



Review

Comorbidity between depression and asthma via immune-inflammatory pathways: A meta-analysis

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ABSTRACT

Background: Depression is often present in patients with asthma and vice versa. In this review, we aimed to summarize reports on the comorbidity of depression and asthma, and to seek evidence that the biological mechanisms of allergy may have an important role linking asthma and depression.

Method: To explore the relationship and pathway underpinning this comorbidity, we reviewed medical articles and undertook a meta-analysis of epidemiological studies on (i) incidence of asthma in patients with depression; (ii) morbidity of depression in patients with asthma; (iii) concentration of cytokines in depressed subjects.

Results: High level of comorbidity of asthma and depression was consistently demonstrated in 10 studies of patients with asthma and four studies of patients with depression. In search of biological connection of the two illnesses, thirty-eight studies were included for Meta-analyses examining differences in allergy related cytokines between patients with depression and non-depressive subjects. In people with depression, concentration of monocytes related cytokines such as IL-1 (1.56 ng/mL, 95% CI: 0.00–3.12, $p=0.05$) was significantly higher than that in non-depressive control subjects. At the same time, some other inflammatory factors including IL-4 (5.77 pg/mL, 95% CI: 2.34–9.21, $p=0.00010$), IL-6 (1.44 ng/mL, 95% CI: 1.05–1.82, $p < 0.00001$) and TNF- α (3.01 ng/mL, 95% CI: 1.76–4.26, $p < 0.00001$) were extremely significantly higher in depressed people compared with the controls. There was no significant differences of the T cell related cytokine levels, IFN- γ (–0.16 ng/mL, 95% CI: –0.85–7.73, $p=0.97$), accompanied with IL-10 (0.67 ng/mL, 95% CI: –0.84–2.18, $p=0.38$) between depressive and non-depressive groups.

Conclusions: The varying levels of certain cytokines play an important role in arousing and remitting asthma and depression. That suggests inflammatory response could be a common pathway adjusting both depression and asthma.

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1. Introduction

Asthma is a common chronic disease affecting >300 million people worldwide (Bateman et al., 2008). It has been reported that about 7–10% children and 5% adults suffers from asthma at various severity (Woolcock and Peat 1997). Asthma is a complex and multifaceted illness characterized mainly by bronchial hypersensitivity and airway inflammation, resulting in bronchoconstriction, airway remodeling and airway obstruction (Melissa and Richard 2009). It is known that several types of cells (such as macrophages, mast cells, monocytes, neutrophils, and natural killer cells) and mediators, especially Th1 and Th2 cytokines, play important parts in the inflammatory response. If individuals are exposed to an allergen or irritant, the balance between Th1 and Th2 cells is to break and certain types of inflammatory cells (e.g., mast cells) are activated (Pleung et al., 1988), leading to the over-expression of Th2 related cytokines and reduction of Th1 related cytokines. Cytokines released from activated pulmonary mast cells can act locally on to the airway surface (e.g., mucosa), bronchial smooth muscles, and vessels to cause bronchoconstriction or airway stenosis. Bronchoconstriction would lead to breathlessness (Pleung et al., 1988).

Depression is the most common mental disorder, and is increasingly recognized as a public health and social problem worldwide. A total of 4–20% of the general population would suffer this disorder some time during their lifetime (Bakish 2001). Depression causes significant physical and psychological difficulties, and affects people's thoughts, emotions, self-awareness, interpersonal relationships, work productivity, physical functioning and overall life satisfaction (Murray and Lopez 1996). Numerous studies have indicated that depression as well other mentally ill conditions are closely associated with physical status (Richardson et al., 2006). In the early 1990s, depression was reported for the first time being an illness characterized by cell-mediated immune activation (Maes, 1993). This observation developed into a novel hypothesis that inflammation and cell-mediated immune activation may be key factors in depression. That inflammatory triggers "neuraxes" conveying metabolic, gastro-intestinal and cardiovascular information to brain and subsequently drive depressive-like behaviors (Maes et al., 1993). Recent evidence suggests that depression is an inflammatory disorder because of the increased production of interleukin (IL)-1 β , IL-6 and tumor necrosis factor (TNF)- α in people with depression (Maes, 2011; Dowlati et al., 2010).

Evidence has shown that individuals with asthma have twice the risk of developing depressive symptoms as compared with those who do not have asthma (Melissa and Richard 2009). Psychological stress and negative emotions can provoke the increase of inflammatory markers (Maes, 1993), and that remission from depression is associated with improvement in asthma symptoms (Loerbroks et al., 2010). Considering the role of inflammatory responses in asthma and depression, ongoing inflammation in the allergic process is very likely to be the "bridge" that connects them. Cytokines modulate inflammatory responses, and the processes they govern may be shared by asthma and depression. In the present review, we aimed to summarize reports on the comorbidity of depression and asthma, and to seek evidence that the biological mechanisms of cell-mediated immunity may have an important role linking asthma and depression.

2. Materials and methods

A database search was carried out using MEDLINE by pairing the word, "asthma," with "depression," "psychological disorders," "allergy" and "cytokines". Additional research by screening the bibliographies of articles retrieved in the MEDLINE search was also identified and reviewed. We selected articles that (i) were English-language only; (ii) assessed the prevalence of depression in patients with asthma alone; (iii) assessed the prevalence of asthma in patients with depression; (iv) measured cytokine concentrations in depressed and non-depressed subjects.

Review Manager ver5.1 was used for the meta-analysis. The program computed the weighted mean difference (WMD) and calculated 95% confidence intervals (CIs) under a random-effect model.

3. Results

3.1. Comorbidity of asthma and depression

Several studies have examined the association between major depression and asthma. The four studies shown in Table 1 have suggested that the prevalence of asthma among patients with major depression ranges from 7.6 to 20.2% (Loerbroks et al., 2010; Scott et al., 2007). According to the first cross-national study of the relationship between asthma and mental disorders published in 2007, 18 surveys were carried out among 85,088 people in 17 countries in the Americas (Colombia, Mexico, the United States), Europe (Belgium, France, Germany, Italy, the Netherlands, Spain, Ukraine), the Middle East (Israel, Lebanon), Africa (Nigeria, South Africa), Asia (Japan, separate surveys in Beijing and Shanghai in the People's Republic of China) and the South Pacific (New Zealand) (Scott et al., 2007). It transpires that the age-sex-adjusted odds of mental disorder among persons with asthma relative to those who do not have asthma were 1.6 (95% CI, 1.4–1.8) for depressive disorders. A second large community sample of 4854 people with complete information indicated that the prevalence of asthma increased across one tertile of depression (p for trend < 0.0001). The odds ratios (ORs) were 1.33 (95% CI, 0.96 to 1.83) and 1.96 (95% CI, 1.44 to 2.65) for those in medium and high tertiles, respectively. Likewise, the prevalence of asthma increased significantly by 27% for each increase in the depressive symptoms score (Loerbroks et al., 2010). Between 1990 and 1992, a population-based random sample of 2818 individuals aged > 65 years had been carried out. Through interview and self-reported diagnoses, 231 subjects were identified as having asthma. Furthermore, a significant connection between asthma and depression (19% vs 10%, p < 0.001) was noted (Hurwitz and Morgenstern 1999). The meta-analysis result (Fig. 1) shows that the prevalence of asthma in depressed people is much higher than it in general population with the odds ratio of 3.17 (95% CI 2.82–3.56, p < 0.00001), which suggests the comorbidity of asthma and depression.

To estimate the prevalence of depression in patients with asthma, we collected epidemiologic data from ten recent studies (Alicja et al., 2012; Valença et al., 2006). (Table 2). The meta-analysis result (Fig. 2) clearly shows that asthmatic patients have significant higher risks of having depression than healthy controls

Table 1
Prevalence of asthma and associated ORs in patients with depression.

Study	Structured interview of questionnaire	Diagnosis of asthma	Study population	N% asthma	OR for asthma 95%CI	p
Loerbroks et al. (2010)	Questionnaire	Self-reported	4854	20.2	1.37(1.27–1.47)	< 0.001
Ho and Jones (1999)	Interview	Self-reported	2755	10.1		< 0.001
Hurwitz and Morgenstern (1999)	Interview	Self-reported	6552	7.6	1.84(1.23–2.75)	–
Scott et al. (2007)	Diagnostic interview	Self-report correspond to actual medical records	85,088		1.6(1.4–1.8)	< 0.05

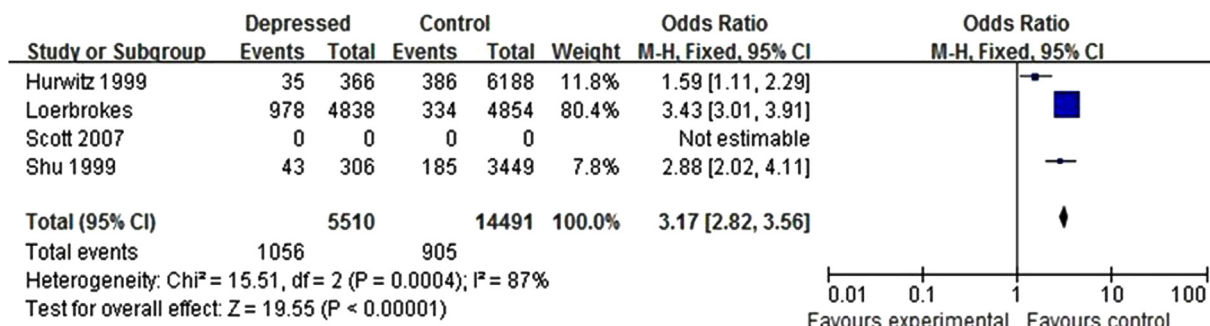


Fig. 1. Meta-analysis of the prevalence of asthma and associated ORs in patients with depression.

Table 2
The prevalence of depression and ORs in patients with asthma.

Study	Structured interview of questionnaire	Diagnosis of asthma	Study population	N% depression	OR for depression 95%CI	p Value
Alicja et al. (2012)	Questionnaire	Physician diagnosis	54	24.1	–	–
Wagena et al. (2004)	Questionnaire	Self-reported	7482	5.9	1.07(0.68–1.68)	–
McCauley et al. (2007)	Phone interviews	Physician diagnosis	767	7.3	1.26	–
Vieira et al. (2011)	Clinical interview	Physician diagnosis	49	–	–	0.72
Yen et al. (2008)	Interview	Physician diagnosis	435	–	4.79(2.41–9.52)	–
Walters et al. (2011)	Database records	Physician diagnosis	1000	2.24	1.59(1.48–1.71)	–
Feldman et al. (2011)	Diagnostic interview	Physician diagnosis	353	7.11	2.52(1.35–4.71)	< 0.01
Prosser et al. (2010)	Interview	Self-reported	18,303	8.1	2.11(1.51–2.93)	–
Prosser et al. (2010)	3 British ministry databases	Diagnosis	2,521,248	24.9	1.44(1.42–1.46)	–
Valença et al. (2006)	Interview	Physician diagnosis	62	24.2	–	–

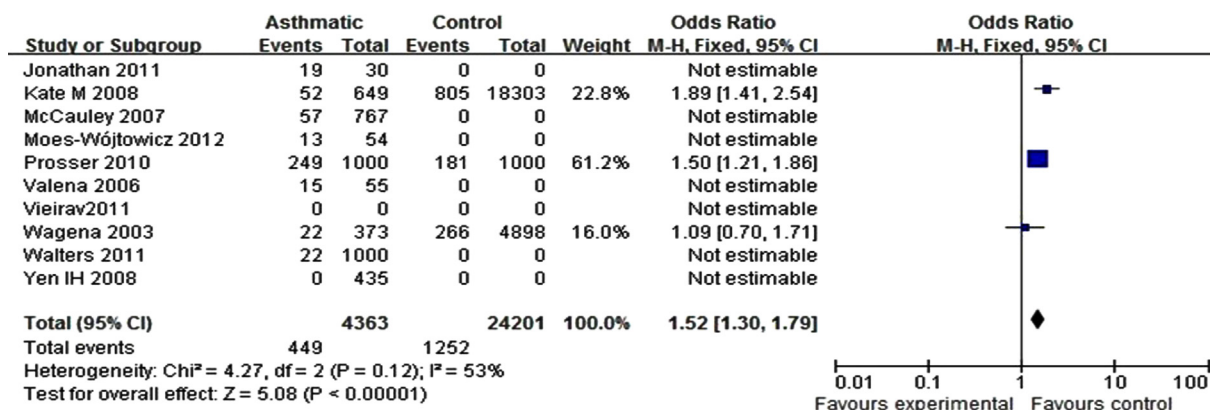


Fig. 2. Meta-analysis of the prevalence of depression and ORs in asthmatics.

($OR = 1.52$; 95% CI, 1.30 to 1.79; $p < 0.00001$). In 2004, cross-sectional data were used in a cohort survey in Denmark. The percentage of depression in 373 asthmatics employees among all the 7482 participants was relatively high ($p < 0.001$) (Wagena et al., 2004). In 2007, phone interviews were conducted in a sample consisting of 767 youths aged from 11 year to 17 years with

asthma; 20 (2.5%) of them had a depressive disorder alone, and 37 (4.8%) had anxiety and depressive disorders (McCauley et al., 2007). There are fewer reports on the impact of mental health problems on the functional status of asthmatic youths. However, asthma functional morbidity was associated significantly with anxiety and depressive symptoms (Vieira et al., 2011). Mental

health factors were more strongly associated with measures of asthma. Thus, exploring psychiatric symptoms in youths with asthma may reduce the functional burden associated with asthma.

3.2. Cytokines and depression

A number of studies have demonstrated that major depression is accompanied with immune responses. It has been reported that the production of several types of cytokines, such as IL-1, IL-6 and TNF- α , can increase in the early stage of activation of the

inflammatory response. To obtain further evidence for the relationship between cytokines and depression, we reviewed 162 studies. 124 studies did not fit the inclusion criteria and were therefore disregarded, the main information of the remaining 38 is listed in Table 3.

A total of 685 participants (327 depressed and 358 non-depressed) from 10 studies were measured. Compared with the control group, the concentration of IL-1 in the depressed group was significantly higher (Fig. 3). The overall weighted mean difference (WMD) was 1.56 ng/mL (95% CI: 0.00–3.12, $p=0.05$).

Table 3

Characteristics of cytokine concentrations in depression.

Study/year	Cytokines included	N (depressed/non-depressed)	Depression diagnosis
Berk et al. (1997)	IL-6	28/21	DSM
Brambilla and Maggioni (1998)	TNF- α /IL-1/IL-6	10/10	DSM
Brambilla et al. (2004)	TNF- α /IL-1 β	11/11	DSM, PRS
Dhabhar et al. (2009)	IL-6/IL-10	12/11	DSM, HAM-D
Eller et al. (2008)	TNF- α /IL-8	100/45	DSM, MADRS
Hernández et al. (2008)	IL-2/IFN- γ /IL-4/IL-10/IL-1 β	31/22	DSM, HAM-D, BDI
Huang and Lee (2007)	TNF- α /IL-1 β /IL-10	42/40	DSM, HAM-D
Jozuka et al. (2003)	IL-2	17/10	DSM, ZDS
Kagaya et al. (2001)	TNF- α /IL-1 β /IL-6	12/12	DSM, HAM-D
Kubera et al. (2000)	IL-6/IL-10	9/10	DSM, HAM-D
Leo et al. (2006)	TNF- α /IL-1 β /IL-6	46/46	DSM, HAM-D
Maes et al. (1995)	IL-6	61/38	DSM, HAM-D
Maes et al. (1990–1991)	IL-6	13/28	DSM, HAM-D
Maes et al. (1997)	IL-6	35/15	DSM, HAM-D
Mikova et al. (2001)	TNF- α /IL-6/IL-8	28/15	DSM, HAM-D
Myint et al. (2005)	IL-4/IFN- γ	18/3	DSM, HAM-D, BPRS
Owen et al. (2001)	TNF- α /IL-6	28/24	DSM, HAM-D
Pavón et al. (2006)	IL-8/IL-10	33/33	DSM, HAM-D
Pike Irwin (2006)	TNF- α /IL-1 β	25/25	DSM, HAM-D
Simon et al. (2008)	IL-6/IL-4/ TNF- α /IL-2	49/49	DSM
Sluzewska et al. (1996)	IL-6	49/15	DSM, HAM-D
Sutcgil et al. (2007)	TNF- α /IL-1 β	23/25	DSM, HAM-D
Tuglu et al. (2003)	IL-6/IL-4/ TNF- α /IL-2	26/17	DSM, HAM-D, BDI
Yang et al. (2007)	IL-8/IL-10	33/23	DSM, HAM-D
Milaneschi et al. (2009)	IL-6	213/778	CES-D
Bremmer et al. (2008)	TNF- α /IL-4/IL-2	184/1101	CES-D
Pan et al. (2008)	TNF- α	312/2977	CES-D
Moorman et al. (2007)	TNF- α /IL-1 β	47/82	DSM
Elomaa et al. (2012)	IFN- γ	58/58	DSM-IV, HAM-D
Gabbay et al. (2009)	IL-1/IFN- γ /IL-4/IL-6	30/15	DSM-IV, CDRS-R
Gabbay et al. (2009)	IL-1/IFN- γ /IL-4/IL-6	30/15	DSM-IV, CDRS-R
Vogelzangs et al. (2012)	IL-6/ TNF- α	1132/494	DSM-IV
Xia et al. (2003)	IL-6/IL-2	15/33	HDRS
Eskandari et al. (2007)	TNF- α /IL-1/IL-6	17/14	DSM-IV
Miller et al. (2002)	IL-6	50/50	DSM-IV
Thomas et al. (2005)	IL-1	19/21	DSM-IV
Moorman et al. (2007)	TNF- α /IL-1/IL-6	47/82	DSM-IV
Gao (2013)	IL-1/IL-10	28/15	SDS

N, number; D, depressed; ND, non-depressed; DSM, Diagnostic and Statistical Manual of Mental Disorders; HAM-D, BDI, Hamilton Depression Scale; MADRS, Montgomery-Asberg Depression Scale; POMS, Profile of Mood States; HDRS, Hamilton Depression Rating Scale; SDS, Self-rating depression scale; IFN, interferon.

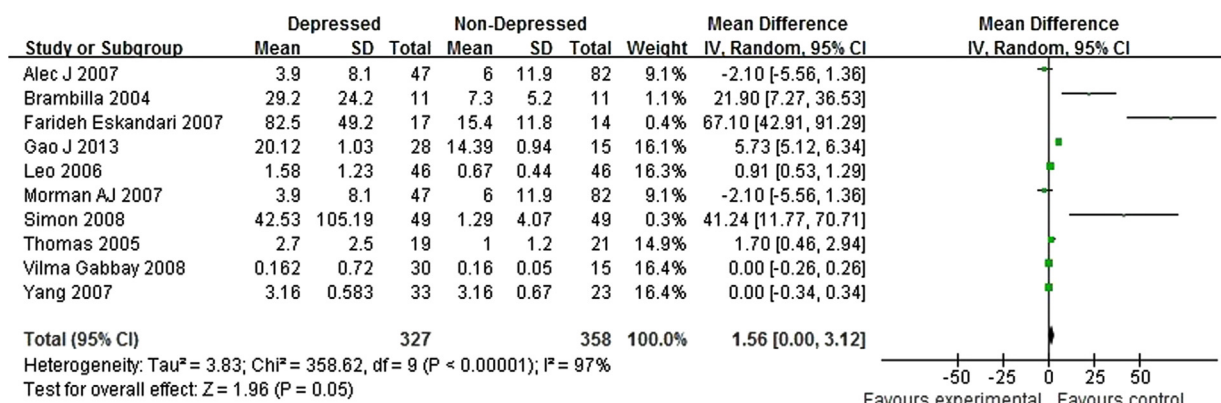


Fig. 3. Meta-analysis of interleukin-1 concentrations.

Measurements were made in 214 depressed and 162 non-depressed subjects (Fig. 4). The concentration of IL-4 was extremely significantly higher in depressed than non-depressed groups. The overall WMD was 5.77 pg/mL (95% CI, 2.34–9.21; $p=0.0010$).

A total of 1840 depressed and 1185 non-depressed participants from 24 studies were involved in the measurement of IL-6

concentration (Fig. 5). The IL-6 concentration of depressed subjects was extremely significantly higher than that in the control group, with an overall WMD of 1.44 ng/mL (95% CI: 1.05–1.82; $p < 0.00001$).

Measurements for IL-10 were taken from 7 studies involving 199 depressed subjects and 215 non-depressed (Fig. 6). The

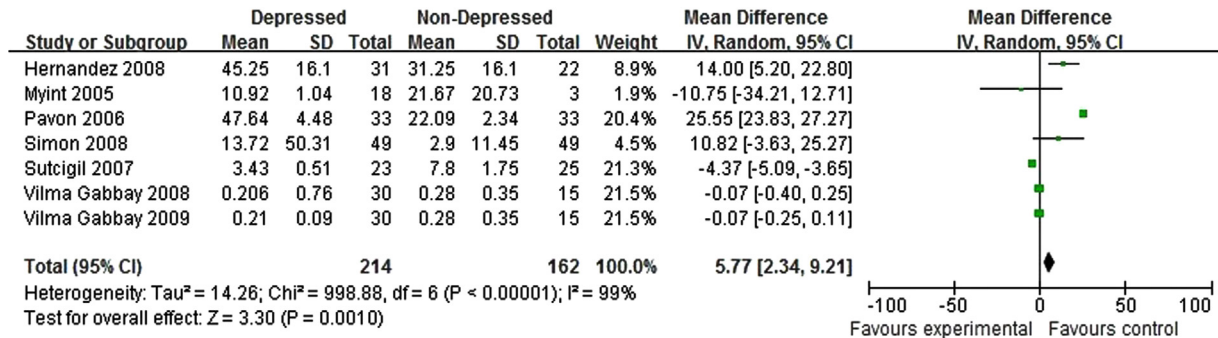


Fig. 4. Meta-analysis of interleukin-4 concentrations.

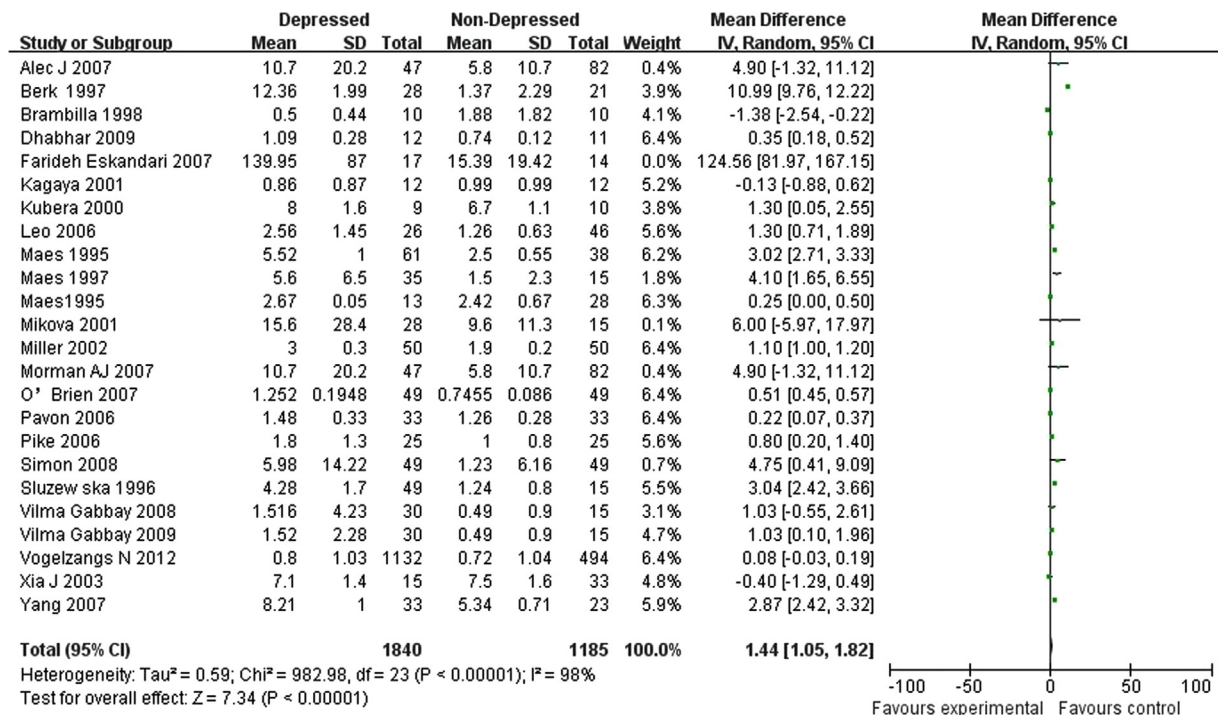


Fig. 5. Meta-analysis of interleukin-6 concentrations.

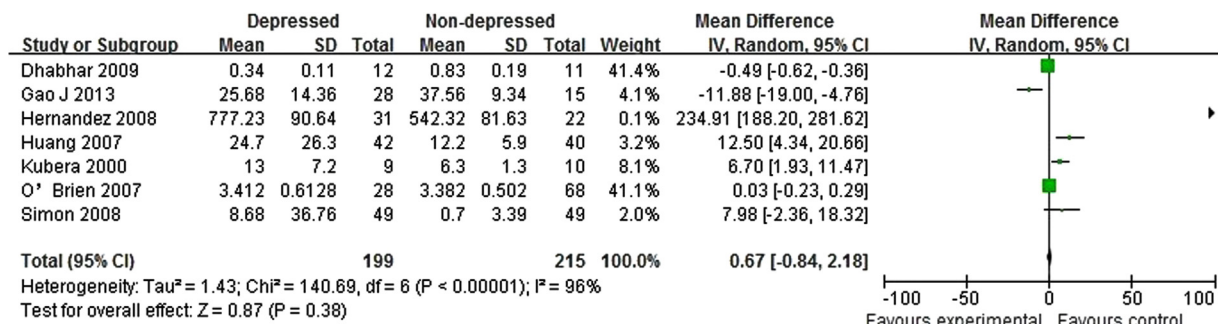
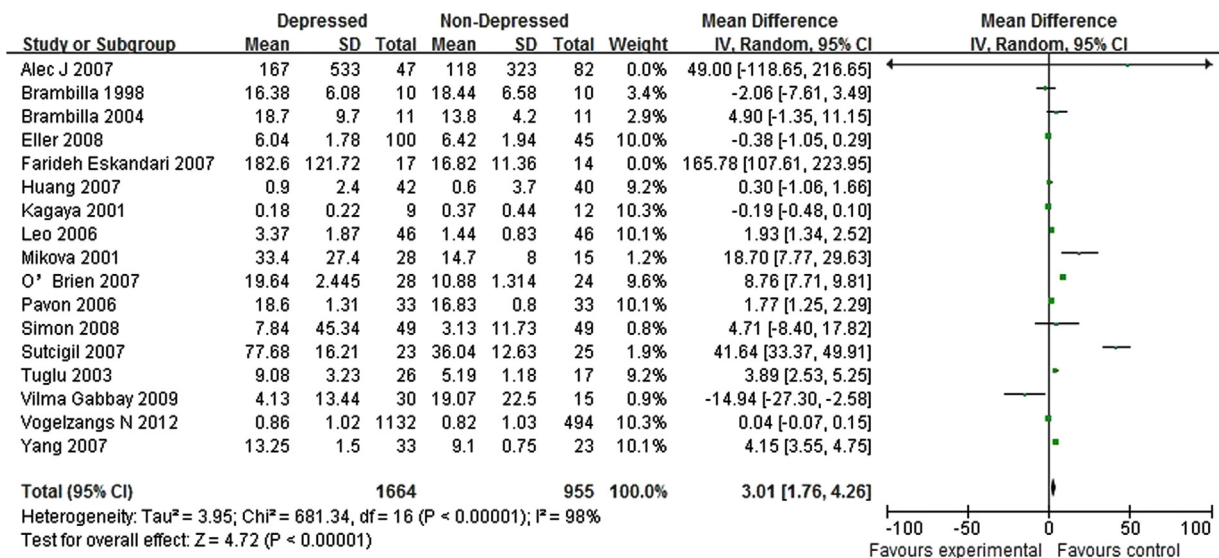
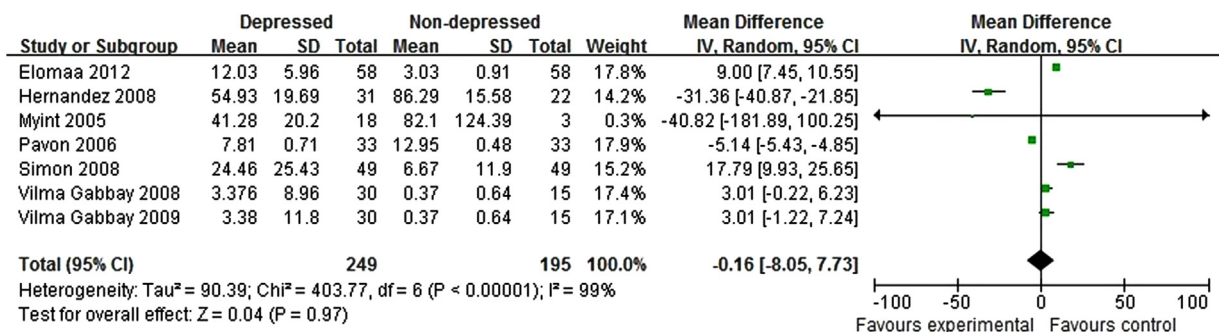


Fig. 6. Meta-analysis of interleukin-10 concentrations.

Fig. 7. Meta-analysis of tumor necrosis factor- α concentrations.Fig. 8. Meta-analysis of interferon- γ concentrations.

concentration of IL-10 in depressed subjects was not significantly different from healthy controls with an overall WMD of 0.67 ng/mL (95% CI, -0.84–2.18; $p = 0.38$).

The measurements of TNF- α concentration were based on 17 studies involving 1664 depressed subjects and 955 healthy controls. A significant difference between these two groups was noted. The concentration of TNF- α was apparently higher in the depressed group with an overall WMD of 3.01 ng/mL (95% CI, 1.76–4.26; $p < 0.00001$) (Fig. 7).

Measuring the IFN- γ concentration of 249 people with depression and 195 healthy individuals, the results showed that the IFN- γ concentration in the depressed group was not significantly different when compared with that in controls. The overall WMD was -0.16 ng/mL (95% CI, -8.05–7.73; $p = 0.97$) (Fig. 8).

This study reported considerably higher concentrations of the cytokines TNF- α , IL-1, IL-4 and IL-6 in depressed patients compared with those in control individuals. This strengthened the theory supporting the comorbidity of asthma and depression. Obvious results supporting the involvement of IL-10 and IFN- γ are lacking.

4. Discussion

Through the meta-analysis described here, we addressed the relationship between depression and asthma. Our results suggested that the allergic reaction is likely to be the key link that connects them. First and foremost, we reviewed 4 epidemiology articles investigating the prevalence of asthma in populations with

depression and 10 medical reports studying the prevalence of depression among people with asthma. The results demonstrated a high comorbidity of the two illnesses, indicating the need for searching possible underlying molecular mechanisms.

Subsequently, we completed a meta-analysis to calculate the difference in concentrations of several cytokines between healthy and depressed subjects: we found significant differences between them. The concentrations of some cytokines in depressed subjects (e.g., IL-1, IL-4, IL-6 and TNF- α) were obviously much higher than in the control group. With respect to IL-10 and IFN- γ , there was no significant difference between them.

Defense cells (such as macrophages, mast cells, monocytes, neutrophils, and natural killer cells) and soluble factors they produce including acute phase proteins, and inflammatory cytokines are key players in the immune system. Sometimes, inflammatory signals can pass through the blood-brain barrier, so cytokines can influence and regulate the nervous system.

Cytokines such as IL-6 and TNF- α can combine exclusively with the specific receptors on neural progenitor cells and reduce the volume of hippocampal gray matter, which is always observed in connection with major depression (Gao, 2013). In addition, cytokines like IL-1 and IL-6 can also bind with specific receptors on hypothalamus and adjust mood by over-activating the hypothalamic-pituitary-adrenal axis which will subsequently lead to the increase levels of Corticotropin-Releasing Hormone, Adrenocorticotrophic Hormone and cortisol in plasma. Furthermore, cytokines IL-1 can probably affect mental disorders by inducing indoleamine-2,3-dioxygenase and indirectly regulate the synthesis and degradation of tryptophan (Yang et al., 2009).

At the same time, the increase of Th-2-like cytokine IL-4 reflects the overaction of Th2 cells and the decrease of Th-1-like cytokine IFN- γ suggests the suppression of Th1 cells. It is acknowledged to compute the IFN- γ /IL-4 concentration ratio and the decreased ratio indicates a shift towards Th-2-like cell-mediated inflammatory response. Thus the balance between Th1/Th2 of human immune system would be broken and generate further allergy reflection even asthma. That explains the abnormal expression of cytokines coexist in depressed and asthmatic patients.

Moreover, oxidative stress could also be a shared pathway that underpins depression and asthma. Oxidative stress may lead to the shift of a Th2-like immune and it has been reported that the antioxidant lever is low while oxidative capacity is high in asthmatic patients (Liao et al., 2004; Wright et al., 2005). The pathogenesis of depression is relevant to the over-activated oxidative system and oxidative damage (Forlenza and Miller 2006). Depression could also suppress the antioxidant functions and aggravate oxidative level (Yamaguchi et al., 2002).

However, limitations of this study may interfere conclusions about causality because of some undetected potentially important factors such as serious or minor medical illnesses, prescription or over-the-counter analgesic use, smoking, and body mass index. Further, some cytokines were very hard to measure in the low concentration ranges, while these publications hadn't reported the analytical CV values obtained in their labs at these very low concentrations.

5. Conclusion

In summary, our analyses have indicated that people with depression is 3.17 times likely to have a comorbidity of asthma compared with that of counterparts without depression, and that patients with asthma is 1.52 times likely to have a comorbid depression compared with those without asthma. At the same time, our results have shown significant differences in concentration of certain cytokines in depressed individuals as compared to those without depression, suggesting that allergy related inflammatory responses may play an important role of linking asthma and depression.

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Conflict of interest

The authors declare that they have no competing interests.

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References

Alicja, M., Piotr, W., Monika, P., Joanna, D.K., 2012. Asthma as a psychosomatic disorder: the causes, scale of the problem, and the association with alexithymia and disease control. *Pneumonol. Alergol. Pol.* 80, 13–19.

Bakish, D., 2001. New standard of depression treatment. Remission and full recovery. *J. Clin. Psychiatry* 62, 5–9.

Bateman, E.D., Hurd, S.S., Barnes, P.J., Bousquet, J., Drazen, J.M., FitzGerald, M., et al., 2008. Global strategy for asthma management and prevention: GINA executive summary. *Eur. Respir. J.* 31, 143–178.

Berk, M., Wade, A.A., Kuschke, R.H., O'Neill-Kerr, A., 1997. Acute phase proteins in major depression. *J. Psychosom. Res.* 43, 529–534.

Brambilla, E., Maggioni, M., 1998. Blood levels of cytokines in elderly patients with major depressive disorder. *Acta Psychiatr. Scand.* 97, 309–313.

Brambilla, F., Monteleone, P., Maj, M., 2004. Interleukin-1beta and tumor necrosis factor-alpha in children with major depressive disorder or dysthymia. *J. Affect. Disord.* 78, 273–277.

Bremner, M.A., Beekman, A.T., Deeg, D.J., Penninx, B.W., Dik, M.G., Hack, C.E., et al., 2008. Inflammatory markers in late-life depression: results from a population-based study. *J. Affect. Disord.* 249–255.

Dhabhar, F.S., Burke, H.M., Epel, E.S., Mellon, S.H., Rosser, R., Reus, V.I., et al., 2009. Low serum IL-10 concentrations and loss of regulatory association between IL-6 and IL-10 in adults with major depression. *J. Psychiatr. Res.* 43, 962–969.

Dowlati, Y., Herrmann, N., Swardfager, W., Liu, H., Sham, L., Reim, E.K., et al., 2010. A meta-analysis of cytokines in major depression. *Biol. Psychiatry* 67, 446–457.

Eller, T., Vasar, V., Shlik, J., 2008. Proinflammatory cytokines and treatment response to escitalopram in major depressive disorder. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 32, 445–450.

Elomaa, A.P., Niskanen, L., Herzig, K.H., Viinamäki, H., Hintikka, J., Koivumaa-Honkanen, H., et al., 2012. Elevated levels of serum IL-5 are associated with an increased likelihood of major depressive disorder. *BMC Psychiatry* 12, 2.

Eskandari, F., Martinez, P.E., Torvik, S., Phillips, T.M., Sternberg, E.M., Mistry, S., et al., 2007. Low bone mass in premenopausal women with depression. *Arch. Intern. Med.* 167, 21.

Feldman, J.M., Acosta, P.E., Canino, G., McQuaid, E.L., Goodwin, R.D., Ortega, A.N., 2011. The role of caregiver major depression in the relationship between anxiety disorders and asthma attacks in island Puerto Rican youth and young adults. *J. Nerv. Ment. Dis.* 199, 313–318.

Forlenza, M.J., Miller, G.E., 2006. Increased serum levels of 8-hydroxy-2'-deoxyguanosine in clinical depression. *Psychosom. Med.* 68, 1–7.

Gabbay, V., Klein, R.G., Guttman, L.E., Babb, J.S., Alonso, C.M., Nishawala, M., et al., 2009. A preliminary study of cytokines in suicidal and nonsuicidal adolescents with major depression. *J. Child Adolesc. Psychopharmacol.* 19, 4.

Gabbay, V., Klein, R.G., Alonso, C.M., Babb, J.S., Nishawala, M., De Jesus, G., et al., 2009. Immune system dysregulation in adolescent major depressive disorder. *J. Affect. Disord.* 115, 177–182.

Gao, J.G., 2013. Correlation between anxiety depression status and cytokines in diarrhea-predominant irritable. *Exp. Ther. Med.* 6, 93–96.

Hernández, M.E., Mendieta, D., Martínez-Fong, D., Loria, F., Moreno, J., Estrada, I., et al., 2008. Variations in circulating cytokine levels during 52 week course of treatment with SSRI for major depressive disorder. *Eur. Neuropsychopharmacol.* 917–924.

Ho, S.F., Jones, D., 1999. Morbidity in older people with self-reported asthma. *Age Ageing* 28, 475–480.

Huang, T.L., Lee, C.T., 2007. T-helper 1/T-helper 2 cytokine imbalance and clinical phenotypes of acute-phase major depression. *Psychiatry Clin. Neurosci.* 61, 415–420.

Hurwitz, E.L., Morgenstern, H., 1999. Cross-sectional associations of asthma, hay fever, and other allergies with major depression and low-back pain among adults aged 20–39 years in the United States. *Am. J. Epidemiol.* 150, 10.

Jozuka, H., Jozuka, E., Takeuchi, S., 2003. Comparison of immunological and endocrinological markers associated with major depression. *J. Int. Med. Res.* 31, 36–41.

Kagaya, A., Kugaya, A., Takebayashi, M., Fukue-Saeki, M., Saeki, T., Yamawaki, S., et al., 2001. Plasma concentrations of interleukin-1beta, interleukin-6, soluble interleukin-2 receptor and tumor necrosis factor alpha of depressed patients in Japan. *Neuropsychobiology* 43, 59–62.

Kubera, M., Kenis, G., Bosmans, E., Zieba, A., Dudek, D., Nowak, G., et al., 2000. Plasma levels of interleukin-6, interleukin-10, and interleukin-1 receptor antagonist in depression: comparison between the acute state and after remission. *Pol. J. Pharmacol.* 52, 237–241.

Leo, R.I., Di Lorenzo, G., Tesaro, M., Razzini, C., Forleo, G.B., Chiricolo, G., et al., 2006. Association between enhanced soluble CD40 ligand and pro-inflammatory and prothrombotic states in major depressive disorder: pilot observations on the effects of selective serotonin reuptake inhibitor therapy. *J. Clin. Psychiatry* 67, 1760–1766.

Liao, M.F., Chen, C.C., Hsu, M.H., 2004. Evaluation of the serum antioxidant status in asthmatic children. *Acta Paediatr. Taiwan* 45, 213–217.

Loerbroeks, A., Apfelbacher, C.J., Bosch, J.A., Stürmer, T., 2010. Depressive symptoms, social support, and risk of adult asthma in a population-based cohort study. *Psychosom. Med.* 72, 309–315.

Maes, M., 1993. A review on the acute phase response in major depression. *Rev. Neurosci.* 4, 407–416.

Maes, M., 2011. Depression is an inflammatory disease, but cell-mediated immune activation is the key components of depression. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 35, 64–75.

Maes, M., Bosmans, E., Suy, E., Vandervorst, C., De Jonckheere, C., Raus, J., 1990–1991. Immune disturbances during major depression: upregulated expression of interleukin-2 receptors. *Neuropsychobiology* 24 (3), 115–120.

Maes, M., Scharpe, S., Meltzer, H.Y., Cosyns, P., 1993. Relationships between increased haptoglobin plasma levels and activation of cell-mediated immunity. *Biol. Psychiatry* 34, 690–701.

Maes, M., Meltzer, H.Y., Bosmans, E., 1995. Increased plasma concentration of interleukin-6, soluble interleukin-2 and transferrin receptor in major depression. *J. Affect. Disord.* 34, 301–309.

Maes, M., Bosmans, E., De Jongh, R., Kenis, G., Vandoollaeghe, E., Neels, H., 1997. Increased serum IL-6 and IL-11 receptor antagonist concentrations in major depression and treatment resistant depression. *Cytokines* 9, 853–858.

- McCauley, E., Katon, W., Russo, J., Richardson, L., Lozano, P., 2007. Impact of anxiety and depression on functional impairment in adolescents with asthma. *Gen. Hosp. Psychiatry* 29, 214–222.
- Melissa, A.R., Richard, J.D., 2009. Affective neural circuitry and mind-body influences in asthma. *Neuroimage* 47, 972–980.
- Mikova, O., Yakimova, R., Bosmans, E., 2001. Increased serum tumor necrosis factor alpha concentrations in major depression and multiple sclerosis. *Eur. Neuropsychopharmacol.* 11, 203–208.
- Milaneschi, Y., Corsi, A.M., Penninx, B.W., Bandinelli, S., Guralnik, J.M., Ferrucci, L., 2009. Interleukin-1 receptor antagonist and incident depressive symptoms over 6 years in older persons: the InCHIANTI study. *Biol. Psychiatry* 65, 973–978.
- Miller, G.E., Stetler, C.A., Carney, R.M., Freedland, K.E., Banks, W.A., 2002. Clinical depression and inflammatory risk markers for coronary heart disease. *Am. J. Cardiol.* 90, 1279–1283.
- Moorman, A.J., Mozaffarian, D., Wilkinson, C.W., Lawler, R.L., McDonald, G.B., Crane, B.A., et al., 2007. In patients with heart failure elevated soluble TNF-receptor 1 is associated with higher risk of depression. *J. Card. Fail.* 13, 9.
- Moorman, A.J., Mozaffarian, D., Wilkinson, C.W., Lawler, R.L., McDonald, G.B., Crane, B.A., et al., 2007. In patients with heart failure elevated soluble TNF-receptor 1 is associated with higher risk of depression. *J. Card. Fail.* 13, 738–743.
- Murray, C.J.L., Lopez, A.D., 1996. *The Global Burden of Disease*. Harvard Univ. Press, Cambridge, MA.
- Myint, A.M., Leonard, B.E., Steinbusch, H.W., Kim, Y.K., 2005. Th1, Th2, and Th3 cytokine alterations in major depression. *J. Affect. Disord.* 88, 167–173.
- Owen, B.M., Eccleston, D., Ferrier, I.N., Young, A.H., 2001. Raised levels of plasma interleukin-1 beta in major and postviral depression. *Acta Psychiatr. Scand.* 103, 226–228.
- Pan, A., Ye, X., Franco, O.H., Li, H., Yu, Z., Wang, J., et al., 2008. The association of depressive symptoms with inflammatory factors and adipokines in middle-aged and older Chinese. *PLoS One* 3 (1), e1392.
- Pavón, L., Sandoval-López, G., Eugenia, H.M., Loria, F., Estrada, I., Pérez, M., et al., 2006. Th2 cytokine response in major depressive disorder patients before treatment. *J. Neuroimmunol.* 172, 156–165.
- Pike, J.L., Irwin, M.R., 2006. Th2 cytokine response in Major Depressive Disorder patients before treatment. *J. Neuroimmunol.* 172, 156–165.
- Pleung, K.B., Flint, K.C., Brostoff, J., Hudspeth, B.N., Johnson, N.M., Lau, H.Y., et al., 1988. Effects of sodium cromoglycate and nedocromil sodium on histamine secretion from human lung mast cells. *Thorax* 43, 756–761.
- Prosser, R., Carleton, B., Smith, A., 2010. The comorbidity burden of the treated asthma patient population in British Columbia. *Chronic Dis. Can.* 30, 2.
- Prosser, R., Carleton, B., Smith, A., 2010. The comorbidity burden of the treated asthma patient population in British Columbia. *Chronic Dis. Can.* 30 (2), 46–55.
- Richardson, L.P., Lozano, P., Russo, J., McCauley, E., Bush, T., Katon, W., 2006. Asthma symptom burden: relationship to asthma severity and anxiety and depression symptoms. *Pediatrics* 118, 1042.
- Scott, K.M., Von Korff, M., Ormel, J., Zhang, M.Y., Bruffaerts, R., Alonso, J., et al., 2007. Mental disorders among adults with asthma: results from the world mental health surveys. *Gen. Hosp. Psychiatry* 29, 123–133.
- Simon, N.M., McNamara, K., Chow, C.W., Maser, R.S., Papakostas, G.I., Pollack, M.H., et al., 2008. A detailed examination of cytokine abnormalities in major Depressive Disorder. *Eur. Neuropsychopharmacol.* 18, 230–233.
- Sluzewska, A., Rybakowski, J., Bosmans, E., Sobieska, M., Berghmans, R., Maes, M., et al., 1996. Indicators of immune activation in major depression. *Psychiatry Res.* 64, 161–167.
- Sutçigil, L., Oktenli, C., Musabak, U., Bozkurt, A., Cansever, A., Uzun, O., et al., 2007. Pro- and anti-inflammatory cytokine balance in major depression: effect of sertraline therapy. *Clin. Dev. Immunol.*, 76396.
- Thomas, A.J., Davis, S., Morris, C., Jackson, E., Harrison, R., O'Brien, J.T., 2005. Increase in interleukin-1 in late-life depression. *Am. J. Psychiatry* 162, 175–177.
- Tuglu, C., Kara, S.H., Caliyurt, O., 2003. Increased serum tumor necrosis factor-alpha levels and treatment response in major depressive disorder. *Psychopharmacology* 170, 429–433.
- Valença, A.M., Falcão, R., Freire, R.C., Nascimento, I., Nascentes, R., Zin, W.A., et al., 2006. The relationship between the severity of asthma and comorbidities with anxiety and depressive disorders. *Rev. Bras. Psiquiatr.* 28 (3), 206–208.
- Vieira, A.A., Santoro, I.L., Dracoulakis, S., Caetano, L.B., Fernandes, A.L., 2011. Anxiety and depression in asthma patients: impact on asthma control. *J. Bras. Pneumol.* 37, 13–18.
- Vogelzangs, N., Duivis, H.E., Beekman, A.T., Kluft, C., Neuteboom, J., Hoogendijk, W., et al., 2012. Association of depressive disorders, depression characteristics and antidepressant medication with inflammation. *Transl. Psychiatry* 2, 79.
- Wagena, E.J., Kant, I., Amelsvoort, L.G., Wouters, E.F., Schayck, C.P., Swaen, G.M., 2004. Risk of depression and anxiety in employees with chronic bronchitis: the modifying effect of cigarette smoking. *Psychosom. Med.* 66, 729–734.
- Walters, P., Schofield, P., Howard, L., Ashworth, M., Tylee, A., 2011. The relationship between asthma and depression in primary care patients: a historical cohort and nested case control study. *PLoS One* 6, 6.
- Woolcock, A.J., Peat, J.K., 1997. Evidence for the increase in asthma worldwide. *Ciba Found. Symp.* 206, 122–134.
- Wright, R.J., Cohen, R.T., Cohen, S., 2005. The impact of stress on the development and expression of atopy. *Curr. Opin. Allergy Clin. Immunol.* 5, 23–29.
- Xia, J., Lin, M., Jin, Z., 2003. Correlations among mood disorder, serum interleukin-2 and interleukin-6 in patients with burning mouth syndrome. *West China J. Stomatol.* 21, 5.
- Yamaguchi, T., Shioji, I., Sugimoto, A., Yamaoka, M., 2002. Psychological stress increases bilirubin metabolites in human urine. *Biochem. Biophys. Res. Commun.* 293, 517–520.
- Yang, K., Xie, G., Zhang, Z., Wang, C., Li, W., Zhou, W., et al., 2007. Levels of serum interleukin (IL)-6, IL-1beta, tumor necrosis factor-alpha and leptin and their correlation in depression. *Aust. N. Z. J. Psychiatry* 41, 266–273.
- Yang, X., Zhou, E.S.H., Qin, P. Mental disorders induced by indoor air pollution via allergic inflammation global strategy for asthma management and prevention: GINA executive summary, Indoor Environment and Health Branch, Chinese Society for Environmental Sciences, 2009-06-05.
- Yen, I.H., Yelin, E., Katz, P., Eisner, M.D., Blanc, P.D., 2008. Impact of perceived neighborhood problems on change in asthma-related health outcomes between baseline and followup. *Health Place* 14, 468–477.