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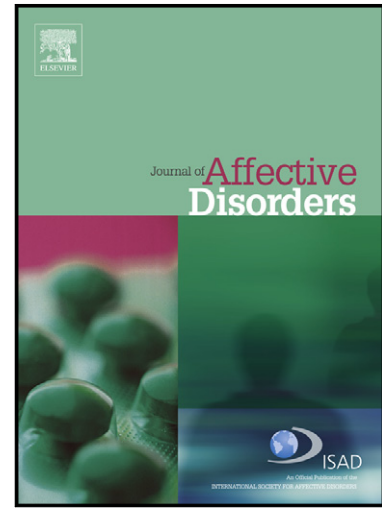
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ATOPIC DISORDERS AND DEPRESSION: FINDINGS FROM A LARGE, POPULATION-BASED STUDY.

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Abstract

Background: Atopy, a common disorder characterized by a sensitivity to allergic reactions, affects a large proportion of the adult population and, as with depression, is associated with immune-inflammatory pathway changes. We sought to determine the role of atopic disorders in depression using data from a randomly-selected, population-based study of men and women.

Methods: Cross-sectional data derived from the Geelong Osteoporosis Study for 942 males and 1,085 females were analysed. Depression [major depressive disorder (MDD), minor depression and dysthymia] was assessed using the Structured Clinical Interview for DSM-IV-TR Research Version, Non-patient edition. Data on medical conditions, including atopic disorders (asthma, hay fever and eczema), smoking status, alcohol consumption, socioeconomic status, and physical activity were documented by self-report. Logistic regression modeling was used to explore the associations between atopic disorders and depression.

Results: Atopic disorders were associated with a 59% increased likelihood of depression [gender and smoking-adjusted odds ratio (OR) 1.50, 95% CI 1.20-1.97]. Sub-group analyses revealed a similar pattern for those with MDD [gender and smoking-adjusted OR 1.54, 95% CI 1.22-1.94]. These associations were independent of socio-demographic characteristics, clinical and lifestyle factors.

Limitations: Reliance on self-report for allergic symptoms and cross-sectional nature of study.

Conclusion: This population-based study provides evidence of the potential contribution of allergic disorders to depression. Further research is required to elucidate the direction of this association and to further explicate its underlying physiology, including immune-inflammation markers.

Keywords: depression; atopy; allergic disorders; immune system; inflammation; cytokines

INTRODUCTION

Atopy is defined as the presence of elevated immunoglobulin E (IgE) levels associated with exposure to allergens commonly occurring in the environment (Johansson et al., 2004). This disorder typically results in the development of allergic symptoms such as eczema, dermatitis, allergic rhinitis/hay fever, allergic conjunctivitis or asthma. Interestingly, its prevalence has increased over the past 20 to 30 years in many parts of the world, including Western nations like the United States and Australia (Jarvis and Burney, 1998); the cause of which is relatively unknown. Historically, atopic disorders have been considered to be “psychosomatic” in origin (Niemeier et al., 2002), but recently the concept of psycho-neuro-immuno-endocrinology, a discipline that studies the close relations between mind, brain, immune and hormonal system, has reformulated perspectives on these relationships (Liezmann et al., 2011) and atopic disorders are now considered to be primarily due to immune dysregulation.

Studies investigating immune system functioning in patients with depression have observed activated inflammatory, cell-mediated immune (CMI) and oxidative and nitrosative stress (O&NS) pathways in these individuals (Maes et al., 2011), (Maes, 2011, Dowlati et al., 2010). This evidence comprises signs of inflammation, such as increased levels of pro-inflammatory cytokines [e.g. interleukin-1 (IL-1), IL-6 and tumor necrosis factor- α (TNF α)], acute phase proteins [e.g. haptoglobin and C-reactive protein (CRP)] and complement factors; CMI and Th1 cell activation, with increased levels of interferon-(IFN) γ and neopterin, lower concentrations of T regulatory (Treg) cells,

oxidative damage to membrane fatty acids and DNA, and nitrosative modifications of proteins (Maes, 1995, Pasco et al., 2010, Maes et al., 2011, Li et al., 2010). Furthermore, the incidence of depression is considerably higher among medically ill patients, particularly in those diseases associated with immune activation (Clarke and Currie, 2009, Sanna et al., 2013), thus providing a rationale for this study.

Antidepressants, such as tricyclic antidepressants and selective serotonin reuptake inhibitors, have specific negative immune-regulatory effects by lowering the production of IFN γ and IL-1 β , and increasing the production of IL-10 and the levels of Treg cells (Maes et al., 1999, Himmerich et al., 2010). Many drugs with anti-inflammatory effects augment the clinical efficacy of antidepressants in the treatment of depression (Maes et al., 2012). For example, TNF α blockers, such as etanercept, may reduce depressive symptoms in patients with psoriasis suffering from depression and in animal models of depression (Tyring et al., 2006, Krugel et al., 2012). In a randomised clinical trial, infliximab a TNF antagonist failed to separate from placebo, although an interaction between higher baseline TNF levels and greater reduction in depression scores with treatment was seen (Raison et al., 2013).

Depression has been linked with several atopic disorders within clinical and some population-based samples of individuals with asthma (Hurwitz and Morgenstern, 1999, Gunn et al., 2012, Afari et al., 2001, Loerbroks et al., 2012, Chun et al., 2008), eczema (Klokk et al., 2010, Yang et al., 2010), dermatitis (Hashiro and Okumura, 1997, Gunn et al., 2012) and allergic rhinitis (Cuffel et al., 1999, Hurwitz and Morgenstern, 1999, Marshall et al., 2002). These comorbidities appear to have an additive negative effect on functional status (Afari et al., 2001) and quality of life (Ford et al., 2003, Slattery et al., 2011, Lu et al., 2013, Goldney et al., 2003, Adams et al., 2004). Depression can compromise treatment adherence (Lehrer et al., 2002) and is thought to influence decision making in self-managed treatment (Adams et al., 2004) in patients with asthma.

Many of the previous studies investigating the relationship between depression and atopic disorders have been limited by an age range (Lu et al., 2013, Timonen et al., 2003, Hurwitz and Morgenstern, 1999, Klok et al., 2010), restricted to clinical settings (Afari et al., 2001, Hashiro and Okumura, 1997), or reliant on self-report inventories to measure depression (Adams et al., 2004, Goldney et al., 2003, Marshall et al., 2002). The purpose of this study was to investigate whether an association exists between a lifetime diagnosis of allergic disorders and history of depression in a population-based sample of adult men and women, using a gold standard psychiatric measure and adjusting for potential confounders.

METHOD

Participants

The Geelong Osteoporosis Study (GOS) (Pasco et al., 2012) is a prospective, cohort study comprising an age-stratified random sample of residents from the Barwon Statistical Division, recruited from the Commonwealth of Australia Electoral Rolls. Female participants were recruited between 1994 and 1997 and males between 2001 and 2006. For the purpose of this study, we utilised cross-sectional data collected at the 10-year follow up assessment for women and the 5-year assessment for men.

Of those enrolled at baseline (1,494 women and 1,540 men), 82% (n=881) and 81% (n=978) of eligible women and men, respectively, returned for follow-up assessments. A further 246 women aged 20-29yr (71% response) consented to participate between 2004 and 2008 and were incorporated into the female cohort, retaining the full adult age range (20+ years). Reasons for non-participation have been detailed elsewhere (Williams et al., 2010, Sanna et al., 2013).

From the pool of 2,105 participants, those who did not undergo psychiatric assessment (n=49; 17 men and 32 women) or did not provide a medical history (n=29; 19 men and 10 women) were excluded from the analyses, resulting in a sample of 2,027 participants

(1,085 women and 942 men). Written informed consent was obtained from all participants and this study was approved by the Barwon Health Human Research Ethics Committee.

Study Measurements

The presence of lifetime allergic disorders, including asthma, hay fever and eczema was self-reported. Participants were asked if they had ever been diagnosed with medical conditions from a list of disease groups including metabolic, cardiovascular, psychiatric, cancer, childhood and respiratory; asthma, hay fever and eczema were listed as medical conditions. Research has shown a reasonable correlation between self-reported chronic diseases, including asthma, diabetes and coronary heart disease, and those identified in medical records (Kriegsman et al., 1996).

Trained personnel with qualifications in psychology conducted the Structured Clinical Interview for DSM-IV-TR Research Version, Non-patient edition (SCID-I/NP) (First et al., 2002) to determine the presence of depression. Data derived from diagnostic interviewing are considered gold-standard for classification of mood disorders. The SCID-I/NP has been used extensively for epidemiological research, demonstrating sound validity and reliability for depression diagnoses as well as inter-rater reliability for depressive disorders. The term depression encompasses those meeting criteria for a lifetime history of major depressive disorder (MDD), minor depression and/or dysthymia.

Body Mass Index (BMI; kg/m^2) was calculated from height, measured to the nearest 0.1 cm, and body weight, measured to the nearest 0.1 kg. Participants were classed as active if they reported participation in light to vigorous activity on a regular basis compared to sedentary behavior. Tobacco smoking was documented and grouped as current or not. The Index of Relative Socioeconomic Advantage/Disadvantage (IRSAD), grouped into quintiles, was used to indicate a participant's socio-economic status (SES). This index was calculated using data from the Socio-Economic Index for Areas (SEIFA)

and the 2006 Australian Bureau of Statistics (ABS) census (Australian Bureau of Statistics, 2006). IRSAD values take into account educational and income level, type of occupation, and some measure of wealth (such as owning a car, or number of bedrooms in a dwelling).

Statistical Analysis

Statistical analysis was performed using Minitab (version 16; Minitab, State College, PA). Differences between those with and without allergic diseases were compared using chi-square and Kruskal-Wallis analyses. Univariate regression models were performed to assess unadjusted associations between dependent and independent variables. Binary logistic regression techniques were used to evaluate the relationship between lifetime allergic disorders and lifetime depression (yes/no). Covariates including age, gender, alcohol consumption, BMI, SES, physical activity and smoking status were tested sequentially as potential confounders and were included in the final model if significant. In the final models, interactions between exposure variables were examined for effect modification. All measures of magnitude were presented as adjusted odds ratios (OR) and 95% confidence intervals (CIs). Post hoc analyses were conducted to investigate the relationship amongst those with MDD only. Values of $p < 0.05$ were accepted as significant (including interaction terms). STROBE guidelines were applied for the reporting of cross-sectional studies (von Elm et al., 2007)

RESULTS

Of the 2,027 participants included in the analyses, 782 (38.6%) of participants had suffered from atopic disorders and 432 (21.3%) met criteria for a lifetime history of depression (MDD [$n=383$], minor depression [$n=36$] and dysthymia [$n=13$]). Participants with a past history of allergic diseases were older and more likely to be female (Table 1).

Allergic disorders were associated with a 73% increase in the likelihood of depression (unadjusted OR 1.73, 95% CI 1.40-2.15, $p<0.001$). Following adjustment for age, the relationship was attenuated (age-adjusted OR 1.59, 95% CI 1.27-1.97, $p<0.001$). This association persisted after further adjustment for gender, smoking and a gender/smoking interaction term (OR 1.50, 95% CI 1.20-1.87, $p<0.001$).

Findings were consistent for MDD (unadjusted OR 1.75, 95% CI 1.40-2.19, $p<0.001$, age-adjusted OR 1.59, 95% CI 1.27-2.00, $p<0.001$). The relationship between MDD and allergic disorders was attenuated following adjustment for gender, smoking and a gender/smoking interaction term (OR 1.54, 95% CI 1.22-1.94, $p<0.001$). Further adjustment for alcohol consumption, BMI, SES and physical activity did not explain the relationship between allergic disorders and MDD.

DISCUSSION

In this cross-sectional population-based study, our results indicate increased likelihood of depression and MDD alone among men and women with allergic disorders. These associations were independent of socio-demographic characteristics, clinical and lifestyle factors.

These findings are concordant with studies conducted in the US; in a study of 6,836 young adults (20-39 years) participating in the Third National Health and Nutrition Examination Survey (NHANES III), a lifetime diagnosis of asthma, hay fever or other allergies was associated with a 1.58-fold increased risk of depression (Hurwitz and Morgenstern, 1999). Akin to our study, NHANES III used a structured clinical interview based on the Diagnostic and Statistical Manual of Mental Disorders Third Edition, although only among young adults. Studies using self-reported scales to diagnose depressive symptoms also report higher rates of depression amongst individuals with allergies (Klokk et al., 2010, Marshall et al., 2002, Hashiro and Okumura, 1997). Klokk and colleagues used the Hospital Anxiety and Depression scale to measure symptoms of depression in the population-based Hordaland Health Study. They reported a 1.25

increased risk of depression amongst participants with eczema in a sample of 15,715 adults in their 40s (Klokk et al., 2010). Findings from the Northern Finland 1966 birth cohort suggested women with skin-prick positive atopy were at 4.7-fold increased risk of depression compared with non-atopic cohort members (Timonen et al., 2003). These investigators used a combination of self-reported doctor-diagnosis of depression and self-reported symptoms.

The comorbidity of depression and atopic disorders may be explained by shared inflammatory pathways including increased production of pro-inflammatory cytokines (IL-1, IL-6 and TNF α) and Th1-related mechanisms (e.g. increased IFN γ production). As described in the Introduction, depression is accompanied by increased levels of pro-inflammatory cytokines, a Th1-shift and suppressed Treg functions (Maes et al., 2011, Maes, 2011, Dowlati et al., 2010). Classically, atopic disorders were regarded to be characterized by a Th2 shift, with increased production of proallergenic cytokines, e.g. IL-4 and IL-5 (Ngoc et al., 2005, Grewe et al., 1998). Recently, it has been shown that Th1 cytokines, for example IFN γ , and suppression of Treg functions, together with the Th2 cytokines, play a key role in maintaining the chronic inflammatory response in allergic disorders (Ngoc et al., 2005). There is now evidence that allergic disorders are accompanied by “allergic inflammation” which is characterized by increased levels of pro-inflammatory cytokines (IL-1, IL-6 and TNF α) and mediators, such as prostaglandins (Bergmann and Sypniewska, 2011). Furthermore, inflammasome and IL-1 β -induced inflammation play a key role in atopic disorders (Krause et al., 2012), whereas, drugs that block IL-1 functions suppress the inflammatory response in allergic disorders (Krause et al., 2012). IL-6 also plays a role in allergic disorders; IL-6 induces proliferation of Th2 effector cells and inhibits the function of Treg cells (Doganci et al., 2005). TNF α has been shown to play a key role in the pathogenesis of asthma and airway inflammation and in refractory asthma (Lykouras et al., 2008, Desai and Brightling, 2010). Anti-TNF treatments may show some efficacy in the treatment of allergic disorders and depression, although the risks have been reported to outweigh the benefits (Desai and Brightling, 2010, Tying et al., 2006).

Increased levels of acute phase proteins, including CRP, have also been established in allergic disorders (Bergmann and Sypniewska, 2011, Howren et al., 2009). Moreover, cytokines such as IL-4 enhance the humoral immune response involved in atopy and, concurrently, affect the metabolism of 5-hydroxytryptamine (5-HT), another factor that may explain the comorbidity between depression and allergic disorders (Maes, 1995, Timonen et al., 2003). Other shared biological factors which may explain the comorbidity between depression and atopic disorders include: excessive histamine production, insufficient polyunsaturated fatty acid intake, intracellular adhesion molecule-1 (ICAM-1), genetic predispositions and, finally, the psychological impact of such disorders, which are often of a visible nature (Van Lieshout et al., 2009, Timonen et al., 2003, Wamboldt et al., 2000, Koo and Lebowitz, 2001). Another possible pathway relates to medications used to treat atopy; corticosteroids used for treatment of atopic disorders, have shown to induce depressive symptoms over the long-term (Bonala et al., 2003). On the other hand, antidepressant medications such as selective serotonin reuptake inhibitors have been shown to reduce inflammation (Tynan et al., 2012), suggesting that appropriate pharmacotherapy for depression has the potential to also benefit atopic conditions.

An important limitation of the current study is the reliance on self-report for allergic disorders, rather than using IgE-levels or skin-prick tests to confirm diagnoses. Self-reporting of these conditions over the life span may have led to recall bias, misclassification or incorrect identification of atopy. This may have resulted in an under-reporting of atopy and thus a possible dilution of effects. On the other hand, shortness of breath associated with anxiety symptoms, often comorbid with depression, may be misdiagnosed as asthma, thus overestimating the prevalence. However, good reliability between self-reported skin complaints and doctor diagnosis has been reported (Dalgard et al., 2003). Furthermore, asthma and eczema have been shown to be associated with depression independently of IgE levels (Yang et al., 2010). Lastly, we acknowledge that due to the cross-sectional nature of the data, we cannot make conclusions about the direction of the relationship. Despite the aforementioned limitations, there are many strengths of the current study. We used the SCID-I/NP to identify depression, a gold

standard tool, whereas majority of studies have used self-report scales to identify depressive symptoms/psychopathological traits (Zorrilla et al., 1996, Klok et al., 2010, Marshall et al., 2002, Hashiro and Okumura, 1997). This population-based study comprises a large sample size, includes a wide age range across both genders and random selection from the general population through the electoral register thereby minimizing selection bias.

In conclusion, our findings support both clinical and epidemiological data suggesting an association between depression amongst men and women and atopic disorders. Given the major psychological impact of atopic disorders, several kinds of psychotherapy, in particular cognitive-behavioral therapy, have been studied in combination with pharmacological treatments (Fleming et al., 2004). Future studies could address the potential integration of such treatment programs for patients presenting with comorbid immune diseases and mood disorders in order to improve quality of life in affected patients. Overall, further research is required to elucidate not only the direction of this association, but to further explicate its underlying physiology including markers of inflammation and treatment options.

Abbreviations

5-HT	5-hydroxytryptamine
ABS	Australian Bureau of Statistics
BMI	body mass index
CI	confidence intervals
CMI	cell-mediated immune
CRP	C-reactive protein
GOS	Geelong Osteoporosis Study
ICAM-1	intracellular adhesion molecule-1
IgE	immunoglobulin E
IL	interleukin

IRSAD	Index of Relative Socioeconomic Advantage/Disadvantage
MDD	major depressive disorder
NHANES III	Third National Health and Nutrition Examination Survey
O&NS	oxidative and nitrosative stress
OR	odds ratio
SCID-I/NP	Structured Clinical Interview for DSM-IV-TR Research Version, Non-patient edition
SES	socio-economic status
SEIFA	Socio-Economic Index for Areas
TNF α	tumor necrosis factor α
Treg	T regulatory

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Table 1. Characteristics for the whole group and participants with and without atopic diseases.

	Total	Atopic Diseases		
		Yes	No	p
	n=2027	n=782	n=1245	
Gender (female)	1085 (53.5%)	512 (65.5%)	573 (46.0%)	<0.001
Age (yr)	55.3 (40.3-69.8)	51.2 (35.7-64.3)	58.5 (43.1-72.5)	<0.001
BMI (kg/m²)	26.8 (24.0-30.2)	26.7 (23.8-30.5)	26.9 (24.2-30.0)	0.958
Alcohol (g/day)	6.2	5.6	6.7	0.343

		(0.6-20.2)	(0.6-19.1)	(0.7-21.4)	
Depression (lifetime)*		432 (21.3%)	212 (27.1%)	220 (17.7%)	<0.001
Smoking (current)		258 (12.8%)	92 (11.8%)	166 (13.4%)	0.300
Physical Activity (Active)		1515 (75.0%)	598 (76.5%)	917 (74.0%)	0.214
SES	Quintile 1 (low)	319 (15.8%)	117 (15.0%)	202 (16.3%)	0.607
	Quintile 2	420 (20.8%)	156 (20.1%)	264 (21.3%)	
	Quintile 3	432 (21.4%)	175 (22.5%)	257 (20.7%)	
	Quintile 4	412 (20.4%)	153 (19.7%)	259 (20.9%)	
	Quintile 5	435 (21.6%)	177 (22.8%)	258 (20.8%)	

Note: Missing values- BMI (n=58), Physical activity (n=6), Alcohol consumption (n= 53), smoking (n=6), SES (n=9)

* Major Depressive Disorder, minor depression, dysthymia

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Contributors

LS and ALS took part in the conception and design of the study, acquisition of the data, data cleaning and statistical analysis, interpretation of the analysis and took primary responsibility for writing the manuscript. JAP, FNJ, MB, MM, AO and PG took part in the interpretation of analysis and critically revised the manuscript. LJW took part in the conception and design of the study, interpretation of the analysis, critically revised and supervised the writing of the manuscript. All authors read and approved the final manuscript.

Conflict of interest

LS, ALS, MM, AO and PG have no conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript.

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