

Association Between Levels of Depression Symptoms and Moderately Increased Levels of the Inflammation Marker Albuminuria Is Explained by Age and Comorbidity.

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Abstract

Background: The study aimed to examine whether there are associations between levels of depression symptoms and levels of the inflammation marker albuminuria.

Materials and methods: The 8303 participants in this cross-sectional study were subjects from the second survey of the Trøndelag Health Study (HUNT, Norway). Depression symptoms were assessed by the Hospital Anxiety and Depression Scale (HADS). Logistic regression analysis was performed to estimate the odds ratio (OR) for moderately increased albuminuria (ACR > 3.0 mg/mmol) according to different HADS subgroups and -scores.

Results: Unadjusted ORs for moderately increased albuminuria were significantly increased in those with HADS > 8 (OR 1.27, 95% CI 1.05-1.54, $p=0.013$) and HADS > 11 (OR 1.59, 95% CI 1.19-2.14, $p=0.002$). However, after adjusting for age and sex, only HADS > 11 was significantly associated with ACR > 3.0 mg/mmol (OR 1.46, 95% CI 1.08-1.98, $p=0.014$), and after multivariable adjustments for cardiovascular risk factors and comorbidity, there were no significant associations.

Conclusion: The positive and significant association between moderately increased albuminuria and symptoms of depression found in unadjusted analyses weakened and disappeared after adjustments. Although individuals with depressive symptoms had albuminuria more often than individuals without such symptoms, albuminuria may reflect other comorbidity and inflammation conditions than depression.

Introduction

The immune system may play a part in the pathophysiology of mood disorders^{1,2}. Major depression has now for several years been a studied area regarding involvement of immune function and inflammation, like oxidative stress-mediated brain damage³. Studies have also shown that use of anti-inflammatory agents in combination with conventional therapy may improve outcomes in mood disorders^{4,5}.

The excretion of moderately increased levels of albumin in the urine, former called microalbuminuria, has been well documented to predict cardiovascular (CV) morbidity and mortality in both diabetic and non-diabetic persons⁶⁻⁸. Severely increased albuminuria is probably a direct cause of inflammation in the kidney interstitium, leading to increased progression towards kidney failure, whereas moderately increased levels are more likely a biomarker of subclinical vascular pathology and atherosclerosis. The link between moderately elevated urine albumin excretion (UAE) and atherosclerosis seems to be inflammation with endothelial dysfunction, leading to increased permeability and leakage of albumin through the vessel wall^{9,10}. Today, moderately increased albuminuria seems to be a crucial renal marker for a generalized damage and systemic inflammation in the vascular system. Studies support this, showing that inflammatory parameters are significantly and independently associated with UAE in prehypertensive, otherwise healthy individuals¹¹.

There have not been many previous studies examining the relationship between depression and albuminuria¹²⁻¹⁴, and to our knowledge, there have not been carried out a study of this kind in a large population, aged 20-90 years, as this health survey. We hypothesised a positive association between moderately increased albuminuria, reflecting inflammation, and levels of the depression dimensions.

Methods

Study subjects

During 1995-1997, the second survey of the Trøndelag Health Study (HUNT, Norway), invited all residents ≥ 20 years ($n=93\ 898$), and a total of 70% participated. The survey comprised questionnaires, which included questions on CVD (angina pectoris, myocardial infarction and stroke), smoking habits, other lifestyle factors, and a clinical examination. Details of the HUNT study design and albuminuria screening have been published previously^{32,43}. All those with self-reported diabetes mellitus and/or treated hypertension and a 5% randomly selected sample of the total population were included in the albuminuria screening study. A total of 9598 participants delivered three morning urine samples for albuminuria analysis (overall response rate 84%). Of these, 8801 had answered questions with depression and/or anxiety dimensions. Those who answered confirmatory to one of the questions about UTI in the previous week, persistent haematuria in the previous year, menstruation at time of urine collection or pregnancy were excluded from the analysis ($n=338$). So were also 160 individuals with severe albuminuria ($ACR \geq 30$ mg/mmol), leaving a total of 8303 subjects included in the main analysis.

Clinical examination

The clinical examination included standardized measurement of height, weight, blood pressure and pulse rate. Height was measured without shoes to the nearest centimetre, and weight was measured to the nearest half-kilogram while wearing light clothing without shoes. Three consecutive standardized blood pressure measurements were recorded with one-minute interval. After a minimum of two minutes rest, the measurements were performed in the sitting position, using an automatic oscillometric method (Dinamap 845XT; Criticon, Tampa, FL).

Measurement of signs and symptoms of clinical depression and anxiety

Symptoms of anxiety and depression were assessed by the HADS¹⁵. HADS consists of seven depression related items (HADS-D) and seven anxiety related items (HADS-A), each with a four-point ordinal scale to describe symptom severity from 0 to 3. Valid HADS response was defined as completed answer on five or more items on the subscale. Missing responses among those who filled in 5 or 6 items were replaced based on the sum of completed items multiplied by 7/5 or 6/5, respectively.

Urine- and blood sampling

The participants included in the albuminuria screening received a unit with three plastic receptacles for three first morning urine samples and three transport tubes, and one envelope for return by mail back to the laboratory. Additionally, the participants received instructions for urine collection, information about the albuminuria-screening and a questionnaire about UTI, haematuria and menstruation.

Blood sampling was carried out whenever subjects attended (i.e. in non-fasting state). Fresh serum and urine samples were analyzed at the Central Laboratory at Levanger Hospital, on Hitachi 91 Autoanalyzer (Hitachi, Mito, Japan). Details of the laboratory methods have been published⁴⁴. Urine albumin and creatinine were measured by using an immunoturbidimetric method (anti-human serum albumin, Dako Norway, Oslo) and Jaffé method respectively. ACR was used as an expression for urine albumin excretion.

Statistical analysis

Body mass index (BMI) was calculated in kilograms per meter squared. Systolic (SBP) and diastolic blood pressure (DBP) were included as the mean of the second and third of three measurements. ACR was calculated as [urine albumin (mg)]/[urine creatinine (mmol)], and was defined as the mean of three ACRs. Moderately increased albuminuria was defined as $ACR \geq 3.0$ mg/mmol and < 30 mg/mmol. We used the t-test for independent samples, Mann-Whitney U statistics and chi-square to examine baseline differences between two means or proportions.

Logistic regression analysis was performed to estimate the odds ratio (OR) for moderately increased albuminuria ($ACR \geq 3.0$ mg/mmol) according to different HADS subgroups and -scores. A priori selected potential confounding factors were used in both bivariate and multivariate adjusted analyses, i.e age, sex (in the total population), SBP, waist circumference, cholesterol, creatinine, history of CVD (yes/no), daily smoking (yes/no), treated hypertension (yes/no), diabetes (yes/no), education (primary and secondary school [≤ 12 years] and college or university [> 12 years]) and strenuous physical activity (< 1 hour/week, ≥ 1 hour/week). All statistical analyses were conducted with the Statistical Package for the Social Sciences, version 25.0 (SPSS Inc., Chicago, USA), and significant alpha criterion was set to 0.05 or above.

Results

The baseline characteristics of the population showed that those with Hospital Anxiety and Depression Scale (HADS)-depression (D) ≥ 8 had significant higher mean albumin/creatinine ratio (ACR) than those with HADS-D < 8 (1.91 mg/mmol v.s. 1.68 mg/mmol, $p=0.030$). They had higher proportion of moderately increased albuminuria ($ACR \geq 3.0$ mg/mmo; 13.3% v.s. 10.8%, $p=0.012$), corresponding result was found in those with HADS-D ≥ 11 . However, in addition to increased albuminuria, those with HADS-D ≥ 8 or ≥ 11 were significant older, had higher BMI, creatinine and lipid levels compared to those with lower HADS-D score. They also had more frequently diabetes, treated hypertension and cardiovascular disease (CVD),

had lower education, and were more often smokers and less physical active than those with HADS-D score < 8 (Table 1).

There was a significant higher prevalence of depression symptoms in those with moderately increased albuminuria (ACR \geq 3.0 mg/mmol) compared to those without albuminuria (ACR < 3.0 mg/mmol), measured by HADS-D \geq 8 (15.9% v.s 13.2%, $p=0.012$) or HADS-D \geq 11 (6.0% v.s 3.9%, $p=0.002$). Stratified by sex, corresponding result was found in men. In women, significant higher prevalence of depression symptoms in those with albuminuria was found only with HADS-D \geq 11 (6.0% v.s 3.6%, $p=0.017$) (Table 2).

Unadjusted OR for moderately increased albuminuria was significantly increased in those with HADS-D \geq 8 (OR 1.27, 95% CI 1.05-1.54, $p=0.013$) and HADS-D \geq 11 (OR 1.59, 95% CI 1.19-2.14, $p=0.002$). However, after adjusting for age and sex, only HADS-D \geq 11 was significantly associated with ACR \geq 3.0 mg/mmol (OR 1.46, 95% CI 1.08-1.98, $p=0.014$), and after multivariable adjustment there were no significant associations (table 3).

The significant association disappeared especially by variables as SBP, smoking, diabetes, CVD, creatinine, and waist circumference.

Discussion

This study demonstrated a significant positive association between the measured depression symptoms and moderately increased albuminuria. However, the association weakened after adjusting for age and sex, and after multivariable adjustment the significant association disappeared. Therefore, the unadjusted correlation between depression symptoms and albuminuria in the study population seemed to be explained by other factors causing possible inflammation, like increased CV risk and other comorbidities.

A positive association between albuminuria and depressive symptoms/depressive episodes has been published by Martens et al ¹². This study has also a cross sectional design, however with fewer participants than ours. As mentioned by the authors, almost 1/3 had diabetes type 2, compared to 16% in our study, and although adjustment of this comorbidity in both studies, the population from Netherlands might have a higher cardiovascular (CV) risk profile. Additionally, the studies differed in methods regarding classification of depressive symptoms (PHQ-9 versus HADS), and Martens et al. also included a clinical interview (MINI) to assess the presence of minor or major depressive episodes, which gives a more valid classification of depressive episodes. HADS is not a diagnostic instrument for clinical diagnoses, but it identifies seven depressive symptoms. A literature review, which includes 31 studies, concluded that the HADS holds good properties for depression in patient populations in primary care and hospital settings ¹⁵. Even high scores of HADS-D do not give a depression diagnosis, but HADS has been used in several studies, including HUNT studies ^{16,17}. Various cut-off levels have been reported from various study populations, and studies comparing HADS with «gold standard» or reference standard

diagnostic interviews for depression disorder have disclosed reasonable validity ^{18,19}. The Norwegian version of HADS is a relatively well validated screening instrument for anhedonia and psychological distress ^{20,21}.

Depression and stress related symptoms may be associated with a chronic, low-grade inflammation response, and studies have shown association between depression and activation of cell-mediated immunity as well as increased oxidative and nitrosative stress ²². Several factors increase the risk for development of depression whilst they also are associated with systemic inflammation; psychosocial stressors, poor diet, physical inactivity, obesity, smoking, altered gut permeability, atopy, dental cares, sleep and vitamin D deficiency ²². Some of these factors are also associated with albuminuria, like physical inactivity ²³, obesity ^{24,25} and smoking ^{26,27}, and were included as confounders in our analyses, and might have been stronger associated with albuminuria than depression symptoms.

The cerebral small vessel disease, defined as a disease of the small blood vessels in the brain, and a frequent cause of stroke and dementia, is also hypothesized to lead to depression (the vascular depression hypothesis) through disruption of neuronal circuits involved in mood regulation ^{28,29}. Although we recently published the results of a positive association between vascular dementia and low-grade albuminuria ³⁰ and have found significant association between lacunar stroke and albuminuria ³¹ in the same HUNT-material, we could not support the vascular depression hypothesis by our results. However, the results may reflect the limitation of HADS in measurement of depression more than the true association between depression and vascular endothelial dysfunction.

There are several strengths of this study. The population-based approach and the high attendance rate make selection bias less likely. The response rate in the albuminuria screening was especially high in the elderly and those with diabetes and treated hypertension ³². Another strength was that albuminuria analyses were performed in fresh urine samples without long-term storing, in contrast to other studies ³³. Several studies conclude that measuring ACR is a specific and sensitive alternative to twenty-four-hour urine collection in population-based albuminuria screenings ^{34,35}.

One of the most important limitations is the self-reported symptoms of depression, which always may lead to misclassification. As the HADS questionnaire does not mirror somatic depressive symptoms, cases with predominantly somatic depressive, i.e. biologically based symptoms, as weight loss, fatigue and insomnia, might be undetected. However, these symptoms overlap with several other morbidities, which might be associated with albuminuria, thus somewhat underestimating than overestimating our results. There is probably considerable variability of inflammation within the depressed population, and there are studies that find subtypes of depression which are more inflammation-related ³⁶. On the other hand, HADS has shown in other studies association with inflammation-variables, as CRP ³⁷. Further, we had no information about medical treatment of depression, where treatment by tricyclic antidepressant could increase CV risk ³⁸ in contrast to selective serotonin reuptake inhibitors which are associated with reduced CV risk ³⁹. Another limitation is the lack of other inflammatory markers. The HUNT study includes

a large population and questions about several diseases, and because of limited resources specific inflammation- or biological parameters for most diseases were not included. Neither we have information about all comorbidities in this epidemiological study since comorbidities are very heterogeneous. We therefore adjust for risk factors and comorbidities most correlated with albuminuria and depression.

Further, the information about use of other medication, which could have influenced albuminuria levels, was lacking, i.e. use of among others angiotensin converting enzyme (ACE) inhibitors and angiotensin II blockers (ATB). However, at the time of HUNT 2, the use of ACE inhibitors and ATB in Norway were still low. Another limitation includes the diagnosis of urinary tract infection (UTI). Those who reported UTI in the previous week were excluded from the analyses, but we were not able to adjust for asymptomatic UTI. This could contribute to a non-differential misclassification that might further weaken the associations found. The cross-sectional design limits the possibility for discovering cause-effect relationships.

Although the association between symptoms of mood disorders and albuminuria was non-significant after multi adjustment in this study, there was a significant increased prevalence of albuminuria in the depressive symptoms sample compared to the non-depressive. Intervention in albuminuria positive individuals with diabetes or hypertensive are recommended and include more aggressive treatment of CV risk factors like blood pressure, smoking, hyperlipidemia and overweight^{40,41}. So far, there are no recommendations of albuminuria screening in otherwise healthy people, although small studies have found reduction of CVD by intervention with ACE inhibition⁴². Individuals with depression and elevated peripheral inflammatory markers, included albuminuria might have benefit of anti-inflammatory agents, such as acetyl-salicylic acid (ASA), statins, ACE inhibitors and ATB to improve the treatment of depression and other mood disorders, leading to reduction of disability, even though there is much more research to be carried out here.

In conclusion, the positive and significant association between moderately increased albuminuria and depressive symptoms found in unadjusted analyses weakened and disappeared after adjustments, indicating that albuminuria is stronger associated with age, other comorbidities, and CV risk factors. Another screening or diagnostic tool for depressive symptoms should also be considered in this case.

Declarations

Ethics declarations

All participants signed written, informed consent. All surveys, protocols and linkage of data were approved by the Norwegian Data Inspectorate and by the Regional Committee for Medical and Health Research Ethics (according to no. 2009/1193 4.2006.2481). All methods and experiments were carried out in accordance with relevant guidelines and regulations.

DATA AVAILABILITY:

All data generated and analyzed during this study are included in this manuscript, They are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS: S.R. and T.H. designed the study. S.R analyzed the data and prepared the tables. S.R. and T.H. wrote the manuscript text.

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Tables

Table 1. Basic characteristics of the study population, stratified by HADS-Ds subgroups. Values are mean (\pm SD) unless other stated. ACR, albumin/creatinine ratio; CVD, cardiovascular disease

TOTAL	HADS-D < 8 n=6676	HADS-D ≥ 8 n=1118	HADS-D ≥ 11 n=343	P value <v.s≥ 8	P value <v.s≥ 11
Age, years	60.2 (11.6)	63.3 (13.4)	63.1 (13.8)	<0.001	0.002
ACR, mg/mmol	1.68 (3.03)	1.91 (3.36)	2.04 (3.74)	0.030	0.093
ACR ≥ 3.00 mg/mmol (%)	10.8	13.3	16.3	0.012	0.002
SBP, mmHg	150 (23)	151 (23)	149 (23)	0.040	0.711
DBP, mmHg	85 (13)	86 (13)	85 (13)	0.710	0.501
BMI, kg/m²	27.9 (4.5)	28.7 (4.8)	28.7 (5.0)	<0.001	0.008
Waist circumference, cm	91.0 (11.9)	93.8 (12.9)	94.7 (13.6)	<0.001	<0.001
Creatinine mmol/l	91.4 (18.9)	93.3 (18.9)	95.2 (21.5)	0.001	0.002
Cholesterol, mmol/l	6.2 (1.2)	6.3 (1.3)	6.4 (1.3)	0.002	0.005
Triglycerides, mmol/l	2.02 (1.22)	2.30 (1.50)	2.45 (1.60)	<0.001	<0.001
Glucose, mg/dl	6.2 (2.5)	6.3 (2.4)	6.5 (2.8)	0.145	0.031
Diabetes (%)	15.4	20.1	20.8	<0.001	0.015
Smoking daily (%)	20.2	22.8	24.2	0.050	0.037
Education high (%)	13.2	6.7	5.8	<0.001	<0.001

Hard physical activity (%)	17.2	12.1	12.5	<0.001	0.020
Treated hypertension (%)	63.6	68.9	69.6	<0.001	0.018
CVD (%)	19.3	29.8	34.1	<0.001	<0.001

Table 2. Prevalence of depression (HADS-D ≥ 8 and ≥ 11)

in subgroups with or without albuminuria (ACR $<$ and ≥ 3.0 mg/mmol),

in the total population and stratified by sex. ACR; albumin/creatinine ratio.

HADS-D score	ACR $<$ 3.0	ACR ≥ 3.0	P value
	n=7365	n=938	
	%	%	
TOTAL			
≥ 8	13.2	15.9	0.012
≥ 11	3.9	6.0	0.002
MEN			
≥ 8	13.7	16.7	0.035
≥ 11	4.2	6.0	0.051
WOMEN			
≥ 8	12.7	14.8	0.206
≥ 11	3.6	6.0	0.017

Table 3. Odds ratio (OR) for moderately increased albuminuria (ACR \geq 3.0 mg/mmol) according to different HADS subgroups/scores.

Multivariable adjusted for age, sex (in the total population), systolic blood pressure, waist circumference, cholesterol, creatinine, cardiovascular disease, daily smoking cigarettes, treated hypertension, diabetes, education, and hard physical activity. ACR; albumin/creatinine ratio.

	TOTAL			MEN			WOMEN		
	OR	95 % CI	P value	OR	95 % CI	P	OR	95 % CI	P value
HADS-D \geq 8									
Unadjusted	1.27	1.05-1.54	0.013	1.31	1.02-1.69	0.035	1.20	0.90-1.60	0.207
Adjusted for age (and sex)	1.14	0.94-1.38	0.186	1.23	0.95-1.60	0.116	1.05	0.79-1.41	0.731
Multivariable adjusted	0.95	0.71-1.26	0.700	1.02	0.71-1.47	0.902	0.83	0.50-1.36	0.450
HADS-D \geq 11									
Unadjusted	1.59	1.19-2.14	0.002	1.49	1.00-2.22	0.052	1.69	1.09-2.62	0.018
Adjusted for age (and sex)	1.46	1.08-1.98	0.014	1.46	0.96-2.21	0.074	1.49	0.96-2.33	0.077
Multivariable adjusted	0.97	0.61-1.54	0.894	0.94	0.53-1.68	0.833	0.95	0.42-2.16	0.896