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There are no association between IgE levels and symptoms of anxiety and depression in the adult female general population. The Hordaland Health Study (HUSK)

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There are multiple reports of increased prevalence of anxiety and depression in patients with asthma, eczema and rhinitis. Suggested biological mechanisms underlying these associations most commonly involve IgE. However, the association between anxiety/depression and IgE has hardly been studied, and the aim of the present study will therefore be to examine the hypothesized association between anxiety/depression and IgE in a general adult female population. A sub-sample of 374 female participants in a population-based general health study in Norway (the Hordaland Health Study) with participation rate 70% was screened for total and allergen-specific IgE. Anxiety and depression were measured employing the Hospital Anxiety and Depression Scale (HADS). This design ensured adequate statistical power, and the population-approach ensured satisfactory variance in both IgE and anxiety/depression. No association between case level or symptom load of anxiety/depression and total or allergen-specific IgE was found. Non-significant tendencies were both positive and negative. This finding was robust across continuous and categorical statistical approaches. Our finding does not question the commonly reported associations between anxiety/depression and asthma, rhinitis and eczema. We do, however, question the relevance of IgE as an aetiological factor in the biological chain underlying these associations.

• *Anxiety, Depression, Epidemiology, IgE.*

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Over the past 30 years, there have been a growing number of publications within the area of psychoneuroimmunology, which is the study of interrelationships of the central nervous system, the neuroendocrine system and the immune system. There are now several reports of associations between mental symptoms and factors in the immune system such as cytokines and histamine (1–5). Several publications report increased prevalence of anxiety and/or depression in the conditions asthma, rhinitis and eczema (5–13).

The literature has suggested IgE-mediated mechanisms underlying the associations between symptoms of mental disorders and asthma, rhinitis and eczema (5, 8, 10, 14–16).

On this background, it is fair to hypothesize that IgE is associated with both anxiety and depression. However, evidence for such an association has been scarce. Despite this, several suggested aetiological models include IgE as

part of the biological chain underlying the association between asthma, rhinitis, eczema and mental symptoms. Among the more frequently suggested mechanisms are immune-mediators such as cytokines and histamine, produced as a consequence of IgE-mediated immune reactions (8, 10, 17). It is well known that IgE-mediated stimulation of mast cells and basophiles in the tissues result in cytokine production (18, 19). According to Dantzer (1), cytokines produced by cells of the innate immune system can act on the central nervous system via afferent and humoral pathways to trigger a brain cytokine system, and there is evidence that prolonged activation of this system can precipitate the development of depressive disorders in vulnerable patients.

Further, cytokine production resulting from IgE-mediated immune reactions can also activate the hypothalamic-pituitary-adrenal axis (HPA-axis) (20, 21), and lead to hypercortisolism and dysfunction of

the corticosteroidreceptor, which are also seen in depression (22–28). Buske-Kirschbaum & Hellhammer (29) propose that HPA axis dysfunction can lead to ineffective immunoregulation under stressful conditions in patients with atopic conditions (such as atopic eczema), which can further lead to aberrant immune responses and subsequent exacerbation of the disease.

Histamine is released from activated mast cells during IgE-mediated hypersensitivity reactions, but is also suggested as a possible neurotransmitter or neuromodulator in the brain (30, 31). According to Ito et al. (30, 31), acute and chronic stresses increase the brain histamine turnover, which could be partly related to the vulnerability for stress-induced anxiety and depression.

Despite the different theories concerning the role of IgE in the association between asthma, rhinitis, eczema and anxiety/depression, only five reports have, to our knowledge, empirically examined the hypothesized association between IgE and symptoms of mental disorders (5, 8, 10, 15, 32). IgE must be associated with anxiety or depression to be an explanatory factor in the association between asthma, rhinitis, eczema and anxiety/depression. Sugerma et al. (32) compared the levels of different immunoglobulins (including total IgE levels) in psychiatric inpatients ($n=96$) and healthy controls ($n=62$), and found no significant differences between the groups. Hashizume et al. (5) investigated correlations between total IgE and trait and state anxiety in patients with atopic dermatitis (AD) ($n=78$). A positive correlation was found between IgE and trait anxiety, whereas a negative correlation was found between IgE and state anxiety. Arima et al. (15) surveyed 51 outpatients with AD. A negative correlation (ρ) of -0.22 was found between total IgE and depression (Beck Depression Index). There are several limitations of the studies of Hashizume et al. (5) and Arima et al. (15): the sample size is small ($n=78$ and $n=51$), and they measured total and not allergen-specific IgE. Most important, though, is the restriction of variance in IgE when including atopic patients only (who all are expected to have elevated levels of IgE).

Timonen et al. (10) found in women a marginally significant association between skin test diagnosed atopy and depression. The strengths of this study were the population-based design and the statistical power ($n=5428$) and the use of skin-prick tests as a valid tool for demonstration of IgE-mediated mechanism underlying atopic symptoms. Limitations include the use of a single self-reported question concerning doctor-diagnosed depression. In addition, the authors themselves mention the lack of IgE measurements (10). It is known that use of long-acting antihistamines in allergy can reduce skin tests but not serum examinations of IgE (33). In a later corresponding study, which is probably the best one

published to date, Timonen et al. (8) examined the association between atopy and depression over again, now using the Hopkins Symptom Checklist-25 measuring depression. However, the authors again mention lack of measures of IgE as a limitation.

In summary, several studies report higher levels of anxiety and depression in patients with asthma, rhinitis and eczema compared with healthy controls. The majority of the suggested aetiological mechanisms involve IgE, but the present and scarce literature gives indistinct support for such an association. Consequently, there is a need for empirical examination of the hypothesized association between IgE and case level and symptom load of anxiety and depression in the general population. This will therefore be the aim of the present study.

Clinical implications of the article

Knowledge of the complex interrelationships of the central nervous system and the immune system makes an important basis for comprehension and satisfactory treatment of compound medical conditions such as asthma, rhinitis and eczema. Immunological factors such as IgE have been suggested to underlie the association between these conditions and mental symptoms. Our finding, that there is no association between IgE and anxiety and depression, implies that aetiological models involving IgE for the association between asthma, rhinitis, eczema, and anxiety and depression might need re-evaluation.

Material and Methods

Participants

The Hordaland Health Study 1997–1999 (HUSK) was designed to survey mental and physical health of a Norwegian adult general population. It was conducted as a collaboration between the National Health Screening Service, the University of Bergen and local health services of Hordaland County in Norway. The target population included 29,400 individuals born between 1953 and 1957, who resided in Hordaland County on 31 December 1997. The participation rate among women was 70% ($n=9,983$) (34).

The present study is a secondary analysis of data collected for the purpose of comparing IgE levels in former and current hairdressers ($n=154$) with controls without any such working experience ($n=220$) in HUSK. Controls were randomly selected after matching on age, smoking, educational level and place of residence. This study is not yet published, but the main finding was that the prevalence in both Positive Phadiatop® and elevated IgE (>100 IU/ml) was indifferent in former/current hairdressers vs. controls (22% and 23% Positive Phadiatop® in controls and hairdressers, respectively ($\chi^2=0.043$, $df=1$, $P=0.835$), and

correspondingly 14% and 16% with IgE levels >100 IU/ml (chi-square = 0.278, $df = 1$, $P = 0.598$). As a result of the selection procedure, the sub-sample with IgE measures ($n = 374$) consisted of more smokers (49% vs. 35%, chi-square = 35.249, $df = 1$, $P < 0.001$) and less educated women (12% vs. 35%, chi-square = 183.314, $df = 1$, $P < 0.001$) than did the general population. Smoking and educational level is obviously related to anxiety and depression, also in our study, but was unrelated to elevated IgE and Positive Phadiatop® (all $P > 0.05$).

Data collection

Data collection in HUSK was performed in two steps. The first, which was identical for all participants, included a self-administered questionnaire (Form 1) and a health examination with blood samples. At the health examination, the participants were given a second form (Form 2), which should be returned by prepaid mail (34).

Measures

ANXIETY AND DEPRESSION

The Hospital Anxiety and Depression Scale (HADS) is a self-report questionnaire comprising 14 Likert-scaled items, each of 4 points, seven for anxiety (HADS-A) and seven for depression (HADS-D). To avoid false positive cases in the context of somatic diseases, no somatic items or items regarding sleeping difficulties are included. In accordance with the findings on anxiety disorders and depression in the National Comorbidity Survey (35), Mykletun et al. found a shared variance between HADS-A and HADS-D of 30% (36). According to a literature review covering 31 studies, HADS has shown good case-finding properties for anxiety and depression in patient populations in primary care and hospital settings (37). A cut-off score of 8 on both sub-scales was found to give an optimal balance between sensitivity and specificity, both at about 0.80, for depression and anxiety according to DSM-III and IV, ICD-8 and 9. This is similar to the sensitivity and specificity of the General Health Questionnaire. Consequently, case level for anxiety and depression was defined as 8 or more on both sub-scales. According to previous use of this scale, HADS anxiety and depression were operationalized in three ways: anxiety symptom load and depression symptom load (shortened to "anxiety and depression symptoms" where appropriate) were measured continuously employing HADS anxiety and depression sum-scores (38), in addition to a HADS total sum-score. Dichotomies (i.e. score of ≥ 8 vs. score of < 8 in the corresponding sub-scale) for case-level anxiety/depression symptom load, shortened to "case-level anxiety/depression" where appropriate, constituted

a categorical approach (39, 40), and IgE was finally analysed across all 14 single items in HADS (41).

SERUM IgE, TOTAL AND ALLERGEN-SPECIFIC LEVELS

All blood-samples were taken between January and March 1997, between 10:00 and 20:00 h. The blood samples were drawn from the cubital vein with the subject sitting in a chair. Eight millilitres of blood was collected in a sterile Vacutainer® without any preservative or anticoagulant. The blood was clotted in the tube at room temperature. The serum (approximately 4 ml) was decanted after centrifugation and deep frozen and stored in the HUSK Biobank. All samples were defrosted at the same point of time 4 years later (2001). The serum samples were analysed for total and allergen-specific IgE using the CAP FEIA system (Pharmacia, Uppsala, Sweden). Allergen-specific IgE was assessed for the main inhalation allergens, using Phadiatop® (*Dermatophagoides farinae*, *D. pteronyssinus*, *Parietaria vulgaris*, cat, horse, dog, timothy grass, birch, olive, *Cladosporium herbarum* and mugwort) (42). The Phadiatop® was analysed in duplicate. The results were given as negative or positive depending on the sample to reference ratio of fluorescence activity. IgE was operationalized in four ways: 1) as continuous measures we used total IgE concentration (IU/ml serum) and 2) log-transformed IgE concentration (log IU/ml). 3) Two dichotomies were employed—the first was labelled elevated IgE (depending on IgE level above or below 100 IU/ml serum). According to Baldacci et al. (33), variations in IgE by sex, age, smoking habits and geography may indicate the use of local reference values. The cut-off level 100 IU/ml is commonly used at Haukeland University Hospital where these samples were analysed. 4) The second dichotomy representing allergen-specific IgE was labelled Positive Phadiatop®.

ASTHMA, RHINITIS AND ECZEMA

Information on asthma rhinitis and eczema was obtained by self-report.

Form 1 in HUSK contained three dichotomous questions concerning eczema: "Have you any time the last year had eczema (red, itching, sore, or fissured skin)?" Responses (yes/no) were given with regard to area, including hands, face and body. Form 1 in HUSK also contained a dichotomous question concerning asthma: "Do you have current or previous asthma (yes/no)?" Form 2 contained a dichotomous question concerning rhinitis: "Do you have current or previous hay fever (yes/no)?"

MENOPAUSE AND HORMONE SUPPLEMENTS

Menopause is hypothesized to be positively associated with level of anxiety and depression (43). Siroux et al.

(44), found a negative association between level of IgE and menopause, and that IgE increased with oral contraceptive use.

Given of the possible hormonal effects on IgE levels, we controlled for menopause, oral contraceptive use, hormone replacement therapy and hormone spiral. Information on these variables was obtained from Form 2 in HUSK and was based on self-report. The onset of menopause was derived from the following question in Form 2: "If you no longer have natural menstrual period, how old were you when it stopped?" The use of hormonal replacement therapy and oral contraceptives or hormone spiral were covered by the following question: "Do you currently use or have you previously used the P-pill (inclusive the Mini-pill), Hormone-spiral or Oestrogen (tablets, suppository, plaster or cream)?" Responses were given as current use, previous use or never used. The onset of menopause, hormonal replacement therapy, oral contraceptives or hormone spiral use was operationalized as dichotomies.

Statistical analyses

Two statistical approaches were used in this study, including logistic regression analyses as well as Spearman correlation analyses. The association between log-scaled IgE and total anxiety and depression symptoms sum-score was displayed as a scatter-plot.

All combinations of operationalizations of anxiety and depression were analysed against all operationalizations of IgE. Across all analyses, anxiety and depression (symptoms and case level) were used as dependent variables and IgE as independent variable. Effects were given as odds ratios (OR), for logistic regression, and

rho for Spearman correlations. For logistic regression, 95% confidence interval was reported. As the variance in age was restricted, there was no need to adjust for this factor in the analyses.

Ethics

The study protocol was approved by the Regional Committee for Medical Research Ethics of Western Norway and the Norwegian Data Inspectorate.

Results

Elevated levels of IgE were found in 54 (14.4%) of the participants and Positive Phadiatop in 83 (22.2%). Further, 95 (25.4%) participants had case-level anxiety and 42 (11.2%) case-level depression. Further population characteristics are reported in Table 1.

Both case level and symptom load of anxiety and depression were not associated with IgE. This finding was robust across a whole range of operationalizations and statistical approaches.

First, logistic regression analyses were employed for IgE (IgE concentration, elevated IgE (>100 IU/ml) and Positive Phadiatop®) in relation to case-level anxiety and case-level depression in six separate regression models (Table 2). Adjustment for menopause ($n=24$) and any hormonal treatment ($n=87$) did not alter the association of interest at all).

Non-significant associations were equally often positive as negative.

We stratified the sample for presence of any allergic condition (asthma, rhinitis or eczema). One or more of these conditions were reported in 151 (40%) of the

Table 1. Population characteristics.

Variable	<i>n</i>	%	Mean	Median	<i>s</i>	Range
Demographics						
Age			44			41–48
Female gender	374	100				
Highest level of education						
Compulsory only	35	9.4				
High school	295	78.9				
University level	44	11.8				
Immunological variables						
IgE concentration, IU/ml			71.4	23	227	4–3550
Elevated IgE (≥ 100 IU/ml)	54	14.4				
Positive Phadiatop®	83	22.2				
Both elevated IgE and positive Phadiatop®	32	8.6				
Anxiety and depression						
Case-level anxiety (HADS-A ≥ 8)	95	25.4				
Case-level depression (HADS-D ≥ 8)	42	11.2				
Both case-level anxiety and depression	35	9.4				
Level of anxiety (HADS-A sum-score)			5.3	5	3.6	0–19
Level of depression (HADS-D sum-score)			3.3	2	3.1	0–16
Total HADS-score (HADS-T sum-score)			8.6	7	6.1	0–35

s, standard deviation; HADS, Hospital Anxiety and Depression Scale.

Table 2. IgE vs. case-level Hospital Anxiety and Depression Scale (HADS) anxiety and depression (four separate logistic regression models).

	OR	95% CI	Wald	Sig.
Dependent variable: Case-level depression				
Elevated IgE	0.986	0.394–2.467	0.001	0.976
Positive Phadiatop®	0.552	0.224–1.359	1.671	0.196
Dependent variable: Case-level anxiety				
Elevated IgE	1.426	0.760–2.672	1.223	0.269
Positive Phadiatop®	0.703	0.389–1.272	1.353	0.245

OR, odds ratio, CI, confidence interval.

participants. We analysed the hypothesized association between IgE and anxiety/depression in both strata. No association between IgE and anxiety/depression were found in sub-samples with ($n = 151$) and without ($n = 223$) allergic symptoms (asthma, rhinitis, eczema), the exception being a negative association ($\rho = -0.187$, $P = 0.022$) between case-level depression and Positive Phadiatop®, which is contrary to the research hypothesis, and also most likely a type I error resulting from multiple testing.

HADS-A and HADS-D sum-scores were analysed across concentration of IgE, elevated IgE and positive Phadiatop® applying Spearman correlation analyses (Table 3). No statistically significant associations were found.

The procedure was repeated also for single items in the HADS anxiety and depression sub-scales (seven items for each) (Table 3), again without any statistically significant finding across the 42 correlations examined.

Visual examination of the scatter-plot of log-scaled IgE concentration vs. total level of anxiety and depression gave no further indication as to any association between the two (Fig. 1).

Finally, to comply with potential challenges related to use of secondary data, we included stratified analyses for current/former hairdressers vs. controls of the hypothesized association between anxiety/depression and IgE. The conclusion that there was no association between IgE and (case level and symptom load of) anxiety and depression was confirmed in both sub-samples.

Discussion

Main findings

No association between IgE, and anxiety and depression symptoms was found in the present population-based study. This finding was robust across methodological

Table 3. Symptom load of Hospital Anxiety and Depression Scale (HADS) anxiety and depression (sum-scores and single items) in relation to IgE and Positive Phadiatop®; Spearman’s rho (two-tailed significance).

	Concentration of IgE	Elevated IgE	Positive Phadiatop®
Level of anxiety and depression (range 0–21)			
HADS-A sum-score	0.046 (0.373)	0.068 (0.189)	−0.023 (0.655)
HADS-D sum-score	0.072 (0.165)	0.010 (0.846)	−0.053 (0.307)
Anxiety items (range 0–3)			
I feel tense or wound up	0.023 (0.664)	0.075 (0.148)	−0.018 (0.734)
I get a sort of frightened feeling*	0.039 (0.451)	0.075 (0.154)	0.004 (0.946)
Worrying thoughts go through my mind	−0.013 (0.807)	0.000 (0.994)	−0.004 (0.940)
I can sit at ease and feel relaxed	0.025 (0.636)	0.042 (0.420)	−0.003 (0.956)
Like butterflies in the stomach†	0.070 (0.177)	0.085 (0.103)	−0.040 (0.448)
I feel restless as if I have to be on the move	0.037 (0.475)	0.007 (0.897)	−0.014 (0.793)
I get sudden feelings of panic	0.054 (0.296)	0.075 (0.148)	−0.017 (0.746)
Depression items (range 0–3)			
I still enjoy the things I used to enjoy	0.031 (0.567)	−0.040 (0.461)	−0.062 (0.251)
I can laugh and see the funny side of things	0.043 (0.411)	0.010 (0.855)	−0.024 (0.645)
I feel cheerful	0.010 (0.841)	0.077 (0.136)	−0.059 (0.256)
I feel as if I am slowed down	0.083 (0.112)	0.054 (0.298)	−0.031 (0.551)
I have lost interest in my appearance	0.055 (0.292)	−0.056 (0.276)	−0.048 (0.355)
I look forward with enjoyment to things	0.073 (0.158)	0.023 (0.662)	−0.044 (0.400)
I can enjoy a good book or TV programme	−0.021 (0.693)	0.003 (0.953)	−0.012 (0.818)

*I get a sort of frightened feeling as if something awful is about to happen.

†I get a sort of frightened feeling like “butterflies” in the stomach.

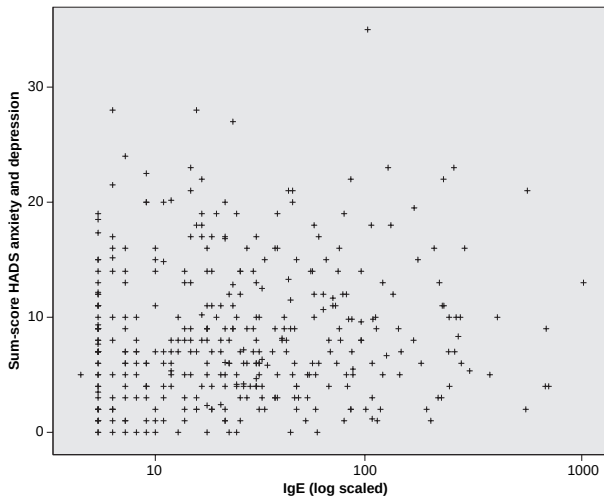


Fig. 1. IgE (log-scaled) vs. Hospital Anxiety and Depression Scale (HADS) anxiety and depression.

approaches. Non-significant directions of effects were both positive and negative.

Comparison with previous studies of IgE vs. anxiety and depression

Our study is the first population-based study of IgE concentration and level in relation to anxiety and depression. There is no clear evidence in the literature for an association between IgE and anxiety or depression. However, the two studies of Timonen et al. (8, 10) give some support for this hypothesis: the first study reported a marginally significant positive association in females only between positive skin-prick test and self-report of life-time doctor diagnosis of depression (10), but there are obvious objections to this study. The study was strongly powered ($n = 5428$), but the association was so weak that removal of less than five females with positive skin-prick test and depression would undermine the conclusion. More problematic, though, is the use of self-reported lifetime doctor-diagnosed depression. Most individuals with depression will never be diagnosed (45), and the chance of being diagnosed increases with contact with general practitioners (GPs). As patients with atopic diseases probably have frequent contacts with their GPs, we suggest Timonen's (10) finding might be biased from this. In Timonen's second study (8), four groups were identified with positive and negative skin-prick test as well as positive and negative symptom presence. The prevalence of depression was increased in individuals with allergic symptoms regardless of skin-prick test result, whereas positive skin-prick test was not associated with depression in the absence of allergic symptoms. In summary, we do not believe Timonen's studies (8, 10) strongly support the hypothesis of an association between depression and skin-prick test, being a proxy for IgE.

The three clinical studies (5, 15, 32) mentioned above all have weaker statistical power than the present study. Our findings are in line with Sugerman et al. (32), however, with the reservation as to his psychiatric diagnosis "abnormals". We question the relevance of the studies of Arima et al. (15) and Hashizume et al. (5), as they both restricted the variance in IgE to elevated levels only.

Strengths

The probably most important advantage of the present study is the population-based design, which gives us normal variation in IgE. This is in contrast to studies of atopic patients only. The study had 83% power to reveal population correlations as weak as 0.15 at alpha 0.05. Consequently, our study is adequately powered. Valid measures on IgE (allergen-specific and total IgE) and anxiety and depression were employed. All procedures for data collection were equal and independent of the participant's mental or atopic state.

Limitations

The use of screening instruments such as HADS might weaken reliability compared with structured clinical interviews, resulting in under-estimation of effect-size. The probably most important limitation of the present study is that our sample includes females only with a narrow age-range, and that smokers, hairdressers and individuals with low educational level were over-represented in the sub-sample studied as compared with the general population. This obviously restrains the generalizability of the study. We cannot exclude these biases to influence the strength of an eventual association between anxiety/depression and IgE. However, as we found no such association, it is perhaps unlikely that the biases of the sub-sample studied could entirely hide an eventual true association in the general population.

Implications for future research

The present study does not challenge previous findings of elevated levels of anxiety and depression in patients with asthma, rhinitis and eczema, but rather questions the role of IgE in the aetiological chain underlying the association between these commonly atopic conditions and anxiety/depression. HPA axis dysfunction and immune mediators like cytokines and histamine are frequently suggested aetiological models in the literature exploring the association between asthma, rhinitis, eczema, and anxiety and depression. IgE is repeatedly suggested as relevant in these biological processes (5, 8, 10, 14–16).

Our finding, that there is no association between IgE and neither symptom load nor case level of anxiety and depression, implies that aetiological models involving IgE for the association between asthma, rhinitis, eczema,

and anxiety and depression might need re-evaluation. We encourage development of new hypotheses for the biological link underlying the association between asthma, rhinitis, eczema, and anxiety and depression.

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