HHS Public Access

Author manuscript

J Psychiatr Res. Author manuscript; available in PMC 2016 November 23.

Published in final edited form as:

J Psychiatr Res. 2014 December ; 59: 179–188. doi:10.1016/j.jpsychires.2014.09.007.

Association between mental disorders and subsequent adult onset asthma

Jordi Alonso[1,2,3], **Peter de Jonge**[4], **Carmen C. W. Lim**[5], **Sergio Aguilar-Gaxiola**[6], **Ronny Bruffaerts**[7], **Jose Miguel Caldas-de-Almeida**[8], **Zhaorui Liu**[9], **Siobhan O'Neill**[10], **Dan J. Stein**[11], **Maria Carmen Viana**[12], **Ali Obaid Al-Hamzawi**[13], **Matthias C. Angermeyer**[14], **Guilherme Borges**[15], **Marius Ciutan**[16], **Giovanni de Girolamo**[17], **Fabian Fiestas**[18], **Josep Maria Haro**[19,20,21], **Chiyi Hu**[22], **Ronald C. Kessler**[23], **Jean Pierre Lépine**[24], **Daphna Levinson**[25], **Yosikazu Nakamura**[26], **Jose Posada-Villa**[27], **Bogdan J Wojtyniak**[28], and **Kate M. Scott**[29]

[1]Health Services Research Unit, IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain [2]CIBER Epidemiología y Salud Pública (CIBERESP), Spain [3]Pompeu Fabra University (UPF), Barcelona, Spain [4]Interdisciplinary Center Psychopathology and Emotion Regulation, University Medical Center, University of Groningen, Groningen, The Netherlands [5]Department of Psychological Medicine, Otago University, Dunedin, New Zealand [6]University of California, Davis, Center for Reducing Health Disparities, School of Medicine, Sacramento, California, USA [7]Universitair Psychiatrisch Centrum - Katholieke Universiteit Leuven (UPC-KUL), Leuven, Belgium [8]Chronic Diseases Research Center (CEDOC) and Department of Mental Health, Faculdade de Ciencias Medicas, Universidade Nova de Lisboa, Lisbon, Portugal [9]Institute of Mental Health, Peking University, Beijing, and People's Republic of China [10]Bamford Centre for Mental Health and Well-Being, University of Ulster, Derry, Northern Ireland [11]University of Cape Town Department of Psychiatry & Mental Health, Groote Schuur Hospital, Cape Town, South Africa [12]Department of Social Medicine, Federal University of Espírito Santo (UFES), Vitória, Brazil [13]Al-Qadisia University College of Medicine, Diwania, Iraq [14]Center for Public Mental Health, Gosing am Wagram, Austria [15]Division of Epidemiological and Psychosocial Research, National Institute of Psychiatry (Mexico) & Metropolitan Autonomous University, Mexico City, Mexico [16]National School of Public Health and Professional Development, Bucharest, Romania [17]IRCCS Centro S. Giovanni di Dio Fatebenefratelli, Brescia, Italy [18]Evidence Generation for Public Health Research Unit, National Institute of Health, Lima, Peru [19]Parc Sanitari Sant Joan de Déu, Sant Boi de Llobregat, Barcelona, Spain [20]CIBER de Salud Mental (CIBERSAM), Spain [21]University of Barcelona, Barcelona, Spain [22]Shenzhen Institute of Mental Health and Shenzhen Kangning Hospital, Guangdong Province, PR China [23]Department of Health Care Policy, Harvard Medical School, Boston, MA, USA [24]Hôpital Saint-Louis Lariboisière Fernand Widal, INSERM U 705, CNRS UMR 8206, Paris, France [25]Mental Health Services, Ministry of Health, Jerusalem, Israel [26]Department of Public Health, Jichi Medical University, Yakushiji, Shimotsuke-shi, Tochigi-ken, Japan [27]Colegio Mayor de Cundinamarca University, CALLE 28 No. 5B-02, Bogota, DC, Colombia [28]National Institute of Public Health-National Institute of Hygiene and Department-

Corresponding author: Jordi Alonso, jalonso@imim.es, Health Services Research Unit, IMIM (Hospital del Mar Research Institute), C. Dr. Aiguader, 88, PRBB building, 08003 BARCELONA, Spain. Phone: (+34) 933 160 760, Fax: (+34) 933 160 797.

Centre of Monitoring and Analyses of Population Health, Warsaw, Poland [29]Department of Psychological Medicine, Otago University, Dunedin, New Zealand

Abstract

Background and objectives—Associations between asthma and anxiety and mood disorders are well established, but little is known about their temporal sequence. We examined associations between a wide range of DSM-IV mental disorders with adult onset of asthma and whether observed associations remain after mental comorbidity adjustments.

Methods—During face-to-face household surveys in community-dwelling adults (n = 52,095) of 19 countries, the WHO Composite International Diagnostic Interview retrospectively assessed lifetime prevalence and age at onset of 16 DSM-IV mental disorders. Asthma was assessed by self-report of physician's diagnosis together with age of onset. Survival analyses estimated associations between first onset of mental disorders and subsequent adult onset asthma, without and with comorbidity adjustment.

Results—1,860 adult onset (21 years+) asthma cases were identified, representing a total of 2,096,486 person-years of follow up. After adjustment for comorbid mental disorders several mental disorders were associated with subsequent adult asthma onset: bipolar (OR=1.8; 95%CI 1.3–2.4), panic (OR=1.4; 95%CI 1.0–2.0), generalized anxiety (OR=1.3; 95%CI 1.1–1.7), specific phobia (OR=1.4; 95%CI 1.2–1.6); post-traumatic stress (OR=1.5; 95%CI 1.1–2.0); binge eating (OR=1.9; 95%CI 1.2–2.9) and alcohol abuse (OR=1.5; 95%CI 1.2–2.0). Mental comorbidity linearly increased the association with adult asthma. The association with subsequent asthma was stronger for mental disorders with an early onset (before age 21).

Conclusions—A wide range of temporally prior mental disorders are significantly associated with subsequent onset of asthma in adulthood. The extent to which asthma can be avoided or improved among those with early mental disorders deserves study.

Keywords

Asthma; Mental Disorders; Population; Epidemiology; Chronic Disease; Comorbidity

INTRODUCTION

Asthma is a major public health problem because a lifetime course and an increasing prevalence (Jenkins *et al.* 1994; Pearce *et al.* 2000). An association between asthma and some mental disorders, in particular, anxiety and depression has been shown (Goodwin *et al.* 2003a; Goodwin *et al.* 2004; Perna *et al.* 1997; Shavitt *et al.* 1992); (Opolski and Wilson, 2005; Toren *et al.* 2006). While some of the previous evidence was based in small number of countries, recent data have extended similar results to a large number of countries; (Jiang *et al.* 2013; Wong *et al.* 2013).

Most of the studies showing an association between asthma and mental disorders were cross-sectional in nature, thus limiting their ability to infer the temporal relationship between asthma and mental disorders. Several longitudinal studies suggest that asthma in childhood

is followed by some subsequent internalizing mental disorders (Alati *et al.* 2005; Goodwin *et al.* 2013; Ramos Olazagasti *et al.* 2012) and with suicidal ideation and suicide attempts (Goodwin and Eaton, 2005). On the other hand, a number of studies have shown a longitudinal association between psychological distress and atopic disorders, mostly asthma, both in children and adults (Chida *et al.* 2008); (Sanna *et al.* 2014).

Only very few of these studies included comprehensive diagnostic measures of mental disorders (i.e., based on standard psychiatric diagnostic criteria such as the Diagnostic Statistical Manual (DSM)) for mood and anxiety (Hasler *et al.* 2005; Wainwright *et al.* 2007); and eating disorders (Goodwin *et al.* 2009; Scott *et al.* 2007; Scott *et al.* 2008). An additional limitation of previous research is that the influence of mental comorbidity in the association of mental disorders and asthma has not been analyzed in depth. Knowing whether anxiety or depression specifically is associated with asthma (after adjusting for comorbidity with the other) can guide research focused on the mechanisms underlying the association with asthma.

We previously reported, based on a large international study including many mental disorders, that there was a concurrent association between 12-month mental disorders and lifetime asthma in many countries, regardless of the important variation in asthma prevalence in these countries (Scott *et al.* 2008). Associations were similar for anxiety, mood and alcohol abuse disorders. In those analyses we did not assess the effect of mental comorbidity and our focus was on associations between current mental disorders and asthma, rather than on associations between temporally prior mental disorders and subsequent onset of asthma. We therefore undertook analyses that considered the sequential order of the mental disorders and asthma comorbidity and reported that early onset (i.e., before age 21) mental disorders predicted subsequent onset of diagnosed adult onset asthma (i.e., after age 21), even after adjusting for childhood adversities, smoking and other relevant variables (Scott *et al.* 2008). However in these analyses, we included a limited set of mental disorders and we did not adjust for mental disorder comorbidity. Nor did we examine whether the association held true for mental disorders starting after the age of 21 and subsequent adult asthma. Therefore, we could not determine whether the associations found between early onset and subsequent asthma were reflecting the onset timing of these disorders (i.e., that they occur at critical developmental periods) or were because early disorders are a risk marker for comorbidity.

Aims of the Study

In this study we analyzed only asthma cases with onset in adulthoods (21+ years of age), as we wanted to test the antecedent model (Scott MK 2009) of mental disorders preceding asthma onset. This model suggests that mental disorders that start early in life and are chronic or recurrent, may have physiological effects akin to chronic stress, leading to Hypothalamus-Pituitary-Adrenal (HPA) dysregulation (Chida Y et al, 2008; Scott KM, 2009). This altered physiological stress response in turn has been associated with immune system dysfunction and increased inflammatory response. These mechanisms could facilitate asthma onset among susceptible individuals, along with the lifestyle risk factors also associated with mental disorders. By selecting only adult-onset asthma cases and

conducting survival analyses based on person years only up to asthma diagnosis, this allowed us to investigate this specific temporal sequence from mental disorder to asthma diagnosis, albeit with the limitation of retrospective data. We did not include childhood asthma as it would be difficult for respondents to clearly recall the temporal priority of mental disorders and asthma symptoms.

We therefore conducted the present study using a larger dataset from the World Mental Health (WMH) Surveys to examine the associations between first onset of 16 mood, anxiety, impulse control and substance use disorders with subsequent adult onset asthma. Our aims were to examine the influence of mental disorder comorbidity on these associations; to investigate whether the associations vary according to the age of mental disorder or asthma onset; and to assess whether they vary by gender. In this study we analyzed only asthma cases with onset in adulthood, as it helped ensure the temporal order of the association of interest: from prior mental disorders to subsequent asthma. For childhood onset of asthma, which is fairly common, it might be difficult for respondents to clearly recall the temporal priority of mental disorders and asthma symptoms. Thus, we improved accuracy of the estimation of the association between mental disorders and asthma, to the expense of some generalization.

METHOD

Samples and Procedures

This study uses data from 19 of the WMH surveys: Colombia, Mexico, Peru, United States, Shenzhen (China), Japan, New Zealand, Belgium, France, Germany, Italy, the Netherlands, Romania, Spain, Portugal, Israel, Iraq, Northern Ireland, and Poland (see Table 1). A stratified multi-stage clustered area probability sampling strategy was used to select adult respondents (18 years+) in most WMH countries. Most of the surveys were based on nationally representative household samples while Colombia, Mexico and Shenzhen were based on nationally representative household samples in urbanized areas.

In most countries, internal subsampling was used to reduce respondent burden and average interview time by dividing the interview into two parts. All respondents completed Part 1, which included the core diagnostic assessment of most mental disorders. All Part 1 respondents who met lifetime criteria for any mental disorder and a probability sample of other respondents were administered Part 2, which assessed physical conditions and collected a range of other information related to survey aims. Part 2 respondents were weighted by the inverse of their probability of selection for Part 2 of the interview to adjust for differential sampling. Analyses in this paper are based on the weighted Part 2 subsample (n= 52,095). Additional weights were used to adjust for differential probabilities of selection within households, to adjust for non-response, and to match the samples to population socio-demographic distributions. Measures taken to ensure interviewer and data accuracy and cross-national consistency are described in detail elsewhere (Kessler and Ustun, 2004). All respondents provided informed consent and procedures for protecting respondents were approved and monitored for compliance by the Institutional Review Boards in each country (Kessler and Ustun, 2004).

Measures

All WMH instruments were cross-culturally adapted following the standard WHO procedures of translation, back-translation, cognitive debriefing and harmonization to make sure data collected would be comparable across countries. Such procedures are described in detail (Kessler and Ustun, 2008).

Mental disorders—All surveys used the WMH survey version of the WHO Composite International Diagnostic Interview (CIDI 3.0) (Kessler and Ustun, 2004), a fully structured interview, to assess lifetime history of mental disorders. Disorders were assessed using the definitions and criteria of the DSM-IV (American Psychiatric Association, 2000). The mental disorders adjusted for in this paper include *anxiety disorders* (panic disorder, agoraphobia without panic, specific phobia, social phobia, post-traumatic stress disorder, generalized anxiety disorder, obsessive compulsive disorder); *mood disorders* (major depressive episode/dysthymia, bipolar disorders I, II and broad); *substance use disorders* (alcohol abuse and dependence, drug abuse and dependence); and *impulse control disorders* (intermittent explosive disorder, bulimia nervosa and binge eating disorder). The selection of these 16 mental disorders was based on their prevalence, including disorders only when there were sufficient numbers of cases to warrant reliable analyses. As a result, for instance anorexia nervosa had to be excluded. We considered early onset mental disorders those with an onset before age of 21 years.

CIDI organic exclusion rules were applied in making diagnoses. Clinical reappraisal studies conducted in some of the WMH countries indicate that lifetime diagnoses of anxiety, mood and substance use disorders based on the CIDI have generally good concordance with diagnoses based on blinded clinical interviews (Haro *et al.* 2006).

Asthma—In a series of questions adapted from the U.S Health Interview Survey, respondents were asked about the lifetime presence of selected chronic conditions. Respondents were asked: "*Did a doctor or other health professional ever tell you that you had any of the following illnesses….asthma?"* Clinical guidelines as those issued by the American Thoracic Society, recommend a combination of methods, including medical history, physical examination and respiratory function tests (Goodwin *et al.* 2003b; Pearce *et al.* 2000) but such methods are generally not feasible in large epidemiological surveys. It is important to note here that an investigation of the correspondence of self-reported chronic conditions in the US National Health Interview Survey with medical records abstracted in the prior 3 years found that self-reported current asthma to be in fairly good agreement with medical records, although underreported by 20–30% (NCHS, 1994). In our survey the definition of asthma was self-report of a diagnosis of asthma –not simply a self-report of asthma. So it may correspond more closely still to actual medical records.

If respondents endorsed this question they were classified as having a history of asthma for these analyses. Respondents were also asked how old they were when they were first diagnosed with asthma. This year is referred to herein as the age of onset of asthma, although it is recognized that the underlying pathology develops over many years and that it is possible to have asthma without being detected. Only adult-onset asthma (onset age 21+)

was investigated in this paper. No difference between atopic/non-atopic asthma was made in our study.

Statistical Analysis

Discrete-time survival analyses (Singer and Willett, 1993) with person-year as the unit of analysis were used to test sequential associations between first onset of mental disorders and subsequent onset of asthma. For these analyses, a person-year data set was created in which each year in the life of each respondent up to and including the age of onset of asthma or their age at interview (whichever came first) was treated as a separate observational record, with the year of asthma onset coded 1 and earlier years coded 0 on a dichotomous outcome variable. Persons who reported asthma onset before age 21 (N=2,186, corresponding to the 54% of all asthma cases in our study) were excluded from analysis. Mental disorder predictors were coded 1 from the year after first onset of each individual mental disorder. This time lag of 1 year in the coding of the predictors ensured that in cases where the first onset of a mental disorder and of asthma occurred in the same year, the mental disorder would not count as a predictor. Only person-years up to the diagnosis of asthma were analyzed so that only mental disorder episodes occurring prior to the onset of asthma were included in the predictor set. Logistic regression analysis was used to analyze these data with the survival coefficients presented as odds ratios, indicating the relative odds of asthma onset in a given year for a person with a prior history of mental disorder compared to a person without that mental disorder (including people without any mental disorder history). It is important to note that, given the retrospective nature of the information collected, results of the above analyses should be considered exploratory in nature. Longitudinal studies will be needed to confirm them.

A series of bivariate and multivariate models was developed including the predictor mental disorder plus control variables. Models controlled for person-years, countries, gender, current age, and in the multivariate models, other mental disorders. Bivariate models investigated association of specific mental disorders with subsequent asthma onset. The next model, a multivariate model, estimated the associations of each mental disorder with asthma onset adjusting for mental disorder comorbidity.

Our approach was to not control for covariates that could be on the causal pathway between mental disorders and subsequent asthma. However, we recognize that these variables may also confound associations so we re-estimated the multivariate model with adjustment for history of smoking (ever/never/current) and educational attainment. This made virtually no difference to associations (all previously significant associations remained significant and none reduced in magnitude – data available on request) so we report the results from the model unadjusted for smoking and education in this paper. We did not include BMI in the adjusted models, as estimates of current body weight only were available, and including this variable in the analyses would result in a biased estimation of the associations.

Our earlier studies of concurrent mental-physical comorbidity in the WMH surveys found that these associations were generally consistent cross-nationally, despite varying prevalence of mental disorder and physical conditions (Lin *et al.* 2008; Von Korff, 2009). This was particularly the case for the association of mental disorders and adult onset asthma (Scott *et*

al. 2007). All analyses for this paper were therefore run on the pooled cross-national dataset. As the WMH data are both clustered and weighted, the design-based Taylor series linearization (Shah, 1998) implemented in version 10 of the SUDAAN software system (SUDDAN, 1999) was used to estimate standard errors and evaluate the statistical significance of coefficients.

RESULTS

Sample information

The survey characteristics are shown in Table 1 together with information about the number of survey respondents reporting a history of adult-onset asthma (n=1,860). They represented a total of 2,096,486 person-years of follow up. Four surveys had limited their eligible population to less than 65. The overall weighted response rate was 78%, ranging from 45.9% in France to 95.2 in Iraq. The prevalence of adult onset asthma ranged from 0.5% in the Shen Zen survey of People's Republic of China to 7.4% in New Zealand. The mean age of adult asthma onset was 41 (SE=0.5) with a median age of onset of 38.

Lifetime prevalence of mental disorders among those with and without asthma

In Table 2 the lifetime prevalence rates of mental disorders are shown for the total sample without adult onset asthma (N= 49,296) and for those participants reporting adult onset asthma (final three columns). 20.8% of the adult onset asthma participants had lifetime MDE or dysthymia, 11.2% had specific phobia, 2% had intermittent explosive disorder, and 8.2%, alcohol abuse. Lifetime prevalence of mood and anxiety disorders among adult onset asthma cases was generally higher than in the total sample without adult onset asthma. It should be noted that the prevalence rates for mental disorders reported in this table represent the history of mental disorders occurring at any age up until the age of interview for each respondent. The analyses that follow include as predictors only those mental disorders occurring prior to the onset of asthma.

Associations between temporally prior mental disorders and subsequent asthma onset

Table 3 shows the associations between the first onset of temporally prior individual mental disorders and subsequent adult asthma onset. These associations were first investigated in a series of bivariate models (i.e., only one mental disorder considered at a time), but adjusted for age cohort, gender, person-year and country. First section of the table shows that 12 (out of the 16) mental disorders predicted adult onset asthma, with statistically significant ORs in the range of 1.5 to 2.8. Bipolar disorder showed the highest bivariate association (OR= 2.8) followed by binge eating disorder (OR= 2.6).

The second section of table 3 shows that many bivariate associations remained significant, although attenuated, after adjusting for lifetime mental disorder comorbidity (that is, adjusting for mental disorders occurring before asthma onset). Dummy variables for all mental disorders were entered simultaneously and the highest multivariate associations observed correspond to binge eating disorder (OR= 1.8), bipolar disorder (OR= 1.8), PTSD (OR= 1.5), and alcohol abuse (OR= 1.5). Of interest, the observed association between major depressive episode/dysthymia became non-significant in the multivariate model. The

global Chi square test for the joint effect of all mental disorders was statistically significant (X^2_{16}= 140.3). That effect was not homogeneous for all mental disorders (X^2_{15}=35.2).

The final section in table 3 shows the coefficients of a multivariate model estimated with dummy predictors for the number of mental disorders without any information about the type of mental disorders, adjusted for age cohort, gender, person-year and country. The joint effect of the number of mental disorders is statistically significant X^2=67.6 and a linear trend is observed, with an OR= 1.4 for exactly one mental disorder only to an OR= 3.1 for 5 or more mental disorders.

We performed analyses with subgroups of countries (i.e., developed vs developing) and found that none of the interactions are significant indicating that there are no country income group differences in these associations. We also tested whether early onset (before age of 21) mental disorders were more strongly associated with subsequent adult asthma relative to late onset (after age of 21) mental disorders. Although we found that this was the case for most of the mental disorders, this difference between early and late onset became non-significant once all mental disorders were included in the models (results shown, but available on request). This suggests that the stronger association for early onset disorders with asthma is because early onset mental disorders are risk factors or risk markers for lifetime mental disorder comorbidity.

Variation over the life-course (timing of asthma diagnoses)

When we investigated whether associations between mental disorders and subsequent asthma varied by timing of the asthma diagnosis, we found significant interaction effects with person years for mood disorders (MDE/Dysthymia), and for GAD, Social phobia, and PTSD (Table 4). In all cases, the significant interactions indicate that the association of these mental disorders with adult asthma is stronger when asthma is diagnosed earlier in adulthood relative to later in adulthood. This is an important qualifier of the findings in Table 3 where the multivariate associations between MDE/dysthymia and Social phobia and asthma are not significant, as these results included adult asthma diagnosed throughout the whole adult lifespan.

Finally, we assessed whether the association between mental disorders and adult onset asthma was different by gender (Table 5). We did find an interaction effect with gender for the association of two disorders with asthma: specific phobia, which was more strongly associated with subsequent asthma among females (stratified OR for female= 1.5) and for PTSD, which was more strongly associated with asthma among males (stratified OR for male= 2.9).

DISCUSSION

The results of this study must be interpreted taking into account several limitations. First, our assessment of asthma and mental disorders as well as their age of onset (AOO) is retrospective, which is associated with underestimates and errors (Wells and Horwood, 2004). Nevertheless, there is evidence that retrospective reported age of onset of asthma is reliable (Pattaro *et al.* 2007) and accurate (Toren *et al.* 2006). In addition, the instrument

used for assessing mental disorders was specifically modified to improve accuracy in reporting age of onset, including decomposition of questions and bounding uncertainty interviewer techniques (Kessler and Ustun, 2004). Moreover, while neuroticism and distress may bias the reporting of disease symptoms (Janssens *et al.* 2009), they do not bias the reporting of diagnosed conditions (Vassend and Skrondal, 1999). Second, our assessment of asthma is based on self-report rather than on the most recommended strategy of combining medical history, physical examination and respiratory function tests (Douwes *et al.* 2011; Goodwin *et al.* 2003b; Pearce *et al.* 2000). But, as mentioned earlier, in our survey the definition of asthma was self-report of a diagnosis of asthma –not simply a self-report of asthma, a strategy that is associated with a lower bias (Baumeister *et al.* 2010; Kriegsman *et al.* 1996). Memory and diagnostic biases might have lead us to inaccurately classify some individuals in relation to their mental disorders and/or asthma status, and misclassification usually results in a bias towards the null, that is, an underestimation of the real association between mental disorders and asthma (Green *et al.* 2010; Loerbroks *et al.* 2012). Overall the retrospective nature of the data leads us to consider our results as preliminary evidence to be confirmed by longitudinal studies. Thirdly, diagnosis requires access to health care and there might be differences in access to health care among the countries and regions included in our study, which we have not studied. However the asthma prevalence found is consistent with previous studies (Akinbami *et al.* 2011; Goodwin *et al.* 2003b; Loerbroks *et al.* 2012), if we consider that we are analyzing adult onset asthma cases only, which correspond to a little less than half (46%) of the total asthma cases in our sample. Also a major strength of the WMH-surveys is that it contains a series of population-based samples in which all participants underwent the CIDI interview. The likelihood of mental disorders being diagnosed thus plays no role as every respondent is scored according to DSM criteria. But there may be substantial cultural differences in the likelihood of asthma being diagnosed. It is quite likely, for example, that in developing countries fewer people will get asthma diagnoses and care. This will result in a non-differential misclassification, that is, respondents being classified as non-asthma cases when in fact they are cases (undiagnosed). The effect of this is to bias associations towards the null. Finally, we did not explore asthma severity nor specific asthma symptoms, which are more strongly associated with depression and anxiety disorders than overall asthma (Opolski and Wilson, 2005).

Notwithstanding these limitations, we believe our study provides valuable knowledge in several respects. Specifically, we confirm an important association of anxiety disorders and subsequent adult onset asthma (PTSD, panic, specific phobia and GAD) and report an even stronger association for bipolar, binge eating, and alcohol abuse disorders. We provide evidence for the first time that the number of comorbid mental disorders shows an additive association with subsequent asthma. We also show that the association of mental disorders and subsequent adult onset asthma is stronger for early onset mental disorders, and some associations are stronger when asthma occurs earlier rather than later in adulthood. Finally, we determine that for the most part associations between mental disorders and subsequent asthma onset are similar for men and women. This is an interesting finding given the higher prevalence of mood and anxiety disorders, and of adult-onset asthma, among women.

The association between anxiety disorders and adult asthma is consistent with previous findings (Deshmukh *et al.* 2008; Goodwin *et al.* 2003a; Goodwin *et al.* 2004; Katon *et al.*

2004; ten and Petermann, 2000). Several studies have shown an association of adult asthma with panic (Goodwin *et al.* 2003b); (Favreau *et al.* 2014), with GAD (Goodwin *et al.* 2003a; Lavoie *et al.* 2011) and with PTSD (Katon *et al.* 2004; Kean *et al.* 2006; Spitzer *et al.* 2009; Spitzer *et al.* 2011), the anxiety disorders which showed the highest association in our study. Less evidence is available about the association of asthma and bipolar disorder (Goodwin *et al.* 2004) and eating disorders (Moreau *et al.* 2009; Stevenson, 2003). It is notable that binge eating was the single disorder most strongly associated with adult asthma in our study. This fact, together with a lack of association with bulimia, strongly suggests that obesity may be a causal mechanism. No doubt, this association deserves further research.

We found a stronger association between specific phobia and asthma for women, and indeed associations between all anxiety disorders (with the notable exception of PTSD) and asthma were somewhat stronger for women, although this gender difference was only significant for specific phobia. This pattern is consistent with prior research suggesting that women have greater psychobiological reactivity to stress, and a more sensitized hypothalamic-pituitary-adrenal axis than men (Meewisse *et al.* 2007). In light of this research suggesting greater physiological stress reactivity in women, the stronger association we observed between PTSD and asthma for men is surprising (Olff *et al.* 2007). It may therefore be a chance finding, or it may reflect complex interactions between gender, traumatic stress and respiratory function that require further investigation to elucidate.

A number of mechanisms have been suggested to explain the association between asthma and mental disorders. Among others, the symptomatic nature of asthma, which might be a life-threatening condition, would lead to developing some psychopathological manifestations (Goodwin *et al.* 2012; Kean *et al.* 2006); and asthma medication, in particular oral steroids, could cause psychological symptoms among asthma patients (Opolski and Wilson, 2005). These mechanisms assume that asthma would be the antecedent (Scott, 2009) leading to the development of mental disorders. But our study suggests that mental disorders can be the antecedent of subsequent adult-onset asthma, as it had been previously indicated (Chida *et al.* 2008; Goodwin *et al.* 2009). Possible pathways for such causation would include alterations in the autonomic nervous (sympathetic-adrenal-medullary -SAM- axis) and/or the neuroendocrine (hypothalamic-pituitary-adrenal –HPA- axis) systems associated to mental disorders, which would increase vulnerability to asthma onset; (Goodwin *et al.* 2012; Scott, 2009; Wright, 2005). The possibility of a causal role of mental disorders in adult onset asthma is reinforced by our observation that the association was stronger among those individuals whose mental disorder started during their childhood or early youth (early onset). It is also possible that certain behaviors or risk factors which are more frequent among individuals with mental disorders, such as smoking (McLeish *et al.* 2011) or obesity (Anto *et al.* 2010), among others, could mediate in the development of asthma in adulthood. It is important to note that the results presented here are adjusted by smoking history and education years. But we could not adjust by obesity due to lack of information regarding obesity prior to asthma onset. Overall our results are compatible with the antecedent model which proposes that mental disorders could, through their association with dysregulated stress physiology and lifestyle risk factors (Chida Y et al, 2008; Scott KM, 2009) contribute to the development of adult-onset asthma. Such mechanisms could occur in concert with others.

The evidence of a possible "bidirectional" association (Chida *et al.* 2008) strongly suggests the existence of mechanisms that are common for both mental disorders and asthma (Van Lieshout and MacQueen, 2012). Inflammation would be one of such mechanisms, as it has been shown to underpin asthma and it has been suggested to have a role in depressive disorders (Dantzer *et al.* 2008); (Berk *et al.* 2013). Recently, a bidirectional pathway between depression and comorbid systemic illnesses has been proposed (Iwata *et al.* 2013; ten and Petermann, 2000), which could imply novel strategies for treating mental disorders. And as stress can affect the autonomous nervous system, its dysregulation could be a mechanism by which stress increases the risk of developing both asthma *and* emotional problems (Van Lieshout and MacQueen, 2012). Stress, endocrine and immune systems are strongly related and very likely mechanisms in such bidirectional relationship between mental disorders and asthma (Wright, 2005).

Shared determinants acting very early in life, maybe in utero, would be also compatible with this bidirectional association. Family and genetic associations between asthma and depression have been described (Van Lieshout and MacQueen, 2012). Childhood adversities are a well-known risk factor for mental disorders, and they have been also found to be risk factors of physical conditions (Scott *et al.* 2011). More recently we showed that childhood adversities were a risk factor for adult onset asthma (Korkeila *et al.* 2012), but we also reported that associations between early onset mental disorders and subsequent onset of asthma were independent of childhood adversities. Further research on common pathways for mental disorders and adult onset asthma might bring clues to new therapeutic approaches.

We found that early mental disorders (before age of 21) are more strongly associated with subsequent adult onset asthma, but many of these associations became non-significant when the presence of other mental disorders prior to asthma onset was taken into account. We interpret this as the result of earlier onset mental disorders being markers for mental comorbidity, rather than the timing of mental disorders per se having an effect on the risk of asthma. The important role of mental comorbidity is supported in our study by the evidence of a linear effect of mental comorbidity on subsequent asthma and by the fact that the statistical model including only the number of comorbid mental disorders had a better fit predicting adult onset asthma than any of the other more complex models analyzed here. Individuals with mental comorbidity should be considered a group with a higher risk of subsequent asthma. From an etiological perspective, the higher risk of asthma with each additional comorbid mental disorder suggests that pathways towards development of adult onset asthma are not totally overlapping.

Our study adds to previous knowledge: a) a large sample of culturally different individuals worldwide; b) a wide range of mental disorders assessed with a face to face diagnostic interview; and c) clear, consistent association between mental disorders and subsequent adult-onset asthma, with adjustment for some obvious confounders. While the cross-sectional nature of the study is a major weakness, our study adds distinctly novel contributions with regard to a) and b) above in particular, with adjustment for some obvious confounders.

In conclusion, in this international study we found that there is an association between a wide range of mental disorders and subsequent adult onset asthma, even after adjusting for mental disorder comorbidity. By analyzing only adult onset asthma cases, this helped ensuring the temporal order of the associations under investigation (from prior mental disorder to subsequent asthma). This also means that our results are generalizable only to adult onset asthma. Earlier onset mental disorders were more strongly associated with asthma than later onset disorders; this was explained by mental disorder comorbidity. Some mental disorders were more strongly associated with asthma when the asthma occurred earlier rather than later in adulthood. Associations were for the most part similar for men and women. The study also reveals the importance of comorbid mental disorders, as they increased risk for subsequent asthma. While pathological mechanisms implicated in the development of asthma and/or improving some of their outcomes among those with preexisting mental disorders should be better understood, the possibilities of avoiding asthma by intervening with potential psychological issues deserve further research.

Reference List

Akinbami LJ, Moorman JE, Liu X. Asthma prevalence, health care use, and mortality: United States, 2005–2009. Natl. Health Stat. Report. 2011:1–14.

Alati R, O'Callaghan M, Najman JM, Williams GM, Bor W, Lawlor DA. Asthma and internalizing behavior problems in adolescence: a longitudinal study. Psychosom. Med. 2005; 67:462–470. [PubMed: 15911911]

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). Fourth. Washington, DC: American Psychiatric Association; 2000.

Anto JM, Sunyer J, Basagana X, Garcia-Esteban R, Cerveri I, de MR, Heinrich J, Janson C, Jarvis D, Kogevinas M, Kuenzli N, Leynaert B, Svanes C, Wjst M, Gislason T, Burney P. Risk factors of new-onset asthma in adults: a population-based international cohort study. Allergy. 2010; 65:1021–1030. [PubMed: 20132157]

Baumeister H, Kriston L, Bengel J, Harter M. High agreement of self-report and physician-diagnosed somatic conditions yields limited bias in examining mental-physical comorbidity. J. Clin. Epidemiol. 2010; 63:558–565. [PubMed: 19959329]

Berk M, Williams LJ, Jacka FN, O'Neil A, Pasco JA, Moylan S, Allen NB, Stuart AL, Hayley AC, Byrne ML, Maes M. So depression is an inflammatory disease, but where does the inflammation come from? BMC. Med. 2013; 11:200. [PubMed: 24228900]

Chida Y, Hamer M, Steptoe A. A bidirectional relationship between psychosocial factors and atopic disorders: a systematic review and meta-analysis. Psychosom. Med. 2008; 70:102–116. [PubMed: 18158379]

Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat. Rev. Neurosci. 2008; 9:46–56. [PubMed: 18073775]

Deshmukh VM, Toelle BG, Usherwood T, O'Grady B, Jenkins CR. The association of comorbid anxiety and depression with asthma-related quality of life and symptom perception in adults. Respirology. 2008; 13:695–702. [PubMed: 18513245]

Douwes J, Brooks C, Pearce N. Asthma nervosa: old concept, new insights. Eur. Respir. J. 2011; 37:986–990. [PubMed: 21532014]

Favreau H, Bacon SL, Labrecque M, Lavoie KL. Prospective impact of panic disorder and panic-anxiety on asthma control, health service use, and quality of life in adult patients with asthma over a 4-year follow-up. Psychosom. Med. 2014; 76:147–155. [PubMed: 24470131]

Goodwin RD, Bandiera FC, Steinberg D, Ortega AN, Feldman JM. Asthma and mental health among youth: etiology, current knowledge and future directions. Expert. Rev. Respir. Med. 2012; 6:397–406. [PubMed: 22971065]

Goodwin RD, Eaton WW. Asthma, suicidal ideation, and suicide attempts: findings from the Baltimore epidemiologic catchment area follow-up. Am. J. Public Health. 2005; 95:717–722. [PubMed: 15798135]

Goodwin RD, Fergusson DM, Horwood LJ. Asthma and depressive and anxiety disorders among young persons in the community. Psychol. Med. 2004; 34:1465–1474. [PubMed: 15724877]

Goodwin RD, Jacobi F, Thefeld W. Mental disorders and asthma in the community. Arch. Gen. Psychiatry. 2003a; 60:1125–1130. [PubMed: 14609888]

Goodwin RD, Pine DS, Hoven CW. Asthma and panic attacks among youth in the community. J. Asthma. 2003b; 40:139–145. [PubMed: 12765315]

Goodwin RD, Robinson M, Sly PD, McKeague IW, Susser ES, Zubrick SR, Stanley FJ, Mattes E. Severity and persistence of asthma and mental health: a birth cohort study. Psychol. Med. 2013; 43:1313–1322. [PubMed: 23171853]

Goodwin RD, Sourander A, Duarte CS, Niemela S, Multimaki P, Nikolakaros G, Helenius H, Piha J, Kumpulainen K, Moilanen I, Tamminen T, Almqvist F. Do mental health problems in childhood predict chronic physical conditions among males in early adulthood? Evidence from a community-based prospective study. Psychol. Med. 2009; 39:301–311. [PubMed: 18507873]

Green JG, McLaughlin KA, Berglund PA, Gruber MJ, Sampson NA, Zaslavsky AM, Kessler RC. Childhood adversities and adult psychiatric disorders in the national comorbidity survey replication I: associations with first onset of DSM-IV disorders. Arch. Gen. Psychiatry. 2010; 67:113–123. [PubMed: 20124111]

Haro JM, Arbabzadeh-Bouchez S, Brugha TS, de GG, Guyer ME, Jin R, Lepine JP, Mazzi F, Reneses B, Vilagut G, Sampson NA, Kessler RC. Concordance of the Composite International Diagnostic Interview Version 3.0 (CIDI 3.0) with standardized clinical assessments in the WHO World Mental Health surveys. Int. J. Methods Psychiatr. Res. 2006; 15:167–180. [PubMed: 17266013]

Hasler G, Gergen PJ, Kleinbaum DG, Ajdacic V, Gamma A, Eich D, Rossler W, Angst J. Asthma and panic in young adults: a 20-year prospective community study. Am. J. Respir. Crit Care Med. 2005; 171:1224–1230. [PubMed: 15764721]

Iwata M, Ota KT, Duman RS. The inflammasome: pathways linking psychological stress, depression, and systemic illnesses. Brain Behav. Immun. 2013; 31:105–114. [PubMed: 23261775]

Janssens T, Verleden G, De PS, Van DI, Van den Bergh O. Inaccurate perception of asthma symptoms: a cognitive-affective framework and implications for asthma treatment. Clin. Psychol. Rev. 2009; 29:317–327. [PubMed: 19285771]

Jenkins MA, Hopper JL, Bowes G, Carlin JB, Flander LB, Giles GG. Factors in childhood as predictors of asthma in adult life. BMJ. 1994; 309:90–93. [PubMed: 8038673]

Jiang CQ, Loerbroks A, Lam KB, Bosch JA, Thomas GN, Zhang WS, Cheng KK, Lam TH, Adab P. Mental HEALTH AND asthma in China: the Guangzhou Biobank Cohort Study. Int. J. Behav. Med. 2013; 20:259–264. [PubMed: 22297917]

Katon WJ, Richardson L, Lozano P, McCauley E. The relationship of asthma and anxiety disorders. Psychosom. Med. 2004; 66:349–355. [PubMed: 15184694]

Kean EM, Kelsay K, Wamboldt F, Wamboldt MZ. Posttraumatic stress in adolescents with asthma and their parents. J. Am. Acad. Child Adolesc. Psychiatry. 2006; 45:78–86. [PubMed: 16327584]

Kessler, RC.; Ustun, TB. The WHO World Mental Health Surveys: Global Perspectives on the Epidemiology of Mental Disorders. New York: Cambridge University Press; 2008.

Kessler RC, Ustun TB. The World Mental Health (WMH) Survey Initiative Version of the World Health Organization (WHO) Composite International Diagnostic Interview (CIDI). Int. J. Methods Psychiatr. Res. 2004; 13:93–121. [PubMed: 15297906]

Korkeila J, Lietzen R, Sillanmaki LH, Rautava P, Korkeila K, Kivimaki M, Koskenvuo M, Vahtera J. Childhood adversities and adult-onset asthma: a cohort study. BMJ Open. 2012; 2

Kriegsman DM, Penninx BW, van Eijk JT, Boeke AJ, Deeg DJ. Self-reports and general practitioner information on the presence of chronic diseases in community dwelling elderly. A study on the accuracy of patients' self-reports and on determinants of inaccuracy. J. Clin. Epidemiol. 1996; 49:1407–1417. [PubMed: 8970491]

Lavoie KL, Boudreau M, Plourde A, Campbell TS, Bacon SL. Association between generalized anxiety disorder and asthma morbidity. Psychosom. Med. 2011; 73:504–513. [PubMed: 21715294]

Lin EH, Korff MV, Alonso J, Angermeyer MC, Anthony J, Bromet E, Bruffaerts R, Gasquet I, de GG, Gureje O, Haro JM, Karam E, Lara C, Lee S, Levinson D, Ormel JH, Posada-Villa J, Scott K, Watanabe M, Williams D. Mental disorders among persons with diabetes--results from the World Mental Health Surveys. J. Psychosom. Res. 2008; 65:571–580. [PubMed: 19027447]

Loerbroks A, Herr RM, Subramanian S, Bosch JA. The association of asthma and wheezing with major depressive episodes: an analysis of 245 727 women and men from 57 countries. Int. J. Epidemiol. 2012; 41:1436–1444. [PubMed: 22879363]

McLeish AC, Cougle JR, Zvolensky MJ. Asthma and cigarette smoking in a representative sample of adults. J. Health Psychol. 2011; 16:643–652. [PubMed: 21346012]

Meewisse ML, Reitsma JB, de Vries GJ, Gersons BP, Olff M. Cortisol and post-traumatic stress disorder in adults: systematic review and meta-analysis. Br. J. Psychiatry. 2007; 191:387–392. [PubMed: 17978317]

Moreau D, Kalaboka S, Choquet M, Annesi-Maesano I. Asthma, obesity, and eating behaviors according to the diagnostic and statistical manual of mental disorders IV in a large population-based sample of adolescents. Am. J. Clin. Nutr. 2009; 89:1292–1298. [PubMed: 19321566]

NCHS. Evaluation of National Health Interview Survey diagnostic reporting. Vital Health Stat. 1994; 2:1–116.

Olff M, Langeland W, Draijer N, Gersons BP. Gender differences in posttraumatic stress disorder. Psychol. Bull. 2007; 133:183–204. [PubMed: 17338596]

Opolski M, Wilson I. Asthma and depression: a pragmatic review of the literature and recommendations for future research. Clin. Pract. Epidemiol. Ment. Health. 2005; 1:18. [PubMed: 16185365]

Pattaro C, Locatelli F, Sunyer J, de MR. Using the age at onset may increase the reliability of longitudinal asthma assessment. J. Clin. Epidemiol. 2007; 60:704–711. [PubMed: 17573986]

Pearce N, Douwes J, Beasley R. The rise and rise of asthma: a new paradigm for the new millennium? J. Epidemiol. Biostat. 2000; 5:5–16. [PubMed: 10885867]

Perna G, Bertani A, Politi E, Colombo G, Bellodi L. Asthma and panic attacks. Biol. Psychiatry. 1997; 42:625–630. [PubMed: 9376459]

Ramos Olazagasti MA, Shrout PE, Yoshikawa H, Bird HR, Canino GJ. The longitudinal relationship between parental reports of asthma and anxiety and depression symptoms among two groups of Puerto Rican youth. J. Psychosom. Res. 2012; 73:283–288. [PubMed: 22980534]

Sanna L, Stuart AL, Pasco JA, Jacka FN, Berk M, Maes M, O'Neil A, Girardi P, Williams LJ. Atopic disorders and depression: findings from a large, population-based study. J. Affect. Disord. 2014; 155:261–265. [PubMed: 24308896]

Scott KM, Von KM, Alonso J, Angermeyer MC, Benjet C, Bruffaerts R, de GG, Haro JM, Kessler RC, Kovess V, Ono Y, Ormel J, Posada-Villa J. Childhood adversity, early-onset depressive/anxiety disorders, and adult-onset asthma. Psychosom. Med. 2008; 70:1035–1043. [PubMed: 18941133]

Scott KM, Von KM, Angermeyer MC, Benjet C, Bruffaerts R, de GG, Haro JM, Lepine JP, Ormel J, Posada-Villa J, Tachimori H, Kessler RC. Association of childhood adversities and early-onset mental disorders with adult-onset chronic physical conditions. Arch. Gen. Psychiatry. 2011; 68:838–844. [PubMed: 21810647]

Scott KM, Von KM, Ormel J, Zhang MY, Bruffaerts R, Alonso J, Kessler RC, Tachimori H, Karam E, Levinson D, Bromet EJ, Posada-Villa J, Gasquet I, Angermeyer MC, Borges G, de GG, Herman A, Haro JM. Mental disorders among adults with asthma: results from the World Mental Health Survey. Gen. Hosp. Psychiatry. 2007; 29:123–133. [PubMed: 17336661]

Scott, K. The development of mental-physical comorbidity. In: Von Korff, MR.; Scott, KM.; Gureje, O., editors. Global Perspectives on Mental-Physical Comorbidity. UK: WHO: Cambridge University Press; 2009. p. 84-94.

Shah, BV. Linearization methods of variance estimation. In: Armitage, P.; Colton, T., editors. Encyclopedia of Biostatistics. Chichester: John Wiley and Sons; 1998. p. 2276-2279.

Shavitt RG, Gentil V, Mandetta R. The association of panic/agoraphobia and asthma. Contributing factors and clinical implications. Gen. Hosp. Psychiatry. 1992; 14:420–423. [PubMed: 1473713]

Singer JD, Willett JB. It's about time: Using discrete-time survival analysis to study duration and the timing of events. Journal of Educational Statistics. 1993; 18:155–195.

Spitzer C, Barnow S, Volzke H, John U, Freyberger HJ, Grabe HJ. Trauma, posttraumatic stress disorder, and physical illness: findings from the general population. Psychosom. Med. 2009; 71:1012–1017. [PubMed: 19834051]

Spitzer C, Koch B, Grabe HJ, Ewert R, Barnow S, Felix SB, Ittermann T, Obst A, Volzke H, Glaser S, Schaper C. Association of airflow limitation with trauma exposure and post-traumatic stress disorder. Eur. Respir. J. 2011; 37:1068–1075. [PubMed: 20729219]

Stevenson J. Relationship between behavior and asthma in children with atopic dermatitis. Psychosom. Med. 2003; 65:971–975. [PubMed: 14645774]

SUDDAN. Anonymous. North Carolina, USA: Research Triangle Park; 1999. SUDDAN Software for the statistical analysis of correlated data (computer program).

ten TC, Petermann F. Reviewing asthma and anxiety. Respir. Med. 2000; 94:409–415. [PubMed: 10868701]

Toren K, Palmqvist M, Lowhagen O, Balder B, Tunsater A. Self-reported asthma was biased in relation to disease severity while reported year of asthma onset was accurate. J. Clin. Epidemiol. 2006; 59:90–93. [PubMed: 16360566]

Van Lieshout, RJ.; MacQueen, GM. Relations between asthma and psychological distress: an old idea revisited. In: Bienenstock, J., editor. Allergy and the nervous system. Chem Immunol Allergy. Vol. 98. Basel: Karger; 2012. p. 1-13.

Vassend O, Skrondal A. The Role of Negative Affectivity in Self assessment of Health: A Structural Equation Approach. J. Health Psychol. 1999; 4:465–482. [PubMed: 22021640]

Von Korff, MR. Global perspectives on mental-physical comorbidity. In: Von Korff, MR.; Scott, KM.; Gureje, O., editors. Global perspectives on mental-physical comorbidity in the WHO World Mental Health Surveys. New York, NY: Cambridge University Press; 2009. p. 1-11.

Wainwright NW, Surtees PG, Wareham NJ, Harrison BD. Psychosocial factors and incident asthma hospital admissions in the EPIC-Norfolk cohort study. Allergy. 2007; 62:554–560. [PubMed: 17441796]

Wells JE, Horwood LJ. How accurate is recall of key symptoms of depression? A comparison of recall and longitudinal reports. Psychol. Med. 2004; 34:1001–1011. [PubMed: 15554571]

Wong KO, Hunter RB, Douwes J, Senthilselvan A. Asthma and wheezing are associated with depression and anxiety in adults: an analysis from 54 countries. Pulm. Med. 2013; 2013:929028. [PubMed: 23577252]

Wright RJ. Stress and atopic disorders. J. Allergy Clin. Immunol. 2005; 116:1301–1306. [PubMed: 16337463]

Table 1

Characteristics of WMH samples and proportion (and number) with history of adult-onset asthma.

Country	Field Dates	Age Range	Sample Size		Response Rate (%)	History of Adult-Onset Asthma Diagnosis[1]	
			Part 1	Part 2 sub-sample		Number Unweighted (N)	Weighted (%)
Americas							
Colombia	2003	18–65	4426	2381	87.7	23	0.7
Mexico	2001–2	18–65	5782	2362	76.6	22	0.7
United States	2002–3	18+	9282	5692	70.9	324	5.6
Peru	2005–6	18–65	3930	1801	90.2	53	2.9
Asia and South Pacific							
Japan	2002–6	20+	4129	1682	55.1	57	2.7
PRC Shenzhen	2006–7	18+	7132	2475	80.0	20	0.5
New Zealand	2003–4	18+	12790	7312	73.3	544	7.4
Europe							
Belgium	2001–2	18+	2419	1043	50.6	26	2.4
France	2001–2	18+	2894	1436	45.9	43	2.4
Germany	2002–3	18+	3555	1323	57.8	40	3.3
Italy	2001–2	18+	4712	1779	71.3	56	3.0
The Netherlands	2002–3	18+	2372	1094	56.4	47	4.0
Spain	2001–2	18+	5473	2121	78.6	77	3.0
Northern Ireland	2004–7	18+	4340	1986	68.4	88	4.0
Portugal	2008–9	18+	3849	2060	57.3	60	2.8
Romania	2005–6	18+	2357	2357	70.9	83	2.7
Poland	2010–11	18–64	10081	4000	50.4	72	1.3
Middle East							
Israel	2002–4	21+	4859	4859	72.6	188	3.9
Iraq	2006–7	18+	4332	4332	95.2	37	1.2
Weighted average response rate (%)					78.0		
Total sample size			98,714	52,095		1,860	3.4

[1]This is the onset of asthma in those 21 years and over.

Table 2

Prevalence of mental disorders across WMH samples

Types of mental disorders	Among the total sample (21+ years) (n= 49296)			Among those with adult-onset asthma (n = 1860)		
	n	%	SE	n	%	SE
I. Mood disorders						
Major Depressive Episode/Dysthymia	11639	12.9	0.2	615	20.8	1.0
Bipolar Disorder (Broad)	1561	1.8	0.1	98	3.2	0.4
II. Anxiety disorders						
Panic Disorder	1670	1.9	0.1	126	4.2	0.5
Generalized Anxiety Disorder	3625	4.3	0.1	270	9.5	0.7
Social Phobia	3646	4.3	0.1	207	7.1	0.6
Specific Phobia	5814	7.2	0.1	354	11.2	0.8
Agoraphobia without Panic	751	0.9	0.0	38	1.2	0.2
Post-Traumatic Stress Disorder	2718	3.4	0.1	221	8.3	0.8
Obsessive Compulsive Disorder	729	1.2	0.1	17	0.4	0.1
III. Impulse-control disorders						
Intermittent Explosive Disorder	1523	2.0	0.1	47	2.0	0.4
Binge Eating Disorder	530	0.7	0.0	39	1.5	0.3
Bulimia Nervosa	355	0.4	0.0	27	0.7	0.1
IV. Substance disorders						
Alcohol Abuse	4806	7.5	0.2	216	8.2	0.7
Alcohol Dependence with Abuse	1627	2.1	0.1	97	3.3	0.4
Drug Abuse	1746	2.4	0.1	72	2.5	0.3
Drug Dependence with Abuse	678	0.9	0.1	34	1.0	0.2

J Psychiatr Res. Author manuscript; available in PMC 2016 November 23.

Table 3

Bivariate and multivariate associations (odds ratios) between DSM-IV mental disorders and the subsequent diagnosis of adult-onset asthma. The WMH Surveys.

	Bivariate Models[1]		Multivariate Type Model[2]		Multivariate Number Model[3]	
	OR	**(95% C.I.)**	**OR**	**(95% C.I.)**	**OR**	**(95% C.I.)**
I. Mood disorders						
Major Depressive Episode/ Dysthymia	1.6*	(1.4–1.9)	1.2	(1.0–1.4)	-	-
Bipolar Disorder (Broad)	2.8*	(2.0–3.9)	1.8*	(1.3–2.5)	-	-
II. Anxiety disorders						
Panic Disorder	2.2*	(1.6–3.1)	1.4*	(1.0–2.0)	-	-
Generalized Anxiety Disorder	2.0*	(1.6–2.4)	1.3*	(1.1–1.7)	-	-
Social Phobia	1.5*	(1.2–1.9)	1.0	(0.8–1.3)	-	-
Specific Phobia	1.7*	(1.4–2.0)	1.3*	(1.1–1.6)	-	-
Agoraphobia without Panic	1.3	(0.9–2.0)	0.8	(0.6–1.3)	-	-
Post-Traumatic Stress Disorder	2.1*	(1.6–2.7)	1.5*	(1.1–1.9)	-	-
Obsessive Compulsive Disorder	0.8	(0.4–1.7)	0.6	(0.3–1.1)	-	-
III. Impulse-control disorders						
Intermittent Explosive Disorder	1.5	(1.0–2.2)	1.0	(0.7–1.4)	-	-
Binge Eating Disorder	2.6*	(1.7–3.9)	1.8*	(1.2–2.9)	-	-
Bulimia Nervosa	1.7	(1.0–3.0)	1.0	(0.5–1.8)	-	-
IV. Substance disorders						
Alcohol Abuse	2.0*	(1.6–2.4)	1.5*	(1.1–2.0)	-	-
Alcohol Dependence with Abuse	2.5*	(1.8–3.4)	1.3	(0.9–2.0)	-	-
Drug Abuse	1.7*	(1.2–2.4)	0.9	(0.6–1.4)	-	-
Drug Dependence with Abuse	1.9*	(1.2–3.1)	0.8	(0.5–1.4)	-	-
Joint effect of all types of disorders, χ^2_{16}				140.3*		
Difference between types of disorders, χ^2_{15}				35.2*		
V. Number of disorders						

	Bivariate Models[1]		Multivariate Type Model[2]		Multivariate Number Model[3]	
	OR	**(95% C.I.)**	**OR**	**(95% C.I.)**	**OR**	**(95% C.I.)**
Exactly 1 disorder	-	-	-	-	1.4*	(1.2–1.6)
Exactly 2 disorders	-	-	-	-	1.6*	(1.4–2.0)
Exactly 3 disorders	-	-	-	-	2.2*	(1.7–2.9)
Exactly 4 disorders	-	-	-	-	2.9*	(2.0–4.1)
5+ disorders	-	-	-	-	3.1*	(2.2–4.2)
Joint effect of number of disorders, χ^2_5						67.6*

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

[1]Bivariate models: each mental disorder type was estimated as a predictor of the physical condition onset in a separate discrete time survival model controlling for age cohorts, gender, person-year and country.

[2]Multivariate Type model: the model was estimated with dummy variables for all mental disorders entered simultaneously, including the controls specified above and additionally adjusted for smoking (ever/never/current) and education (number of years).

[3]Multivariate Number model: the model was estimated with dummy predictors for number of mental disorders without any information about type of mental disorders, including the controls specified above.

Table 4

Interaction between mental disorder and person-year in predicting the subsequent diagnosis of adult-onset asthma. The WMH Surveys.

Type of Mental Disorders	Mental disorder*Person-year interaction[1]		
	OR (95% C.I.)	χ^2_1	[p]
Major Depressive Episode/Dysthymia	0.97* (0.96–0.98)	49.4*	[0.000]
Generalized Anxiety Disorder	0.99* (0.97–1.00)	5.3*	[0.021]
Social Phobia	0.99* (0.98–1.00)	5.5*	[0.019]
Post-Traumatic Stress Disorder	0.98* (0.97–0.99)	12.1*	[0.001]

*OR significant at the 0.05 level, 2-sided test

[1]A series of multivariate models were estimated. For example, the model for depression included the dummy variables for all mental disorders plus the cross-product term for depression and person-year (as a continuous variable), plus the controls specified for earlier models.

Table 5

Multivariate type models for adult-onset asthma, stratified by gender. The WMH Surveys.

Type of Mental Disorders	Stratified Multivariate Type Models			
	Male		Female	
	OR	(95% C.I.)	OR	(95% C.I.)
Specific Phobia	0.9	(0.6–1.3)	1.5*	(1.2–1.7)
Post-Traumatic Stress Disorder	2.9*	(1.6–5.4)	1.2	(0.9–1.6)

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