



Generalized Anxiety Disorder is Prospectively Associated With Decreased Levels of Interleukin-6 and Adiponectin Among Individuals from the Community

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ABSTRACT

Background: Anxiety disorders have been related to cardiovascular diseases via low-grade inflammation, but longitudinal studies on the association between generalized anxiety disorder (GAD) and inflammatory biomarkers are sparse. Furthermore, no studies have examined the association between GAD and the “cardio-protective” adipocytokine adiponectin in this context so far.

Methods: In a Swiss population-based sample of 2,415 adults participating in baseline and follow-up exams (mean follow-up duration = 5.5 years), we diagnosed a total of 55 persons (2.3%) with GAD using a validated semi-structured psychiatric interview. We prospectively examined the relation between GAD and circulating levels of inflammatory biomarkers (i.e., C-reactive protein, interleukin (IL)-1 β , IL-6, tumor necrosis factor- α , and adiponectin), in linear regression models, statistically controlled for the baseline inflammatory marker, socioeconomic status, cardiovascular risk factors, health behaviors, and psychiatric disorders.

Results: Compared to those without GAD, individuals with GAD had lower IL-6 ($\beta = -0.249$, 95%-CI -0.493–(-0.004), $p = 0.046$), and adiponectin ($\beta = -0.264$, 95%-CI -0.482–(-0.045), $p = 0.018$) levels at follow-up after adjustment for all covariates. Moreover, GAD was unrelated to several other inflammatory measures.

Conclusion: Individuals with GAD do not seem to exhibit chronic low-grade inflammation, suggesting different underlying biobehavioral mechanisms to those from other anxiety disorders. Low adiponectin levels may be linked to symptoms of GAD through brain areas directly involved in the processing of fear and anxiety.

1. Introduction

The link between anxiety disorders, including Generalized Anxiety Disorder (GAD), and an increased risk of incident cardiovascular disease (CVD) might be related to inflammatory changes such as C-reactive protein (CRP), interleukin (IL)-6, tumor necrosis factor (TNF)- α (Kaptoge et al., 2014), and the “cardio-protective” adiponectin (Li and Wu, 2012). Proinflammatory changes are linked to altered hypothalamic-pituitary (HPA) axis responses caused by chronic stress as

represented by persistent anxiety states, thereby increasing the risk for excessive systemic inflammation (Mehta and Binder, 2012). In this context, adiponectin might not only operate as a cardio-protective factor (Li and Wu, 2012; Garfinkel et al., 2014; Zhang et al., 2017). The latter is derived mainly from white adipose tissue, a major endocrine organ that secretes adipokines involved in systemic inflammation of cardiovascular, metabolic and autoimmune diseases. Different isoforms (polymers) of adiponectin exist in the blood, which may also differ in their binding activity to membrane receptors and signal distinct effects

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in the cardiovascular system. Low plasma levels of adiponectin were associated with obesity, type 2 diabetes, and coronary artery disease (CAD) compared to healthy individuals. Additionally, hypoadiponectinemia showed a higher risk and prevalence of obesity-related diabetic and cardiovascular disorders (Li and Wu, 2012). While the beneficial role of adiponectin on cardiovascular functions and energy homeostasis via directly modulating IL-6 has been known for some time, more recent studies indicate that higher levels of adiponectin may also appear as an inducer of inflammatory factors aggravating inflammatory response in autoimmune diseases (Li and Wu, 2012). However, further research is needed to investigate the pleiotropic features of adiponectin better and to find out if such an interaction between adiponectin and IL-6 might also apply to GAD.

IL-6 is one of the best examined proinflammatory cytokines with prototypical features contributing to cell proliferation and differentiation, as well as to host defense. In response to acute infections or tissue damage, IL-6 is produced by immune-mediated cells like macrophages and monocytes. IL-6 is also generated by endothelial cells, by adipocytes like adiponectin, mesenchymal cells, fibroblasts, and numerous other cells in response to miscellaneous stimuli (Tanaka et al., 2016). „IL-6 signaling is mediated by building a complex of IL-6, the transmembrane IL-6 receptor (mIL-6R) or with soluble forms of IL-6R (sIL-6R), and the signal-transducing subunit molecule gp130.“ (Tanaka et al., 2016) These pathways help to explain the pleiotropic functions of IL-6. “The control of IL-6 signaling is regulated through the induction of suppressor molecules after activation of the IL-6 pathways as well as through the presence of sIL-6R and gp130 forms in the blood. Vice versa, an overproduction of IL-6 and a dysregulation of the IL-6 signaling pathways can result in inflammatory and autoimmune disorders suggesting that IL-6 plays a significant role in the human cytokine network.” (Tanaka et al., 2016) The ubiquitary involvement of IL-6 in immune function may also have a potential impact in anxiety states.

In a recent systematic review and meta-analysis on peripheral cytokines in GAD, CRP was found to be significantly higher in individuals with GAD compared to controls (Costello et al., 2019). However, only CRP data were sufficient for the meta-analysis and 5 of 14 studies meeting inclusion criteria for review showed no group differences in any cytokine measured (Costello et al., 2019). There was some indication for higher IL-6 and TNF- α in individuals with versus without GAD from cross-sectional analyses, although most studies had small sample sizes and did not sufficiently adjust for confounders. We found anxiety disorders associated with lower high sensitive (hs)-CRP cross-sectionally, but the association was probably attributed to the low body mass index of participants with anxiety disorders (Glaus et al., 2014). The only longitudinal study on the association between GAD and CRP cited was in adolescents (Costello et al., 2019), whereas IL-1 β , IL-6 and TNF- α have not been studied longitudinally so far in GAD according to the review (Costello et al., 2019). The available data let the authors conclude that high heterogeneity across studies means that findings should be interpreted with caution and that further longitudinal studies are needed (Costello et al., 2019). A more recent longitudinal cohort study not included in that meta-analysis found no association between GAD and low-grade inflammation in terms of CRP and IL-6 (Lamers et al., 2019). Based on our own cohort data, we also found no prospective association between current or remitted GAD with hs-CRP, IL-6, and TNF- α (Glaus et al., 2018). However, the division in two categories of anxiety reduced statistical power, and we also did not control for latent classes of psychiatric disorders systematically.

Therefore, we aimed to extend our prospective investigation on changes in circulating markers of low-grade inflammation among individuals with lifetime GAD compared to those without in a large community-based sample, while taking into account several health-related covariates commonly associated with both inflammation and CVD risk. The novelty of our work are measurements on adiponectin and IL-1 β , which have not been examined in this context so far. We hypothesized that individuals with GAD will show subsequent increases of

CRP, IL-1 β , IL-6 and TNF- α on the one hand, and a decrease in adiponectin on the other (Kaptoge et al., 2014).

2. Material and Methods

The data for the present study are derived from the CoLausPsyCoLaus cohort study (Glaus et al., 2018) implemented to better understand the relationship between psychiatric disorders and CVD. Information on mental disorders at baseline was collected using the semi-structured Diagnostic Interview for Genetic Studies completed with questions from the Schedule for Affective Disorders and Schizophrenia - Lifetime and Anxiety disorder version to extend the anxiety sections. The follow-up took place 5.5 years (2009–2012) after the baseline exam.

A total of 2,415 participants were assessed twice (at the somatic baseline and follow-up exams) for inflammatory markers including hs-CRP, IL-1 β , IL-6, TNF- α , and adiponectin, and had no missing information on covariates. Subjects with hs-CRP > 10 mg/L, indicative of acute infection, were excluded from the analyses.

For statistical analyses, inflammatory measures were log10-transformed and then z-standardized to normalize distributions. In order to classify distinct patterns of DSM-IV psychiatric comorbidity we conducted a latent class analysis. Associations between lifetime GAD at baseline and levels of inflammatory markers at follow-up serially adjusted for the respective levels at baseline and additional covariates including classes of psychiatric disorders were determined using multiple linear regression models.

3. Results

On average, participants were 50 years old and 47% were male. A total of 2.3% (n=55) of the participants reported lifetime GAD at baseline (mean duration of GAD \pm SD: 14.5 years \pm 16.7 (range: 1–61)). A large proportion of the participants were physically inactive (39%), and were prior or present smokers (61%). The comparison between participants with versus those without GAD showed no significant difference in demographics, cardiovascular risk factors or health behaviors. However, individuals with GAD were more frequently female and reported more concomitant anxiety and mood disorders (Table 1). Participants with GAD showed significantly lower IL-6 and adiponectin levels at follow-up than those without GAD after adjustment for all covariates (Table 2). In contrast, levels of hs-CRP, IL-1 β , and TNF- α at follow-up did not significantly differ between groups.

4. Discussion

In this Swiss community-based sample of 2,415 adults we found a significant decrease in adiponectin and IL-6 over time in individuals with GAD compared to those without, whereas IL-1 β and TNF- α , but also hs-CRP showed no significant group differences. With a prevalence of 2.3% and a women-to-men ratio of 2:1 for GAD, our sample may be considered to be representative of the community (Wittchen et al., 2002).

This is the first study that examined the prospective association of GAD with adiponectin and IL-1 β . The work is novel in showing decreased levels of adiponectin over time in individuals with GAD compared to those without. No definite interpretation can be made as to whether high adiponectin exert pro- or anti-inflammatory effects (Kaptoge et al., 2014). Low adiponectin levels have been associated with a higher risk for coronary artery disease, with obesity-related type 2 diabetes, and also with obesity compared to healthy individuals directly affecting IL-6 (Kaptoge et al., 2014). However, IL-6 showed a decrease over time, whereas the other inflammatory markers did not significantly change in our study. A parsimonious interpretation of these findings is that GAD does not seem to be associated with an increase in low-grade inflammation over time in terms of major

Table 1

Baseline characteristics in the whole sample and according to presence or absence of generalized anxiety disorder (GAD) at baseline (n = 2,415).

	All(n = 2,415)	GAD(n = 55, 2.3%)	No GAD(n = 2,360, 97.7%)	Statistics	p value
Socio-demographic characteristics					
Age, years	50.0 ± 8.8 (35.0 - 66.6)	52.1 ± 8.4 (37.3 - 65.7)	49.9 ± 8.9 (35.0 - 66.6)	t = -1.8	0.077
Gender, male / female	47% / 53 %	33% / 67%	47% / 53%	$\chi^2 = 4.4$	0.036
Socioeconomic status ^a	3.4 ± 1.3 (1.0 - 5.0)	3.3 ± 1.3 (1.0 - 5.0)	3.4 ± 1.3 (1.0 - 5.0)	t = 0.9	0.359
Length of follow-up ^b , years	5.5 ± 0.4 (4.8 - 8.5)	5.5 ± 0.4 (5.0 - 7.8)	5.5 ± 0.4 (4.8 - 8.5)	t = 0.4	0.679
Cardio-metabolic risk factors					
Systolic blood pressure, mmHg	124.5 ± 16.0 (81.5 - 219.0)	122.4 ± 16.4 (86.5 - 157.5)	124.6 ± 16.0 (81.5 - 219.0)	t = 1.0	0.316
Body mass index, kg/m ²	25.1 ± 4.1 (15.7 - 59.2)	25.4 ± 3.6 (19.4 - 34.8)	25.1 ± 4.1 (15.7 - 59.2)	t = -0.5	0.594
Glucose, fasting state, mmol/L	5.5 ± 0.9 (0.3 - 21.2)	5.6 ± 1.2 (4.2 - 11.7)	5.4 ± 0.9 (0.3 - 21.2)	t = -1.3	0.182
LDL/HDL-cholesterol	2.1 ± 0.9 (0.3 - 8.5)	2.2 ± 0.9 (0.6 - 5.2)	2.1 ± 0.9 (0.3 - 8.5)	t = -0.8	0.428
Behavioral factors					
Smoking status				$\chi^2 = 1.6$	0.459
Current	27%	20%	27%		
Former	34%	40%	34%		
Never	39%	40%	39%		
Physical inactivity ^c	39%	35%	39%	$\chi^2 = 0.6$	0.458
Psychiatric disorders, DSM-IV					
Healthy and depressive disorder class	78%	33%	79%	$\chi^2 = 97.4$	< 0.001
Anxiety and mood disorder class	16%	65%	15%		
Substance disorder class	6%	2%	6%		

Data are given as mean ± standard deviation (range) or percentage values. χ^2 /t: comparison with subjects with no GAD based on χ^2 tests (categorical variables) / t-tests (continuous variables).

LDL, low-density lipoprotein; HDL, high-density lipoprotein; DSM, Diagnostic and Statistical Manual of Mental Disorders.

^a A value of “3” represents a socioeconomic status of III (middle class) on the Hollingshead Scale.

^b Duration between somatic evaluation at baseline and somatic evaluation at follow-up.

^c Physically inactive if less than 20 minutes twice a week.

inflammatory biomarkers of an increased CVD risk.

Adiponectin might have another function in GAD, which might not become apparent in inflammatory and autoimmune diseases, perhaps due to a different genetic allocation of adiponectin receptors in the context of fear heredity. Indeed, a deficiency of adiponectin in GAD might be referred to functional magnetic resonance imaging (fMRI) studies, which support the hypothesis, that adiponectin might alleviate fear extinction (Garfinkel et al., 2014; Vuong et al. 2020; Zhang et al., 2017) through the adiponectin receptor 2 (AdipoR2) (Zhang et al., 2017). AdipoR1 and AdipoR2 are primarily allotted in the hypothalamus and hippocampus (Garfinkel et al., 2014) and are also closely

associated with anxiety modulating the hypothalamic-pituitary axis (Vuong et al. 2020). These findings are also supported by a recent meta-analysis, which found an inverse association between anxiety and adiponectin levels in obsessive-compulsive disorder, phobic anxiety, panic disorder, antenatal anxiety, and posttraumatic anxiety stress disorder (Vuong et al. 2020). Thus, low adiponectin levels might be linked to symptoms of anxiety through brain areas directly (such as the prefrontal cortex, amygdala, insula, and hippocampus) involved in the processing of fear and anxiety (Garfinkel et al.; 2014, Vuong et al. 2020; Zhang et al., 2017).

Three cross-sectional studies found increased IL-6 in GAD, one in

Table 2

Associations between lifetime General Anxiety Disorder status at baseline and inflammatory measures at follow-up (n = 2,415).

	All participants (n = 2,415) Median (IQR)	General Anxiety Disorder at baseline		Crude		Model 1		Model 2	
		Yes(n = 55, 2.3%) Median (IQR)	No(n = 2,360, 97.7%) Median (IQR)	t	p	β^a	95CI	β^a	95CI
Inflammatory markers at baseline									
Hs-CRP, mg/l	1.0 (0.5-2.1)	1.2 (0.6-2.7)	1.1 (0.5-2.1)	-0.8	0.406				
Interleukin-1 β , pg/ml	0.4 (0.1-2.0)	0.3 (0.1-3.8)	0.4 (0.1-2.0)	-0.3	0.749				
Interleukin-6, pg/ml	1.2 (0.5 -3.0)	1.3 (0.7-3.2)	1.2 (0.5-3.0)	-0.8	0.406				
TNF- α , pg/ml	2.7 (1.7-4.4)	3.3 (2.0-5.0)	2.7 (1.7-4.3)	-1.4	0.159				
Adiponectin, mg/l	8.3 (5.2-12.8)	8.3 (5.4-14.4)	8.3 (5.2-12.7)	-0.7	0.468				
Inflammatory markers at follow-up									
Hs-CRP, mg/l	1.1 (0.6-2.3)	1.4 (0.7-2.3)	1.1 (0.6-2.3)	-0.9	0.386	0.040	-0.175, 0.256	0.028	-0.190, 0.245
Interleukin-1 β , pg/ml	0.7 (0.1-2.6)	1.0 (0.1-4.3)	0.7 (0.1-2.5)	-0.9	0.375	0.109	-0.124, 0.342	0.107	-0.131, 0.345
Interleukin-6, pg/ml	2.4 (0.9-8.2)	1.7 (0.7-5.5)	2.5 (0.9-8.3)	1.3	0.190	-0.221	-0.460, 0.018	-0.249*	-0.493, -0.004
TNF- α , pg/ml	4.6 (2.4-8.0)	4.6 (2.7-8.7)	4.6 (2.4-8.0)	-0.2	0.866	-0.043	-0.288, 0.202	-0.099	-0.349, 0.152
Adiponectin, mg/l	3.8 (2.4-6.1)	3.3 (1.9-5.6)	3.8 (2.4-6.1)	1.2	0.218	-0.278*	-0.494, -0.062	-0.264*	-0.482, -0.045

Values for inflammatory measures were log-transformed and standardized and are given as medians (interquartile ranges).

t: comparison of subjects with versus without GAD based on t-tests.

GAD, General Anxiety Disorder; hs-CRP, high-sensitive C-reactive protein; TNF, tumor necrosis factor; IQR, interquartile range; 95CI, 95% confidence intervals.

Model 1 = adjusted for the corresponding inflammatory marker at baseline, length of follow-up, and socio-demographic variables (age, gender, socioeconomic status).

Model 2 = Model 1 + behavioral cardiovascular risk factors (physical activity, smoking status), physical cardiovascular risk factors (body mass index, glucose level, systolic blood pressure, low density lipoprotein/high density lipoprotein ratio) at baseline, and Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV classes.

^a Multiple regression with log-transformed and standardized cytokine or hs-CRP or adiponectin.

* p < 0.05.

saliva, all with less rigorous adjustment for potentially confounding variables than in our study (Costello et al., 2019). The only two longitudinal studies found no association between GAD and IL-6 (Glaus et al., 2018; Lamers et al., 2019), whereas we found decreased IL-6 levels in GAD only after systematically controlling for all psychiatric classes in the final statistical model. Therefore, based on the currently available data it would be premature to make a final judgment about an independent relationship of GAD with increased or decreased levels of IL-6.

To sum up, this study showed a decrease over time in both adiponectin and IL-6 in individuals with GAD compared to their counterparts implicating that chronic low-grade inflammation is unlikely a plausible link between GAD and incident CVD. Future longitudinal studies should explore alternative mechanisms underlying the potential association between GAD and the CVD risk.

5. Ethics Statement

The CoLauS|PsyCoLauS study was approved by the Institutional Ethics Committee of the University of Lausanne. Before all participants signed a written informed consent in accordance with the Declaration of Helsinki, they received a detailed description of the goal and funding of the study.

6. Contributors

Conceived and designed the experiments: ENW MP PV RvK. Performed the experiments: ENW RvK. Analyzed the data: ENW CV MPS MG RvK. Contributed reagents/materials/analysis tools: ENW CV MG JG MP PV RvK. Wrote the paper: ENW MPS CV RvK.

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Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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