Original Article

Co-morbid psychological dysfunction is associated with a higher risk of asthma exacerbations: a systematic review and meta-analysis

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Background: The longitudinal associations between psychological dysfunction (PD) and asthma exacerbations (AE) have not been adequately addressed. This study aimed to systematically assess the influence of PD on AE, and to determine whether different PD affects AE differentially.

Methods: Electronic databases (PubMed, Cochrane library, Web of Science, Embase, and Ovid) were searched for prospective cohort studies on the influence of PD on AE in individuals with asthma. Relative risk (RR) and adjusted RR (RR_{adj}) were pooled across studies. Subgroup analyses assessed the effects of different types of PD and the time-dependent response to the duration of PD exposure.

Results: Ten articles that involved 31,432 adults with asthma with follow-up of 6.0–86.4 months were included. PD significantly increased the risk of AE [RR_{adj} =1.06, 95% confidence interval (95%CI): 1.04–1.09, P<0.001], presenting as hospitalizations (RR_{adj} =1.22, 95% CI: 1.12–1.34, P<0.001), unscheduled doctor visits (RR =4.26, 95% CI: 2.52–7.19), and emergency department (ED) visits (RR_{adj} =1.06, 95% CI: 1.01–1.10, P=0.009) because of asthma. Depression significantly increased the risk of AE (RR_{adj} =1.07, 95% CI: 1.04–1.11, P<0.001), presenting as hospitalizations (RR_{adj} =1.26, 95% CI: 1.07–1.49, P=0.007) and ED visits (RR_{adj} =1.06, 95% CI: 1.02–1.11, P=0.007) because of asthma. Anxiety was only associated with an increased risk of AE in pregnant women (RR =1.05, 95% CI: 1.01–1.08), possibly due to the small amount of data available on anxiety. The influence of PD on AE was only significant when the PD exposure time exceeded one year.

Conclusions: Co-morbid PD adversely affects AE, and there are differential effects of depression and anxiety. Asthmatic subjects with PD may benefit from more attention when establishing a treatment regimen in clinical practice.

Keywords: Asthma; exacerbation; psychological dysfunction (PD); anxiety; depression

Submitted Sep 25, 2015. Accepted for publication Apr 06, 2016.
doi: 10.21037/jtd.2016.04.68
View this article at: http://dx.doi.org/10.21037/jtd.2016.04.68

Introduction

Asthma is a serious global health problem affecting 1–18% of the population, and is a significant financial burden because of the healthcare costs and productivity loss (1). The heavy burden of asthma appears to be related to poor asthma control, and the cost could be greatly decreased if disease control was improved (2). According to the American Thoracic Society and European Respiratory Society, asthma control should include good symptom control and normal activity level, referred to as "clinical asthma control", and should minimize the further risk of exacerbations, fixed airflow limitation, and side-effects (1,3).

The prevention of asthma exacerbations (AE) is an important component of optimal asthma control. It could be argued that AE are the most important outcome of asthma, because they are the key cost driver in asthma management, cause the greatest risk to patients, and increase the mortality of asthma (3). AE are common clinical incidents in patients with severe asthma and are often defined as hospitalizations, emergency department (ED) visits, systemic corticosteroid (SCS) use, or unscheduled doctor visits related to asthma (3). Achieving optimal asthma control relies on a good partnership between the individual with asthma and the healthcare provider and good self-management skills including effective communication, therapy adherence, self-monitoring, and regular visits to a care provider (2).

Psychological dysfunction (PD), including anxiety and depression, is more common in individuals with asthma than in healthy individuals, and asthma patients who experienced asthma symptoms had a significantly higher risk prevalence of depression than asthma patients who did not experience asthma symptoms (4,5). Psychological or emotional factors may impact the behavioral precautions taken by patients with asthma (6). PD is significantly associated with poor asthma control or intractability in asthma, damaged quality of life, more hospitalized days, and frequent AE (7-9). However, existing studies of the relation between PD and asthma outcomes are mainly cross-sectional or retrospective. Published prospective cohort studies of the relation between PD and AE have conflicting results (10-12). The results of pooled analyses of the effectiveness of psychological interventions for individuals with asthma are also inconsistent (13-15). Therefore, we undertook a systematic review and meta-analysis of prospective cohort studies to explore the influence of co-morbid PD on AE, and to determine whether different kinds of PD differentially affect AE.

Methods

Our systematic review and meta-analysis conformed to standard methodological guidelines for meta-analysis of observational studies (16).

Search strategy and inclusion criteria

A study protocol was formulated before starting the systematic review. The following databases were searched using a highly sensitive search filter: PubMed (1966 to January 2016), Cochrane library (up to January 2016), Web of Science (1994 to January 2016), Embase (1974 to January 2016), and Ovid (1946 to January 2016). The keywords used in the search were "asthma", "psychological dysfunction", and "asthma exacerbations" and their variations. The detailed search strategy is described in the Supplementary materials.

Studies were eligible for inclusion if they were prospective cohort studies that reported the influence of PD on AE, with adequately available data on either the number of individuals with AE during the follow-up period or the relative risk estimates (RRs) such as risk ratio, incidence rate ratio, hazard ratio, or odds ratio with 95% confidence interval (95% CI), and if PD exposure was measured by a relevant psychometric scale or diagnosed by a psychological specialist. Disagreements were solved by a third reviewer (GW).

Data extraction and quality assessment

A standardized data extraction form was completed prior to the commencement of data extraction. The full text of all articles that definitely or possibly met the inclusion criteria was accessed independently by two reviewers, and the relevant details were extracted. Study quality was assessed as described in our previous study (17). The data extraction and quality assessment are described in detail in the Supplementary materials.

Primary and secondary outcomes

AE or RRs of AE in subjects with PD were specified *a priori* as the primary outcome. The details of AE such as hospitalization, ED visit, unscheduled doctor visit, and SCS use were secondary outcomes (3). Where available, adjusted RRs of AE with 95% CI were also extracted and the adjusted confounding factors were noted.

According to the American Thoracic Society and European Respiratory Society (3), SCS use and hospitalizations or ED visits because of asthma are clinical indicators of severe AE. If a study reported either SCS use or hospitalizations or ED visits because of asthma as outcomes rather than AE directly, we interpreted these outcomes as AE. If a study reported two or even three of these events as outcomes, we first used the outcome of SCS use, and then ED visits because of asthma, and finally hospitalizations because of asthma. If different kinds of PD were defined, we selected one set of data to represent the effect of PD on AE, but performed sensitivity analyses for the other sets of data.

Statistical analysis and quality of the evidence assessment

The number of subjects who experienced AE during the follow-up period was treated as a dichotomous variable, and the pooled relative risk (RR) with 95% CI was calculated. Summary RR for the association between PD and different outcomes (AE, hospitalization because of asthma, ED visit because of asthma, unscheduled doctor visit because of asthma, and SCS use) were calculated using Stata Version 11.0 (Stata Corp. LP, College Station, TX). Heterogeneity in every effect estimate was assessed using the I^2 statistic and the Cochran Q method, as in our previous studies (17,18). A random-effects meta-analysis model was used to calculate pooled estimates when substantial heterogeneity was observed (I^2>50.0% and P<0.10), otherwise a fixed effects meta-analysis model was used. Sensitivity analysis was performed on the study population and quality of the included studies to assess the robustness of the results. Where original data had been adjusted for potential confounding factors, adjusted RR (RR_{adj}) with 95% CI was also pooled. In the subgroup analysis, trials were further stratified by the type of PD. The time-dependent response of AE to PD exposure was also plotted. To flexibly plot the relation between RR and duration of PD exposure, we divided the included studies into three groups according to the duration of the follow-up period (≤1, >1 year and <2, ≥2 years). A two-sided P value <0.05 was considered statistically significant throughout the analysis.

The quality of the evidence was evaluated according to the suggestions of the Grading of Recommendations Assessment, Development, and Evaluation Working Group using GradePro software (Version 3.6) (19).

Results

Characteristics and quality of included studies

Our search strategy initially identified 4,585 studies. Ten of these were eligible prospective cohort studies and were included in the analysis (10-12,20-26). The flowchart for screening studies is shown in *Figure 1*. *Table S1* shows the characteristics of the included studies. All the included studies were published between 2001 and 2014, and the duration of the follow-up period ranged from 6.0 to 86.4 months. There were 31,432 adults with asthma included, and 175 of these were pregnant women. In the study by Sumino *et al*. (20), the sample was divided into three independent groups by age (18–45, 46–64, and ≥65 years), and the adjusted risk ratio for AE and asthma-related hospitalizations in each group was calculated.

Most of the included studies were of high quality with Newcastle-Ottawa Quality Assessment Scale scores ranging from 5 to 9 (mean and standard deviation: 8.10±1.32; *Tables S1*, *S2*).

Exposure to psychological dysfunction (PD)

In the included studies, exposure to PD was ascertained according to one of eight psychometric tools (10,12,21-26), the International Classification of Diseases, 9th Revision, diagnosis of co-morbidities (21), or patient self-report (11). The eight psychometric tools used were all produced in the 1900s. Two were diagnostic tools (the Diagnostic and Statistical Manual of Mental Disorders, 4th edition and the Primary Care Evaluation of Mental Disorder) (21,23) and six were screening tools. Most have good reliability and validity, but they have varying specificity and sensitivity in different populations with different time frames (*Table S3*). The Diagnostic and Statistical Manual of Mental Disorders, 4th edition, is the standard classification of mental disorders used by mental health professionals for patient diagnosis and treatment in the United States and is widely used as the criterion standard in validity studies for many other psychometric scales (21,24,25). The Primary Care Evaluation of Mental Disorder is the origin of several other psychometric scales (21,27,28). It is composed of a one-page patient questionnaire and a 12-page clinician evaluation guide. The patient questionnaire should be completed by the patient before seeing the doctor, and the clinician evaluation guide is a structured interview that the physician uses to follow up on positive responses on the patient questionnaire (29).

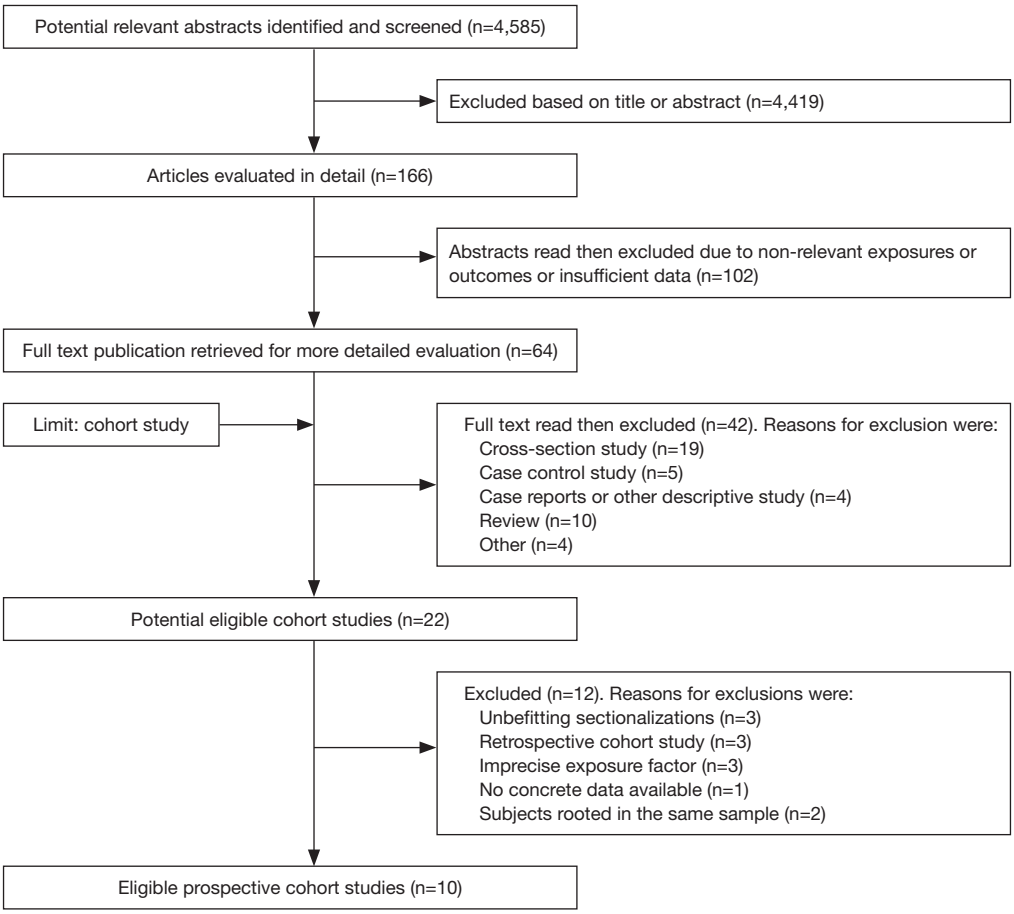

Figure 1 Flow of study identification, inclusion, and exclusion.

Primary outcome

In the study by Schneider *et al.* (24), the impact of panic disorder and depression on hospitalizations and ED visits because of asthma was reported separately. When the data of the effect of depression was included, the pooled estimates showed that asthma patients with co-morbid PD had increased risk of AE (RR =1.07, 95% CI: 1.05–1.10, P<0.001, I^2=38.9%, Q=18.01, P=0.081; RR_{adj} =1.06, 95% CI: 1.04–1.09, P<0.001, I^2=0.0%, Q=3.52, P=0.940; *Figure 2* and *Table 1*), and when the data about the effect of panic disorder was included instead, the result maintained the same (RR =1.11, 95% CI: 1.05–1.17, P<0.001, I^2=50.7%, Q=22.33, P=0.022; RR_{adj} =1.06, 95% CI: 1.04–1.09, P<0.001, I^2=0.0%, Q=7.88, P=0.546) (10-12,20-26). Subgroup analyses to investigate the effects of depression and anxiety on AE indicated that depression was associated with a higher risk of AE (RR_{adj} =1.07, 95% CI: 1.04–1.11, P<0.001, I^2=0.0%, Q=2.21, P=0.900) (10,12,20,22,24) but anxiety was not (RR_{adj} =1.23, 95% CI: 0.65–2.30, P=0.525, I^2=65.6%, Q=5.82, P=0.055; *Figure 3*) (21,24,26).

Secondary outcomes

In patients with asthma, PD significantly increased the risk of hospitalizations (RR =1.25, 95% CI: 1.14–1.37, P<0.001, I^2=3.0%, Q=5.15, P=0.397; RR_{adj} =1.22, 95% CI: 1.12–1.34, P<0.001, I^2=12.3%, Q=5.70, P=0.337; *Figure 4* and *Table 1*) (10,20,21,23), unscheduled doctor visits (RR =4.26, 95% CI: 2.52–7.19, P<0.001) (25), and ED visits because of asthma (RR =1.36, 95% CI: 0.86–2.14, P=0.185, I^2=82.0%, Q=22.26, P<0.001; RR_{adj} =1.06, 95% CI: 1.01–1.10, P=0.009, I^2=8.7%, Q=3.29, P=0.350; *Figure 4* and *Table 1*) (10,12,21,22,25), but did not increase the risk of SCS use (RR =1.17, 95% CI: 0.97–1.41, P=0.110; RR_{adj} =1.20, 95% CI: 0.93–1.56, P=0.160) (12).

In the subgroup analysis, depression significantly

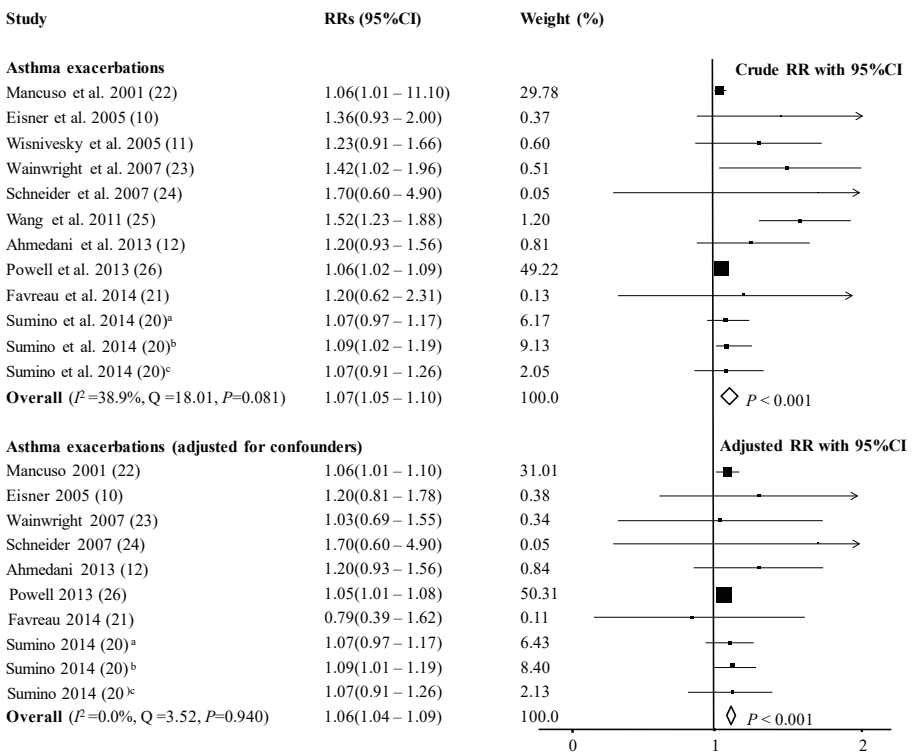

Figure 2 Effects of psychological dysfunction on asthma exacerbations. CI, confidence interval; RR, relative risk; RRs, relative risk estimates. [a,b,c], this study was regarded as three independent studies, separated according to the age of the participants.

Table 1 Overall effects of psychological dysfunction on asthma exacerbations

Outcome	Number of studies	Sample size	Relative risk (95% CI)	Heterogeneity (I^2)	P for heterogeneity
Primary outcome					
Asthma exacerbations	10	31,432	1.06 (1.04–1.09)	0.0%	0.940
Secondary outcomes					
Hospitalizations for asthma	4	28,531	1.22 (1.12–1.34)	12.3%	0.337
ED visits for asthma	5	2,198	1.06 (1.01–1.10)	8.7%	0.350
Unscheduled doctor visits for asthma	1	568	4.26 (2.51–7.19)	NA	NA
SCS use for asthma	1	287	1.20 (0.93–1.56)	NA	NA

CI, confidence interval; ED, emergency department; NA, not available; SCS, systemic corticosteroid.

increased the risk of hospitalizations (RR_{adj} =1.26, 95% CI: 1.07–1.49, P=0.007, I^2=57.7%, Q=9.45, P=0.051) (10,20,24) and ED visits because of asthma (RR_{adj} =1.06, 95% CI: 1.02–1.11, P=0.007, I^2=12.2%, Q=3.42, P=0.332; *Figure 3*) (10,12,22,24). However, anxiety did not significantly increase the risk of hospitalizations (RR_{adj} =1.47, 95% CI: 0.46–4.71, P=0.515, I^2=50.5%, Q=2.02, P=0.156) (21,24) or ED visits because of asthma (RR_{adj} =1.79, 95% CI: 0.31–10.38, P=0.515, I^2=82.3%, Q=5.66, P=0.017; *Figure 3*) (21,24).

Time-dependent response to psychological dysfunction (PD)

For studies with exposure time ≤1 year, the relation between PD and AE was not significant (RR =1.24, 95% CI: 0.96–1.59, P=0.095, I^2=82.8%, Q=11.65, P=0.003) (11,25,26). For studies with exposure time >1 year, <2, and ≥2 years, the relation between PD and AE was significant, but there was

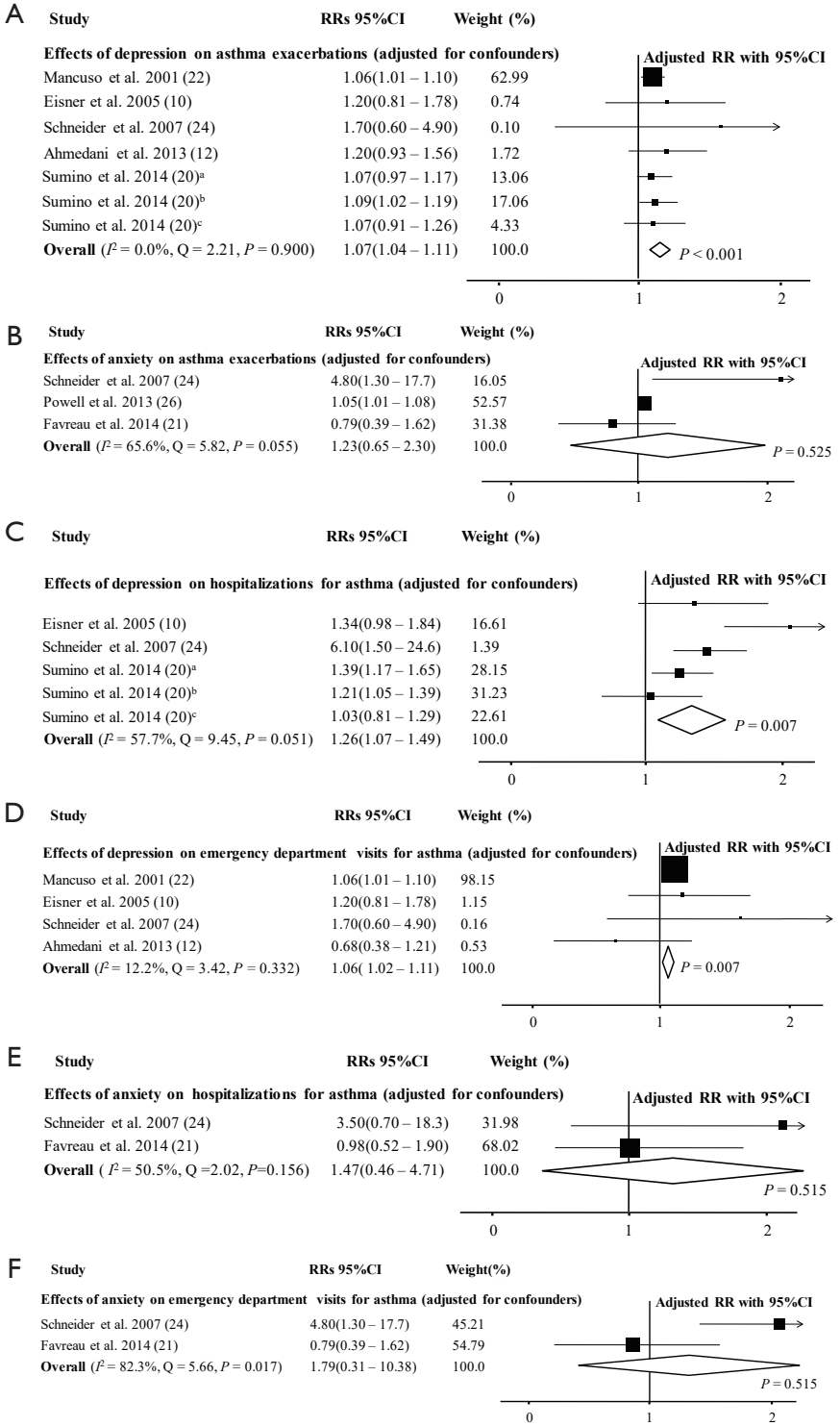

Figure 3 Effects of depression and anxiety on asthma outcomes. (A) Effects of depression on asthma exacerbations; (B) effects of anxiety on asthma exacerbations; (C) effects of depression on hospitalizations because of asthma; (D) effects of depression on emergency department visits because of asthma; (E) effects of anxiety on hospitalizations because of asthma; (F) effects of anxiety on emergency department visits because of asthma. CI, confidence interval; RR, relative risk; RRs, relative risk estimates. [a,b,c], this study was regarded as three independent studies, separated according to the age of the participants.

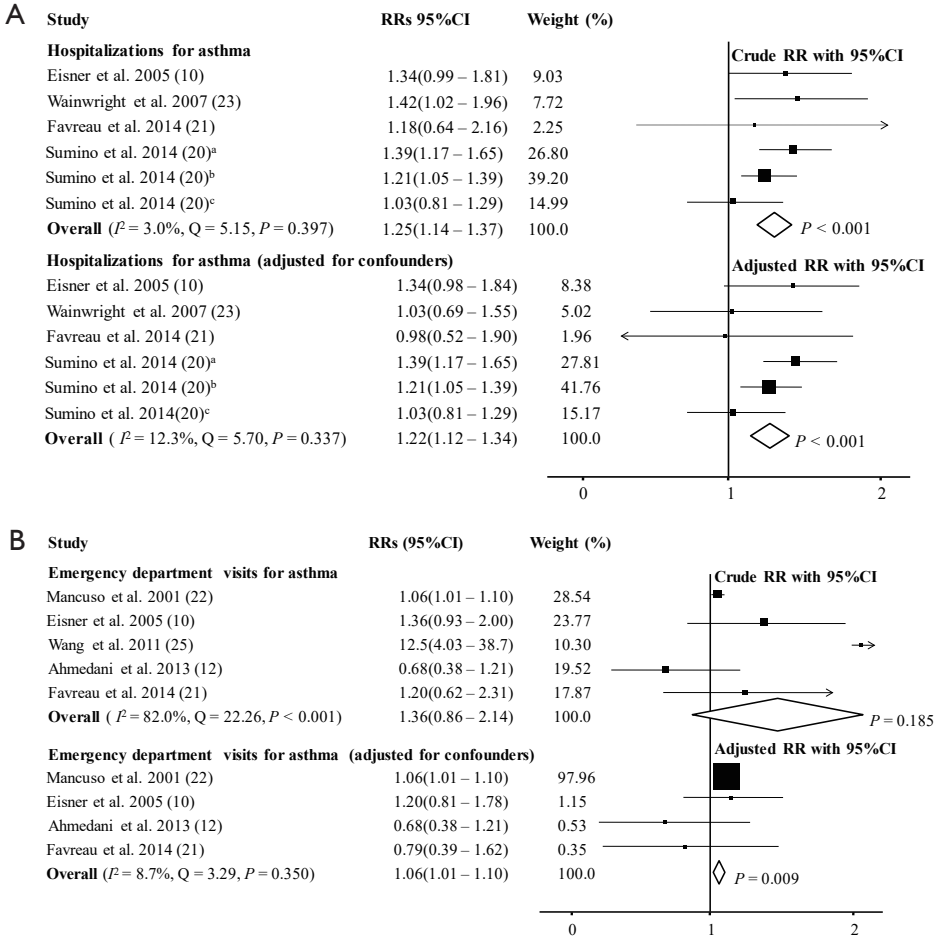

Figure 4 Effects of psychological dysfunction on hospitalizations (A) and emergency department visits (B) because of asthma. CI, confidence interval; RR, relative risk; RRs, relative risk estimates. [a,b,c], this study was regarded as three independent studies, separated according to the age of the participants.

no specific time-dependent response [RR_{adj} =1.07, 95% CI: 1.02–1.11, P=0.003, I^2=0.0%, Q=1.22, P=0.544 (10,12,22) and RR_{adj} =1.08, 95% CI: 1.02–1.14, P=0.011, I^2=0.0%, Q=0.88, P=0.927 (20,21,23), respectively; *Figure 5*].

Sensitivity analyses

The effects of PD on AE were unchanged statistically when the low-quality study by Wainwright *et al.* (23) was excluded (RR =1.07, 95% CI: 1.05–1.10, P<0.001; I^2=37.6%, Q=14.43, P=0.108; RR_{adj} =1.06, 95% CI: 1.04–1.09, P<0.001; I^2=0.0%, Q=2.72, P=0.909) and when the study of pregnant women by Powell *et al.* (26) was excluded (RR =1.09, 95% CI: 1.05–1.12, P<0.001; I^2=44.7%, Q=16.26, P=0.062; RR_{adj} =1.07, 95% CI: 1.03–1.11, P<0.001; I^2=0.0%, Q=2.19, P=0.948).

Quality of evidence

Table 2 shows the quality of evidence for the relation between PD and AE extrapolated according to the recommendations of the Grading of Recommendations Assessment, Development, and Evaluation Working Group. In adults with asthma, the evidence was of low or moderate quality for every asthma outcome.

Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis of prospective cohort studies on

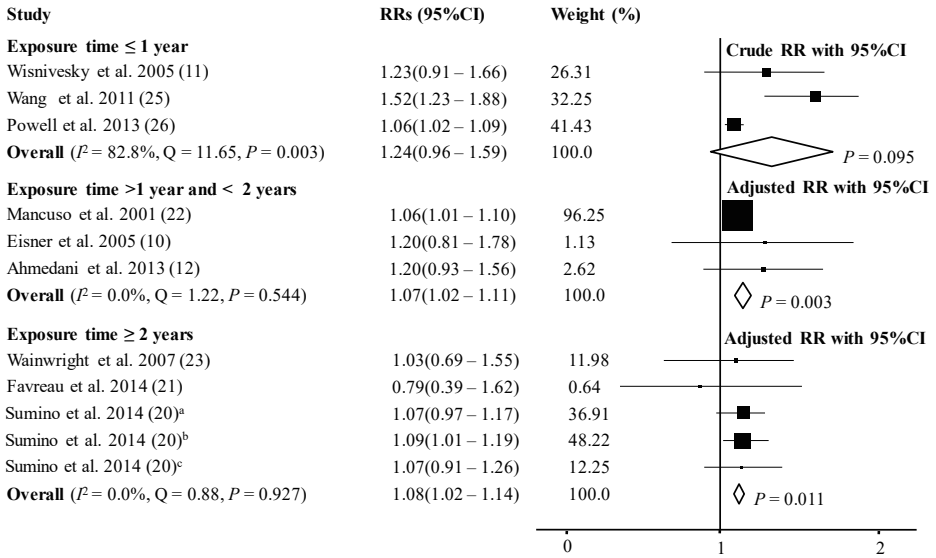

Figure 5 Dose-dependent relation between psychological dysfunction and asthma exacerbations. CI, confidence interval; RR, relative risk; RRs, relative risk estimates. [a,b,c], this study was regarded as three independent studies, separated according to the age of the participants.

Table 2 Evidence quality for each outcome

Asthma outcomes	Quality assessment							Effect		Quality	Importance
	Mean follow-up duration (months)	No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Relative risk (95% CI)	Strong association		
Asthma exacerbation	86.4	6	Observational	No serious	No serious	No serious	No serious	1.06 (1.04–1.09)	No	Moderate	Critical[1]
Hospitalization because of asthma	43.6	4	Observational	No serious	No serious	No serious	No serious	1.22 (1.12–1.34)	No	Moderate	Important
Unscheduled doctor visit because of asthma	12	1	Observational	No serious	No serious	No serious	Serious[2]	4.26 (2.52–7.19)	Yes[3]	Low	Important
ED visit because of asthma	23.6	5	Observational	No serious	No serious	No serious	No serious	1.06 (1.01–1.10)	No	Moderate	Important
SCS use for asthma	15	1	Observational	No serious	No serious	No serious	Serious[4]	1.20 (0.93–1.56)	No	Low	Important

CI, confidence interval; ED, emergency department; SCS, systemic corticosteroid. [1], exacerbations are the most important outcome for patients with asthma (3); [2], sample size =287; [3], the relative risk for an unscheduled visit for asthma was 4.257; [4], the Optimal Information Size criterion was met, the 95% CI overlapped with no effect, and the CI failed to exclude important harm.

the effects of PD on AE. Our results indicated that subjects with co-morbid asthma and PD were at higher risk of AE, presenting as hospitalizations, unscheduled doctor visits, and ED visits because of asthma. The subgroup analysis indicated that depression was significantly associated with higher risk of AE, presenting as hospitalizations, unscheduled doctor visits, and ED visits because of asthma, but anxiety only increased the risk of AE in pregnant women. There was a significant effect of PD on AE only when the exposure time of PD exceeded 1 year.

It should be noted that, in our analysis, anxiety did not have a significant influence on hospitalizations or ED visits because of asthma, and this is inconsistent with our prior study (25). The current analysis on anxiety was limited by a small amount of data, and the effects of anxiety on AE should be further considered.

Contrary to our conclusions, several prior cross-sectional studies showed that probable PD, including anxiety or depression symptoms, was not significantly associated with higher levels of medical services for asthma (10,30,31). However, the cross-sectional study design and possible recall bias may weaken the validity of these cross-sectional studies. The current analysis was based on prospective cohort studies that can measure events in chronological order.

An interesting result in our subgroup analysis was that the influence of PD on AE was only significant when the PD exposure time exceeded one year, and the RR did not increase any more when the exposure time exceeded two years. This implies that there is a cumulative effect of PD on AE over the first year, and that the effect becomes stable when the exposure time exceeds 1 year. This may also indicate that psychological interventions delivered within a time window of one year may be able to prevent the poor asthma outcomes in asthmatic individuals with co-morbid PD.

We found substantial heterogeneity in the outcome of AE. After adjusting for some confounding factors such as age, sex, and race of the participants, glucocorticoid use, and prior exacerbations, the heterogeneity among the studies was reduced (21,22,25). Substantial heterogeneity also existed in the outcome of ED visits because of asthma, and adjustment for confounding factors such as age, sex, race, years of education, smoking, asthma control, inhaled corticosteroid dose, and medication adherence resulted in a significant statistical difference for the relation between PD and ED visits because of asthma (10,12,20,21). We therefore infer that the heterogeneity among the studies was mainly caused by differences in the baseline characteristics, clinical characteristics, asthma medications, and medication adherence of the study participants, and these factors may have a significant impact on ED visits because of asthma.

It should be recognized that, in *Figures 2*,*3*, the studies by Mancuso *et al.* (22) and Powell *et al.* (26) had much larger weight than the study by Sumino *et al.* (20), which included the largest sample size. The weight given to each study in the meta-analysis was determined using the inverse of the variance of the effect estimate (32). As a general rule, if the variance of the effect estimate is the decisive factor for the weight given to a study, studies with a larger sample size will have a larger weight than studies with a smaller sample size, as they typically have smaller variance. However, perhaps because of large variation in the characteristics of the participants in the study by Sumino *et al.*, including asthma severity, asthma control level, and the presence of severe co-morbidities, this study had large variance (95% CI) in the effect estimate even though it had the largest sample size. As a result, a small weight was given to this study in the meta-analysis.

The mechanism underlying the interactions between PD and asthma or asthma outcomes is not well understood. In asthma patients, PD, including depression and anxiety, may reduce self-esteem, decrease internal feelings of control, and ultimately undermine the self-efficacy of asthma control (33). This may explain why patients with PD have reduced asthma-related emotional functioning and response to stimuli and have more difficulty dealing with their disease. This could lead to further activity limitations and non-adherence to medicines, which then results in poor asthma outcomes. Furthermore, in our recently published magnetic resonance imaging and voxel-based morphometry study, we reported structural changes in the right superior temporal gyrus in female asthma patients with depression, and reduced gray matter volume in the right superior temporal gyrus was associated with increased airway hyper-responsiveness (34). This suggests that the right superior temporal gyrus may play a critical role in the link between asthma and depression. This brain region may also play a role in the link between depression and AE. In a study based on a murine model of asthma, Forsythe *et al.* reported that inflammatory cell numbers in bronchoalveolar lavage fluid were significantly increased after long-term stress stimulations, and these changes in airway inflammation might result from the loss of anti-inflammatory response to endogenous corticosterone (35). In humans, the possible exacerbated chronic inflammatory response induced by repeated stress may translate to increased long-term damage of the airway and gradual deterioration in function through

remodeling (35). It is also speculated that depression could directly influence the autonomic nervous system and act on direct respiratory resistance, symptom perception, and AE (36,37). Other studies also report that risk behaviors such as smoking, physical inactivity, obesity, and health-service seeking associated with depression might influence asthma outcomes (38,39). All of these factors may contribute to the association between PD and AE. Goodwin *et al.* suggested that the association between PD and asthma may reflect the effects of common factors associated with both asthma and PD, rather than a direct causal link (40). Further studies are needed to clarify the specific mechanisms contributing to these associations.

Our analysis indicated that PD was significantly associated with adverse asthma outcomes. We therefore have reason to believe that psychological intervention may be an effective therapeutic measure for asthmatic patients with co-morbid PD. A systematic review did not support the effectiveness of psychological interventions for subjects with asthma (13,14); however, the psychological interventions were varied, did not have a clear theoretical underpinning, and were always used in addition to pharmacological treatments rather than as an alternative (13). Additionally, psychological co-morbidity is difficult to characterize and often not diagnosed (14), and it was often difficult to discern whether the aim of a psychological intervention was for general adjustment to asthma or for a psychological co-morbidity, because no detailed descriptions of the need for the psychological treatment were provided (14). All of these factors made it difficult for the review to make firm conclusions and any results must be viewed with caution.

Several limitations of our study should be addressed. Firstly, the definitions of PD were not identical in the studies included in our analysis. Eight different tools with different time frames were used. Nevertheless, most of the tools have high sensitivity and specificity and good reliability and validity when compared with other criterion standards, and there is evidence that the psychological status of patients with stable asthma remains clinically stable over a 5-year period (41). Anxiety and depression are common co-morbid psychological disorders and it was difficult to identify groups of patients presenting with only anxiety or only depression clearly. Secondly, the definitions of AE were also not consistent in the studies included in our analysis. To address this, we referred to the report by the American Thoracic Society and European Respiratory Society and adopted secondary outcomes to accurately describe AE (3). Thirdly, of the studies included in our analysis, none adjusted for the severity of asthma, only one adjusted for asthma control level (12), and only one adjusted for prior AE (21) despite it being widely recognized that all of these factors are significantly associated with further AE (2). Fourthly, the studies included in our analysis reported different measures of RRs, such as odds ratio, hazard ratio, risk ratio and incidence rate ratio. The data were directly pooled as RR with 95%CI, which is typically reported in similar studies (42,43).

Conclusions

Our meta-analysis based on prospective cohort studies strongly suggests that PD is associated with significantly increased risk of AE presenting as hospitalizations, unscheduled doctor visits, and ED visits because of asthma. Depression had a stronger influence on the outcomes than anxiety. PD only showed a significant association with AE when the PD exposure time exceeded 1 year. These findings support the adverse impact of co-morbid PD on AE and suggest the existence of an asthma psycho-phenotype. Physicians should consider the psychological state of the patient before establishing treatment and intervention regimens. Further studies are needed to clarify the mechanisms underlying the interaction between PD and AE.

Acknowledgements

Funding: This study was partly supported by the National Natural Science Foundation of China (No. 81370122), Ministry of Science and Technology of China (2012BAI05B02), Youth Science Funding of Sichuan University (No. 2011SCU04B17), and Program for New Century Excellent Talents in University (No. NCET-12-0380).

Footnote

Conflicts of Interest: Dr. G Wang received funding from the China AstraZeneca Lung Foundation in 2013. The other authors have no conflicts of interest to declare.

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Cite this article as: Zhang L, Zhang X, Zheng J, Wang L, Zhang HP, Wang L, Wang G. Co-morbid psychological dysfunction is associated with a higher risk of asthma exacerbations: a systematic review and meta-analysis. J Thorac Dis 2016;8(6):1257-1268. doi: 10.21037/jtd.2016.04.68

Supplementary

Methods

Details of the search strategy and article screening

Electronic databases were searched using the following key words based on previous studies and MeSH database of PubMed: (asthma OR wheezing) AND (emotion* OR behavior* OR psych* OR mental* OR anxi* OR depress* OR distress* OR panic* OR personality) AND [(exacerbat* OR attack OR episode OR acute) OR (glucocorticoid OR corticosteroid OR cortin OR steroid) OR emergency OR (hospitalization OR admission) OR (unplanned OR unscheduled)] (1,44). All titles and abstracts identified by this search were assessed independently by two reviewers. The full text of each article that potentially met the inclusion criteria was obtained for further assessment. The reference lists of all relevant reviews and potentially relevant articles were also searched. Search results were not restricted to a particular language.

Details of the extracted data and quality assessment

The data extracted from each article included the elementary characteristics of the study (first author, year of publication, study population, sample size, follow-up duration, and follow-up loss), baseline characteristics of the participators (age at recruitment, gender, ethnicity, socioeconomic status, and smoking history), and clinical characteristics (diagnosis, duration, severity, lung function, asthma control status, asthma medications, adherence to treatment, and exacerbations during the previous year) (45,46).

Study quality was assessed and scored independently by two reviewers (LZ and XZ) using the Newcastle-Ottawa Quality Assessment Scale (47). The Newcastle-Ottawa Quality Assessment Scale is a validated tool for assessing the quality of non-randomized studies, including cohort studies. It consists of three parts (study selection, compatibility, and study outcomes) and has a maximum score of nine. Any problems or disagreements between the two reviewers were solved by a third reviewer (GW).

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Table S1 Characteristics of included studies

Study	N	Female (%)	Age, mean (SD) years	Race	Method of asthma diagnosis	Follow-up period (months)	NOS score	Asthma severity	Asthma control	Number of exacerbations in the last year, mean (SD)	PD exposure	PD measurement	Psychologist involved	Outcomes	Measurements of outcomes	Risk expression	Confounders included in adjustment
Mancuso *et al.* 2001 (22)	224	83.0	41 [11]	White/Black/Hispanic	ICD-9	23.8	9	Moderate[$]	NA	NA	D	GDS	No	ED visits and any urgent care	Self-report	Partial regression coefficient	Age, sex, and time in study
Eisner *et al.* 2005 (10)	743	69.7	Exposed group 55 [14]; non-exposed group 61 [16]	White	ICD-9	15.6	9	Severity-of-asthma score[&], mean (SD): exposed group 15.4 (4.9); non-exposed group 12.5 (3.9)	NA	Hospitalizations, n (%): 151 (20.3)	D	CES-D	No	Hospitalizations and ED visits	Discharge diagnosis code for asthma	Hazard ratio	Age, sex, race, education, and smoking history
Wisnivesky *et al.* 2005 (11)	170	78.0	49.9 (17.4)	White/Black/Hispanic	ICD-9	6.0	5	NA	NA	ED visits 3.7 (6.1); hospitalizations 1.5 (2.9)	D	Self-report	No	Hospitalizations or ED visits	NA	Number of subjects	NA
Wainwright *et al.* 2007 (23)	1,477	60.5	NA	White	ICD-10	86.4	7	NA	NA	NA	D or A	DSM-IV	No	Hospitalizations	ICD-10 code for asthma	Odds ratio	Age, sex, social class, deprivation, physical functional health, and obesity
Schneider *et al.* 2008 (24)	256	61.7	56.3 (16.4)	White	Doctor-diagnosed	12.0	9	Intermittent 23.0%[¥]; mild persistent 24.6%; moderate persistent 35.9%; severe persistent 7.4%	NA	NA	A and D	PHQ and DSM-IV	No	Hospitalizations and ED visits	Self-report	Risk ratio	Age, sex, medication adherence guideline, and smoking
Wang *et al.* 2011 (25)	290	44.1	Exposed group[1] 37.0 (11.7); exposed group[2] 43.1 (11.8); non-exposed group 35.9 (11.7)	Yellow	GINA	12.0	9	Intermittent 25.2%[¨]; mild persistent 47.6%; moderate persistent 16.9%; severe persistent 10.0%	ACT score, mean (SD): exposed group[1] 17.9 (2.6); exposed group[2] 16.6 (3.3); non-exposed group 19.0 (3.1)	NA	A and D	HADS	No	Exacerbations, hospitalizations, unscheduled visits, and ED visits	Self-report	Number of subjects	NA
Ahmedani *et al.* 2013 (12)	568	72.0	45.2 (9.2)	White/Black/African/ American	ICD-9	15.0	8	NA	ACT controlled 64.5%	NA	D	Two-item depression case finding	No	ED visits and oral steroid use	NA	Number of subjects and risk ratio	Age, sex, race, study group, asthma control, and adherence to inhaled corticosteroids
Powell *et al.* 2013 (26)	175*	100	28.5 (5.4); between 12 and 20 weeks of gestation	White	Doctor-diagnosed	Gestation period	7	NA	ACQ score, median (IQR) 0.85 (0.29, 1.14)	NA	A	STAI-6	No	Exacerbations	Medical records and self-report	Odds ratio	NA
Favreau *et al.* 2014 (21)	646	32.5	Exposed group 46 (13.2); non-exposed group 49 (14.2)	White	Doctor-diagnosed	51.6	9	NA	ACQ score, mean (SD): exposed group 1.9 (1.2); non-exposed group 1.5 (1.0)	ED visits: exposed group 0.3 (0.4); non-exposed group 0.2 (0.4). Hospitalizations: exposed group 0.1 (0.3); non-exposed group 0.1 (0.3)	A	PRIME-MD	No	Hospitalizations and ED visits	Self-report	Risk ratio	Age, sex, year of education, inhaled corticosteroid dose, pack-year, major depression, and follow-up time
Sumino *et al.* 2014 (20)[a]	8,364	31.3	37.4 (6.3)	White/Black/Hispanic	ICD-9	38.4	9	NA	NA	NA	D	ICD-9	Yes	Exacerbations and hospitalizations	VA database and CMMS data	Risk ratio	Exacerbations outcome: race, prior exacerbations, glucocorticoids, lipid-lowering agents, PPIs, and NSAIDs. Hospitalizations outcome: race, prior exacerbations, prior hospitalizations, glucocorticoids, glucocorticoids, calcium channel blockers, nitrates, diuretics, and PPIs
Sumino *et al.* 2014 (20)[b]	11,823	15.5	54.4 (5.1)	White/Black/Hispanic	ICD-9	34.8	9	NA	NA	NA	D	ICD-9	Yes	Exacerbations and hospitalizations	VA database and CMMS data	Risk ratio	Exacerbations outcome: race, prior exacerbations, primary care visits, glucocorticoids, anti-arrhythmias, lipid-lowering agents, diuretics, and NSAIDs. Hospitalizations outcome: race, prior exacerbations, primary care visits, glucocorticoids, digoxin, nitrates, diuretics, histamine antagonists, and PPIs
Sumino *et al.* 2014 (20)[c]	5,788	4.4	73.6 (5.7)	White/Black/Hispanic	ICD-9	34.8	9	NA	NA	NA	D	ICD-9	Yes	Exacerbations and hospitalizations	VA database and CMMS data	Risk ratio	Exacerbations outcome: Race, prior exacerbations, glucocorticoids, diuretics, and NSAIDs. Hospitalizations outcome: race, prior exacerbations, glucocorticoids, nitrates, anti-arrhythmias, diuretics, and PPIs

Abbreviations: A, anxiety; ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test scale; CES-D, Center for Epidemiologic Studies Depression Scale; CMMS, Centers for Medicare and Medicaid Services; D, depression; DSM-IV, Diagnostic and Statistical Manual of Mental Disorder 4th ed.; ED, emergency department; GDS, Geriatric Depression Scale; GINA, Global Initiative for Asthma; HADS, Hospital Anxiety and Depression Scale; ICD-9, International Classification of Diseases, 9th Revision; ICD-10, International Classification of Diseases, 10th Revision; IQR, Inter-quartile range; NA, not available; NOS, Newcastle-Ottawa Quality Assessment Scale; NSAIDs, Non-Steroidal Antiinflammatory Drugs; PHQ, Patient Health Questionnaire; PD, psychological dysfunction; PPIs, proton pump inhibitors; PRIME-MD, Primary Care Evaluation of Mental Disorder; STAI-6, Six-Item Short-Form State Trait Anxiety Inventory; VA, veterans affairs. Exposed group[1], anxiety or depression; Exposed group[2], anxiety and depression; *, participants were pregnant women with asthma; [$], patients under treatment require medicines daily, but not oral corticosteroids (48); [&], severity-of-asthma score was based on the frequency of current asthma symptoms, asthma medicines and intubation and the possible total scores range from 0 to 28, with higher scores representing more severe asthma (49-51); [¥], asthma severity was evaluated according to the international levels of asthma severity (52); [¨], asthma severity was defined according to Global Initiative for Asthma (53); [a,b,c], this study was regarded as three independent studies, separated according to the age of the participants.

Table S2 The methodological quality of included studies

Study	Selection				Compatibility	Outcome			Total score
	S-1	S-2	S-3	S-4		O-1	O-2	O-3	
Mancuso *et al.* 2001 (22)	1	1	1	1	2	1	1	1	9
Eisner *et al.* 2005 (10)	1	1	1	1	2	1	1	1	9
Wisnivesky *et al.* 2005 (11)	1	1	0	1	0	1	0	1	5
Wainwright *et al.* 2007 (23)	1	1	1	1	0	1	1	1	7
Schneider *et al.* 2008 (24)	1	1	1	1	2	1	1	1	9
Wang *et al.* 2011 (25)	1	1	1	1	2	1	1	1	9
Ahmedani *et al.* 2013 (12)	1	1	1	1	2	1	1	0	8
Powell *et al.* 2013 (26)	0	1	1	1	2	1	0	1	7
Favreau *et al.* 2014 (21)	1	1	1	1	2	1	1	1	9
Sumino *et al.* 2014 (20)	1	1	1	1	2	1	1	1	9

S-1, representativeness of the exposed cohort (score 0–1); S-2, selection of the non-exposed cohort (score 0–1); S-3, ascertainment of exposure (score 0–1); S-4, demonstration that the outcome of interest was not present at start of study (score 0–1); compatibility: study controls for relevant confounders (score 0–2); O-1, assessment of outcome (score 0–1); O-2, was follow-up long enough for outcomes to occur? [defined as 1 year (54); score 0–1]; O-3, adequacy of follow-up of cohorts (score 0–1).

Table S3 Characteristics and diagnostic accuracy of psychometric tools

Tool	Developed year	Item source	Population	Target psychological dysfunction	Time frame	Score range or number of items	Cut-point	Specificity (%)	Sensitivity (%)	Reliability and validity	Criterion standard	Diagnostic or screening
GDS (22,27)	1982	A 100-item large-scale	Older adults	Depression	One week	0–30	11	95	84	Yes	The 100-item large-scale	Screening
CES-D (10,27)	1972	BDI, SDS, RDS, MMPI	General population	Depression	One week	0–60	16	68.2–99	73–100	Yes	Raskin scale	Screening
DSM-IV (23,55,56)	1994	NA	General population	Psychotic disorders	NA	NA	NA	NA	NA	Yes	NA	Diagnostic
PHQ (24,27,28,57)	Mid-1900s	PRIME-MD	Primary care setting	Depression	Two weeks	Nine items	According to the answers*	90	83	Yes	MHP interview and DSM-IV	Screening
				Panic disorder	Past month	Five items	All answered positively	91	86			
HADS (25,27,28,58,59)	1983	NA	Clinical population	Depression	One week	0–21	8	80	80	Yes	GHQ and DSM-IV	Screening
				Anxiety	One week	0–21	8	80	80			
Two-item Depression Case Finding (12,60)	1997	PRIME-MD	Primary care setting	Depression	One month	Two items	Any affirmative answer	57	96	Yes	QDIS	Screening
STAI-6 (26,27,61)	1992	STAI	Adult population	Anxiety	NA	20–80	NA	NA	NA	Yes	STAI	Screening
PRIME-MD (21,29,62)	1994	NA	General population and primary care setting	Panic disorder	One month	NA	NA	99	57	Yes	DSM-IV and DSM-III-R	Diagnostic
				Major depression			NA	98	57			

Abbreviations: BDI, Beck Depression Inventory; CES-D, Center for Epidemiologic Studies Depression Scale; DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition; DSM-IV, Diagnostic and Statistical Manual of Mental Disorder 4th ed.; GDS, Geriatric Depression Scale; GHQ, General Health Questionnaire; HADS, Hospital Anxiety and Depression Scale; MHP interview, Mental Health Professional interview; MMPI, Minnesota Multiphasic Personality Inventory; NA, not available; PHQ, Patient Health Questionnaire; PRIME-MD, Primary Care Evaluation of Mental Disorder; QDIS, Quick National Institute of Mental Health Diagnostic Interview Schedule; RDS, Raskin's Depression Scale; SDS, Zung's Self-rating Depression Scale; STAI, State Trait Anxiety Inventory; STAI-6, Six-Item Short-Form State Trait Anxiety Inventory; Yes, yes, this is reported. *, major depression if five or more questions are answered with 'symptoms on more than half of the days'; minor depression if two, three, or four questions are answered with 'symptoms on more than half of the days'.