of these GMCs.

In summary, in this large community-based cross-sectional study, we found that individuals with prior onset of PEs were more likely to self-report subsequent development or diagnosis of a wide range of general medical conditions (i.e., arthritis, back or neck pain, other chronic pain, frequent or severe headache, heart disease, high blood pressure, diabetes, and peptic

ulcer) independent of comorbid mental disorders. A higher burden of PEs was associated with higher odds of subsequent GMC onset. In addition, 3 of the 12 GMCs studied (i.e., other chronic pain, frequent or severe headache, asthma) were significantly associated with subsequent onset of PEs. Although the temporal directions of the associations observed here will need to be confirmed in prospective designs, this study contributes substantial evidence in support of the proposition that PEs are associated with GMCs even after controlling for mental disorder comorbidity. It remains to be determined whether these associations are causal, but there are several plausible causal mechanisms. Behavioural and biological mechanisms that could mediate these associations between PEs and physical morbidity are an important area for future research. Clinicians should be aware that psychotic symptoms, independent of comorbid psychotic or other mental disorder, may be risk markers for a range of adverse health outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Prevalence of general medical conditions (GMC) among respondents with and without lifetime psychotic experiences (PEs) (n = 28,002)

General medical conditions	Total Sample			Respondents without lifetime PEs			Respondents with lifetime PEs			Respondents endorsing both lifetime GMC and PE										
										PEs prior to GMC onset			GMC in the same year as PEs onset			GMC prior to PEs onset			Goodness-of-fit test for equal proportion[a]	
	n	%[b]	SE	n	%[b]	SE	n	%[b]	SE	n	%[b]	SE	n	%[b]	SE	n	%[b]	SE	χ^2_1	p-value
Arthritis	5640	18·1	0·4	5132	17·7	0·4	508	26·1	1·4	308	61·0	3·6	22	4·2	1·3	178	34·9	3·4	22·5*	<·0001
Back or neck pain	7839	24·3	0·4	7043	23·6	0·4	796	38·3	1·7	439	55·7	2·9	32	4·1	1·1	325	40·2	2·7	14·8*	0·0001
Frequent or severe headaches	6701	19·3	0·4	5958	18·5	0·4	743	34·1	1·5	324	43·9	2·6	55	7·0	1·3	364	49·1	2·7	2·1	0·1475
Other chronic pain	2527	7·1	0·2	2152	6·6	0·2	375	17·0	1·3	213	57·8	4·0	12	4·0	1·4	150	38·2	3·9	11·1*	0·0008
Heart disease	1949	6·3	0·2	1791	6·2	0·2	158	9·1	1·1	103	72·6	5·4	7	5·9	2·2	48	21·5	5·2	32·0*	<·0001
High blood pressure	4808	15·4	0·3	4372	15·1	0·3	436	21·2	1·4	306	69·3	3·2	21	4·2	1·1	109	26·6	3·1	201·8*	<·0001
Asthma	2397	7·8	0·2	2103	7·5	0·2	294	15·0	1·3	105	31·3	3·9	15	4·6	1·6	174	64·2	4·1	68·8*	<·0001
Diabetes	1463	4·6	0·2	1331	4·5	0·2	132	6·1	0·8	97	80·8	4·3	4	2·4	1·6	31	16·8	4·0	_[c]	_[c]
Peptic ulcer	1826	5·5	0·2	1622	5·3	0·2	204	9·5	0·9	123	62·6	4·9	8	2·1	0·8	73	35·3	4·8	60·2*	<·0001
Cancer	868	2·9	0·1	759	2·8	0·1	109	4·5	0·5	75	68·2	5·9	4	3·0	1·8	30	28·8	5·8	91·6*	<·0001
Other chronic lung diseases	435	1·3	0·1	387	1·3	0·1	48	2·0	0·6	32	73·8	9·6	2	3·6	2·8	14	22·6	9·0	13·4*	0·0003
Stroke	467	2·0	0·1	415	1·9	0·1	52	2·5	0·5	39	77·1	7·6	4	6·9	4·4	9	16·0	6·4	110·5*	<·0001

SE, standard error

*Significant at the ·05 level, 2-sided test.

[a]Chi square tests comparing the proportion of respondents with PE onset prior to GMC onset versus the proportion of respondents with GMC onset prior to PE onset.

[b]Estimates are based on weighted data.

[c]Unstable estimates due to small design effect.

Table 2

Associations between temporally prior psychotic experiences (PEs) and the subsequent onset of general medical conditions (GMCs)

Type of GMCs	Any PE		Number of PE types								PE Frequency metric	
			Exactly 1 PE type		Exactly 2 PE types		3 or more PE types		Joint significance of the 3 number-of-PE type measures		> 0·3 episodes/year	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	χ^2_3	[p-value]	OR	(95% CI)
I. No adjustment for antecedent mental disorders[a]												
Arthritis	1·8*	(1·5–2·1)	1·6*	(1·3–2·0)	2·2*	(1·5–3·1)	2·3*	(1·4–3·8)	$\chi^2_3 = 55·3$*	P <·001	1·8*	(1·3–2·4)
Back or neck pain	1·8*	(1·5–2·1)	1·7*	(1·4–2·0)	2·0*	(1·4–2·9)	2·3*	(1·5–3·7)	$\chi^2_3 = 55·7$*	P <·001	2·0*	(1·6–2·5)
Frequent or severe headaches	1·7*	(1·5–2·0)	1·6*	(1·3–2·0)	1·7*	(1·2–2·5)	3·2*	(2·1–4·8)	$\chi^2_3 = 73·3$*	P <·001	2·3*	(1·8–3·0)
Other chronic pain	2·3*	(1·8–3·0)	2·2*	(1·7–2·8)	3·1*	(1·8–5·2)	2·2*	(1·2–3·9)	$\chi^2_3 = 49·1$*	P <·001	2·3*	(1·7–3·1)
Heart disease	1·9*	(1·4–2·5)	1·7*	(1·2–2·4)	2·3*	(1·4–3·6)	3·2*	(1·1–9·6)	$\chi^2_3 = 25·5$*	P <·001	2·2*	(1·4–3·5)
High blood pressure	1·4*	(1·2–1·7)	1·3*	(1·0–1·6)	1·8*	(1·1–2·9)	1·9	(1·0–3·8)	$\chi^2_3 = 14·5$*	P = 0·002	1·6*	(1·2–2·1)
Asthma	1·3	(1·0–1·7)	1·2	(0·9–1·7)	1·7*	(1·0–2·8)	1·2	(0·5–2·5)	$\chi^2_3 = 5·3$	P = 0·150	1·8*	(1·2–2·8)
Diabetes	1·7*	(1·2–2·3)	1·9*	(1·3–2·7)	1·1	(0·6–2·2)	0·9	(0·4–2·5)	$\chi^2_3 = 12·8$*	P = 0·005	2·3*	(1·4–3·8)
Peptic ulcer	1·9*	(1·5–2·5)	1·8*	(1·3–2·5)	1·5	(0·9–2·6)	6·2*	(2·8–13·6)	$\chi^2_3 = 33·4$*	P <·001	2·1*	(1·3–3·2)
Cancer	1·2	(0·8–1·6)	1·1	(0·8–1·6)	1·1	(0·5–2·5)	1·8	(0·7–4·6)	$\chi^2_3 = 2·4$	P = 0·499	1·4	(0·9–2·3)
Other chronic lung diseases	1·8	(0·8–3·7)	1·0	(0·5–1·8)	4·7*	(1·4–15·7)	3·2*	(1·2–8·8)	$\chi^2_3 = 10·5$*	P = 0·015	1·4	(0·6–3·2)
Stroke	1·4	(0·9–2·3)	1·4	(0·8–2·4)	2·0	(0·7–5·6)	_[c]	_[c]	_[c]	_[c]	1·8	(0·7–4·4)
II. Adjusted for antecedent mental disorders[b]												
Arthritis	1·5*	(1·3–1·8)	1·5*	(1·2–1·8)	1·8*	(1·4–2·4)	1·6	(0·9–3·0)	$\chi^2_3 = 36·8$*	P <·001	1·5*	(1·1–2·0)
Back or neck pain	1·5*	(1·3–1·8)	1·5*	(1·3–1·8)	1·7*	(1·3–2·3)	1·5	(0·9–2·5)	$\chi^2_3 = 32·6$*	P <·001	1·7*	(1·3–2·1)
Frequent or severe headaches	1·5*	(1·3–1·7)	1·4*	(1·2–1·8)	1·4*	(1·0–1·9)	2·0*	(1·3–3·1)	$\chi^2_3 = 28·9$*	P <·001	1·8*	(1·4–2·4)
Other chronic pain	1·9*	(1·4–2·4)	1·8*	(1·4–2·4)	2·3*	(1·3–3·9)	1·1	(0·5–2·2)	$\chi^2_3 = 25·8$*	P <·001	1·8*	(1·3–2·4)
Heart disease	1·7*	(1·3–2·3)	1·6*	(1·1–2·2)	1·9*	(1·1–3·2)	2·7	(0·9–7·9)	$\chi^2_3 = 14·1$*	P = 0·003	2·0*	(1·2–3·1)
High blood pressure	1·3*	(1·1–1·5)	1·2	(1·0–1·4)	1·5	(1·0–2·4)	1·5	(0·8–2·9)	$\chi^2_3 = 7·5$	P = 0·058	1·4*	(1·1–1·8)

Type of GMCs	Any PE		Number of PE types								PE Frequency metric	
			Exactly 1 PE type		Exactly 2 PE types		3 or more PE types		Joint significance of the 3 number-of-PE type measures		> 0·3 episodes/year	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	χ^2_3	[p-value]	OR	(95% CI)
Asthma	1·2	(0·9–1·6)	1·1	(0·8–1·6)	1·5	(0·9–2·4)	0·9	(0·4–2·1)	$\chi^2_3 = 3·0$	P = 0·395	1·6*	(1·1–2·5)
Diabetes	1·6*	(1·1–2·2)	1·8*	(1·2–2·6)	1·0	(0·5–2·0)	0·8	(0·3–2·1)	$\chi^2_3 = 10·4$*	P = 0·015	2·1*	(1·2–3·5)
Peptic ulcer	1·6*	(1·2–2·1)	1·5*	(1·1–2·1)	1·2	(0·7–2·0)	4·1*	(1·7–9·9)	$\chi^2_3 = 14·4$*	P = 0·002	1·7*	(1·1–2·7)
Cancer	1·1	(0·8–1·5)	1·1	(0·7–1·5)	1·0	(0·5–2·2)	1·4	(0·6–3·7)	$\chi^2_3 = 0·6$	P = 0·887	1·3	(0·8–2·1)
Other chronic lung diseases	1·4	(0·6–3·1)	0·8	(0·5–1·5)	3·3	(0·8–14·0)	2·2	(0·8–5·9)	$\chi^2_3 = 5·0$	P = 0·174	1·1	(0·5–2·3)
Stroke	1·2	(0·7–2·0)	1·2	(0·7–2·1)	1·7	(0·6–4·7)	_[c]	_[c]	_[c]	_[c]	1·6	(0·6–4·2)

OR, odds ratio; CI, Confidence interval

*Significant at the ·05 level, 2-sided test.

[a]PE (any PE, number of PE types, and PE frequency metric) was used as a predictor of general medical condition outcomes in separate discrete-time survival models. These models control for age at interview, sex, person-year, and country.

[b]These models additionally control for 21 antecedent mental disorders. See supplementary table S2c for the list of mental disorders.

[c]Unstable estimates due to small cell counts.

Table 3

Associations between temporally prior general medical conditions (GMCs) and the subsequent onset of psychotic experiences (PEs)

	Base model[a]		Multivariate model (M1)[b]		Multivariate model (M2)[c]		Multivariate model (M3)[d]		Multivariate model (M4)[e]	
	OR	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**
I. Type of GMCs										
Arthritis	1·9*	(1·5–2·5)	1·4*	(1·1–1·9)	-	-	1·4*	(1·0–2·0)	1·4	(1·0–2·0)
Back or neck pain	1·9*	(1·5–2·4)	1·4*	(1·1–1·8)	-	-	1·4*	(1·0–1·9)	1·3	(1·0–1·8)
Frequent or severe headaches	2·1*	(1·7–2·5)	1·7*	(1·4–2·1)	-	-	1·7*	(1·4–2·2)	1·5*	(1·2–1·9)
Other chronic pain	2·7*	(2·1–3·5)	2·0*	(1·5–2·6)	-	-	2·0*	(1·4–2·8)	1·7*	(1·2–2·4)
Heart disease	1·5	(0·9–2·4)	1·0	(0·6–1·7)	-	-	1·1	(0·6–1·8)	1·0	(0·6–1·7)
High blood pressure	1·7*	(1·2–2·3)	1·3	(0·9–1·8)	-	-	1·4	(0·9–1·9)	1·3	(0·9–1·8)
Asthma	1·8*	(1·4–2·4)	1·7*	(1·3–2·2)	-	-	1·7*	(1·2–2·3)	1·6*	(1·2–2·1)
Diabetes	1·1	(0·7–1·9)	0·9	(0·5–1·5)	-	-	0·9	(0·5–1·5)	0·9	(0·5–1·5)
Peptic ulcer	1·7*	(1·2–2·5)	1·3	(0·9–1·9)	-	-	1·3	(0·9–2·0)	1·2	(0·8–1·8)
Cancer	1·6	(0·9–2·7)	1·3	(0·7–2·1)	-	-	1·3	(0·8–2·3)	1·2	(0·7–2·1)
Other chronic lung diseases	0·9	(0·4–2·0)	0·6	(0·3–1·3)	-	-	0·6	(0·3–1·3)	0·6	(0·3–1·2)
Stroke	1·2	(0·5–2·7)	0·8	(0·4–1·8)	-	-	0·9	(0·4–1·8)	0·9	(0·4–1·9)
Joint significance of all GMCs, χ^2_{12} [p - value]	N/A		$\chi^2_{12} = 175{\cdot}0^*$, p < ·001		N/A		$\chi^2_{12} = 41{\cdot}4^*$, p < ·001		$\chi^2_{12} = 26{\cdot}7^*$, p = 0·009	
Difference between GMCs, χ^2_{11} [p - value]	N/A		$\chi^2_{11} = 27{\cdot}0^*$, p = 0·005		N/A		$\chi^2_{11} = 23{\cdot}9^*$, p = 0·013		$\chi^2_{11} = 17{\cdot}4$, p = 0·097	
II. Number of GMCs										
Exactly 1 GMC	-	-	-	-	1·6*	(1·3–2·0)	-	-	-	-
Exactly 2 GMCs	-	-	-	-	3·0*	(2·3–3·9)	1·3	(0·9–1·9)	1·3	(0·9–1·9)
Exactly 3 GMCs	-	-	-	-	3·2*	(2·3–4·5)	0·9	(0·5–1·7)	0·9	(0·5–1·6)
4 or more GMCs	-	-	-	-	4·4*	(3·2–6·1)	0·8	(0·3–1·9)	0·8	(0·3–1·8)
Joint significance of number-of-GMCs, χ^2_4 [p - value]	N/A		N/A		$\chi^2_4 = 117{\cdot}9^*$, p < ·001		$\chi^2_4 = 6{\cdot}4$, p = 0·094		$\chi^2_4 = 6{\cdot}5$, p = 0·089	

OR, odds ratio; CI, Confidence interval

*Significant at the ·05 level, 2-sided test.

[a]Each model was estimated with one GMC entered at a time as predictor of PE onset controlling for age at interview, sex, person-year, and country.

[b]M1: Model was estimated with dummy variables for all GMC entered simultaneously as predictors of PE onset including the controls specified in (a).

[c]M2: Model was estimated with dummy variables for all number of GMC without any information about type entered simultaneously as predictors of PE onset including the controls specified in (a).

[d]M3: Model was estimated with dummy variables for type and number of GMC (exactly 2 GMCs,.., 4 or more GMCs) entered simultaneously as predictors of PE onset including the controls specified in (a).

[e]M4: Model was estimated with dummy variables for type and number of GMC (exactly 2 GMCs,.., 4 or more GMCs) entered simultaneously as predictors of PE onset including the controls specified in (a) and 21 antecedent mental disorders.