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The role of the inflammatory markers ferritin, transferrin and fibrinogen in the relationship between major depression and cardiovascular disorders – The German Health Interview and Examination Survey

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Objective: To determine levels of inflammation (ferritin, transferring and fibrinogen) in major depression (MDD) and comorbid cardiovascular disease (CVD) in an adult population.

Method: In 4181 participants of the German Health Interview and Examination Survey MDD was assessed through the Composite International Diagnostic Interview (CIDI). Coronary heart disease, stroke, and hypertension were diagnosed by a computer-assisted physician interview. Analyses were performed using anova models stratified for gender.

Results: Ferritin, transferrin and fibrinogen levels showed opposing patterns in individuals with either CVD or MDD alone. In comorbidity analyses, male participants with MDD plus comorbid CHD or hypertension had lower levels of ferritin and lower fibrinogen levels in hypertension compared to men without MDD, while in women, results were inconsistent.

Conclusion: Opposing patterns of inflammatory markers in CVD or MDD alone were reversed when both conditions were present. MDD reduced levels of ferritin, transferrin and fibrinogen in CVD in a gender-specific way.

Introduction

Major depression (MDD) is a highly prevalent disorder in the general population and a large proportion of patients with frequent medical diseases, such as cardiovascular disease (CVD) or cancer, suffer from depressive disorders. Almost half of the latter can be classified as major depression (1). Among patients with CVD the prevalence of depression among those with coronary heart disease is 16% to 23% (2) and high incidences and prevalence rates of affective disorders are also observed in individuals with chronic heart failure or stroke (3, 4).
A variety of hypotheses have emerged over past years suggesting biological mechanisms by which depression might increase the risk of cardiovascular disease (5). A frequently cited hypothesis describes a chronic inflammation process as the biological explanation for a relationship of coronary heart disease and depression (6–8). Most prior studies addressing this inflammation process analysed the C-reactive protein as a biomarker of inflammation. However, other biomarkers, such as ferritin, transferrin and fibrinogen, have also been suggested to be involved in systemic inflammation. Important determinants of the inflammatory process are the release of cytokines and alterations of the iron metabolism characterized by decreased serum iron (Fe) and transferrin (Tf) levels with normal or increased ferritin levels (9, 10). Inflammation and alterations in iron metabolism seem to be closely related, since iron is involved in inflammation through free radical production with subsequent decrease of serum iron (11).
Previous studies in individuals with CVD found that coronary heart disease is related to increased levels of fibrinogen (12) and decreased levels of transferrin (13). Ferritin may also be increased in CVD (14) and cardiovascular risk factors (15, 16), but findings have been inconsistent (17–20). Prior studies in patients with depression suggested that systemic, low-grade inflammation plays a role in the onset and the course of the disease (21). Increased fibrinogen (22) and ferritin (23) and decreased transferrin serum levels (23) as markers of inflammation have been related to MDD. Furthermore, genes promoting inflammation have been involved in the pathogenesis of MDD (22).
Since most of these studies were performed in clinical patient samples with more severe forms of MDD and/or CVD conditions, it is not known, if levels of these inflammation markers are also related to milder forms of MDD and CVD. Studies in the general population have the potential advantages to capture milder forms of MDD and
CVD and to analyse different cardiovascular diseases in the same setting and the same time.

Aims of the study

Aim of this study was to determine levels of three markers of inflammation (fibrinogen, ferritin, transferrin) in individuals with and without MDD and three cardiovascular conditions (coronary heart disease, stroke or hypertension). It was hypothesized that the inflammatory markers ferritin and fibrinogen were increased and transferring decreased in individuals with MDD or CVD only and in the situation where both conditions were comorbid present.

Material and methods

Sample

The German Health Interview and Examination Survey consisted of a core survey (GHS-CS) and several supplemental surveys including the Mental Health Supplement (GHS-MHS). The study was commissioned by the German Ministry of Research, Education and Science (BMBF) and approved by the relevant institutional review board and ethics committee. Its sample was a stratified random sample from 113 communities throughout Germany with 130 sampling units (random sampling steps: 1. selection of communities, 2. selection of sampling units, and 3. selection of inhabitants from population registries). Data collection was done between October 1997 and March 1999. The response rate of the core survey was 61.4% (n = 7124). Of the non-responders, 1860 (41%) did at least fill out a short questionnaire for a non-responder-analysis (gender, age, educational level, self-rated subjective health status, smoking status). There were no significant differences between these and the sample with regard to gender and age (exception: 70–79 year old women; but these were not eligible for the mental health part, see below) and to self-rated subjective health status and smoking status, but there was a tendency to have a lower educational level in the non-responders. Thus, the sample of the core survey up to 65 years (N = 6159) was regarded as sufficiently representative to be utilised as a starting sample for the mental health supplement (GHS-MHS).

A screening questionnaire for mental disorders with eleven questions representing essential DSMIV and ICD-10 criteria (CID-S) (24) had been administered at the end of the medical examination of the core survey. All of the participants from the core survey who answered at least one of these items with yes (screen positives) and a random sample of the 50% of the participants who answered all screening questions in the negative (screen negatives) were included in the mental health supplement. Non-response did not differ between screen-negative and screen-positive respondents from the core survey. To account for the over-sampling of screen positives and for differential non-response among subgroups, data were weighted by selection probabilities and demographic characteristics (age, gender, and region) in the later analyses.
Respondents of the core survey older than 65 years were excluded from the GHS-MHS because the psychometric properties of the CIDI, the interview used in the study, have not yet been satisfactorily established for use in older populations (25). The conditional response rate of the GHS-MHS was 87.6%, resulting in a total of n = 4181 respondents (out of the eligible n = 4775) who completed the mental health assessment. Sociodemographic characteristics of this sample matched the German general population aged 18–65 years in terms of age, gender and social status. The presented (weighted) results can be regarded as representative with regard to age, gender and East-West Germany distribution for the German non-institutionalized adult population from 18 to 65 years of age with sufficient language skills to follow the interviews. Written informed consent was obtained for both surveys. Participants did not get any financial compensation for their study participation. A full description of the study methodology and sampling can be found elsewhere (24, 26).

Assessment of cardiovascular diseases

The core survey consisted of (1) a self-report questionnaire, (2) a standardized computerassisted medical interview, (3) anthropometric and blood pressure measurements and the collection of blood and urine samples, and (4) a screening for mental disorders, which served as the first stage of the GHS-Mental Health Survey (MHS). All examinations and interviews were done in study centres at the respective sample points throughout Germany. The self-report questionnaire evaluated the subjects_ current and past physical symptoms and complaints, health care utilization, and impairments and disabilities. Completion of this questionnaire was followed by a face to face computer assisted medical interview by a study physician who inquired about previous physician diagnoses (27, 28).
Given the cross-sectional study design all respondents with medical diseases were survivors of any previous life threatening events, e.g. myocardial infarction or stroke, including those having had revascularisation procedures. No estimations of the prevalence of CVDs among non-survivors were available (27, 28). This analysis was restricted to three diagnostic groups, hypertension, coronary heart disease and stroke. Blood pressure was measured during the examination by means of three consecutive measurements allowing for 3 min intervals between each measure. According to the WHO guidelines hypertension was defined as systolic blood pressure ‡140 mmHg and diastolic blood pressure ‡90 mmHg (29). All three measures had to be above either diastolic or systolic or both criteria to qualify as hypertensive. Participants with the previous diagnosis of hypertension, but normal blood pressure were considered as hypertensive. Coronary heart disease comprises participants with previous ischemic heart disease, previous non-fatal myocardial infarction or heart failure. Stroke included all major stroke types and transitory ischemic attacks (30).
Social status was classified into three strata (low, medium, and high social status), through use of the Winkler Social Index. The latter includes information about income, education, and current occupation and yields a summary score ranging from 3 to 21 points. Established cut-offs were then used to categorize individuals into the three social strata (low, medium, high). The Winkler Social Index is a well established score applied to several National Surveys in Germany (31).

Assessment of mental disorders

Psychopathological and diagnostic assessments were based on the computer-assisted version of the Munich Composite International Diagnostic Interview. The DIA-X/M-CIDI is a modified version of the World Health Organization CIDI, version 2.1 (32), supplemented by questions to cover DSM-IV and ICD-10 criteria. The DIAX/M-CIDI is a fully structured interview that allows for the assessment of symptoms, syndromes, as well as 4-week, 12-months and lifetime diagnoses of DSM-IV mental disorders. With regard to Major Depression (MDD) reliability and validity of this instrument is good to very good. Details of the psychometric properties of the CIDI are reported elsewhere (33). MDD was used as a lifetime categorisation. We additionally analysed single episode MDD and recurrent MDD

separately to detect potential dose-response relationships. Most interviews of the mental health assessment were done within 2 to 4 weeks after the core survey medical examination at the homes of the respondents (average duration: 63 min) by study doctors specifically trained in the use of the computer-assisted version of the Munich Composite International Diagnostic Interview (DIAX / M-CIDI).

Laboratory assessment

Blood drawing followed a standard protocol, fasting time was recorded and all laboratory tests were performed in a central laboratory. The Microparticles-Enzyme-Immunoassay (MEIA) from Abbot was used to measure ferritin, whereas the Nephelometry method from Siemens was used to measure transferrin and fibrinogen.

Statistical analyses

All laboratory parameters (ferritin, transferrin, and fibrinogen) were log-transformed to achieve normal distribution of the data. Mean values of the three log-transformed markers were first compared across categories of sociodemographic and disease categories using linear regression (in case of more than two categories) or Student_s T-Test (in case of only two categories). In these models the respective inflammatory marker was the dependent variable. Further analyses were carried out stratified for men and women, and for CVD type using adjusted means from Analysis of Variance (anova) models. In these models means of each biomarker were compared between participants with and without MDD after adjustment for age, social status, body mass index, smoking status and alcohol consumption.
Analyses were performed by use of spss (version 15.0), which includes procedures for the analysis of weighted data (34).

Results

Sample characteristics

In total, 4181 participants aged 18–65 years were assessed for mental health disorders. About 49.7% of the sample were women, mean age of all participants was 43.5 years (min 18; max 65; SD 11.6). The overall lifetime prevalence of major depression was 14.8%. It was significantly higher in women as compared to men (20.7% vs. 8.9%; P = 0.0005). Single lifetime episodes of major depression were diagnosed in 9.3% (n = 388) of the participants whereas the prevalence of recurrent MDD was 5.5% (n = 231).
Of the total study population, 18.4% were classified as hypertensive while prevalence rates of CHD and stroke were 4.9% and 1.5% respectively. MDD was more frequent among participants with, compared to those without, any of the three examined types of CVD (CHD 6.7% vs. 4.6%, P = 0.041; stroke 2.7% vs. 1.2%, P = 0.006; hypertension 19.6% vs. 18.2%; P = 0.43). Ferritin, transferrin and fibrinogen levels across the sample Table 1 presents log-transformed ferritin, transferring and fibrinogen levels according to sociodemographic variables and MDD and CVD status. While ferritin and fibrinogen levels increased with age, transferrin decreased in higher age groups. Men had higher ferritin values as compared to women, whereas transferrin and fibrinogen were significantly higher in female than in male participants. Social status was significantly related to transferrin and fibrinogen levels.
Participants with MDD had lower ferritin levels (log-transformed mean, 4.08 vs. 4.2; P = 0.003), transferrin levels (1.03 vs. 1.05; P = 0.056) and fibrinogen levels (1.02 vs. 1.05; P = 0.009) if no stratification for CVD status was done, compared to those without MDD. A different pattern emerged for the same analyses in participants with CVDs, again without stratification for MDD status. While ferritin did not vary between those with and without any of the three CVDs (4.2 vs. 4.1; P = 0.15), both other markers were significantly increased in participants with CVD as compared to those without (transferrin 1.07 vs. 1.03, P = 0.0005; and fibrinogen 1.06 vs. 1.03, P = 0.002).
Additional stratification for type of CVD (Table 1) showed that the presence of coronary heart disease was related to lower ferritin levels and higher transferrin levels. Hypertension was associated with higher levels of all three markers, while no significant variation of any marker with the presence of stroke was observed. Ferritin, transferrin and fibrinogen in men and women Further analyses were carried out to compare levels of inflammatory markers according to MDD status and comorbidity with

CHD, stroke and hypertension These results are presented in Table 2. In men, MDD was related to significantly lower ferritin values in participants with either CHD or hypertension, but not with stroke. In contrast, ferritin levels in women were not different among those with or without MDD across all types of CVD. Transferrin levels showed no significant differences according to MDD status in any of the examined CVD types in men. Levels were significantly lower in hypertensive women with MDD compared to non-depressive women with hypertension. Fibrinogen levels were lower in men with MDD and any of the three CVDs, compared to those without MDD. However, the difference was only statistical significant in those with hypertension. In women fibrinogen levels were not related to the comorbid situation.
Finally, when testing a potential dose-response relationship between the frequency of MDD episodes and levels of inflammatory markers, we found no stronger effect of recurrent MDD episodes compared to a single one for any of the three inflammation markers.

Discussion

In this analysis we examined levels of the inflammatory markers ferritin, transferrin and fibrinogen in the comorbid relation between MDD and three frequent types of cardio-/cerebrovascular diseases in an adult general population. MDD was related to lower levels of all three markers, while CVD was associated with higher levels. In the comorbid situation with both conditions present MDD was, with one exception, associated with lower levels of the three inflammation markers in both genders. However, not all differences were statistically significant. MDD was significantly related to lower ferritin levels in male participants with a history of CHD and hypertension and to lower fibrinogen levels in men with hypertension. In women MDD was related to lower transferring levels in women with hypertension only.
Our findings contribute to the emerging literature on the role of inflammation in the relationship between CVD and MDD (35, 36). However, no previous study has particularly analysed ferritin, transferrin and fibrinogen in this relationship. Recent gender-specific analyses support the inflammation hypotheses for CVD and comorbid depression. A recent study in women investigating inflammatory markers in the relationship between suspected coronary ischemia and depression found a robust association of CRP levels with depression, although inflammatory biomarkers explained only a small portion of the association between depression and CVD incidence (37). On a similar note, while a recently published prospective study found evidence of a positive association between depressive symptoms and risk of incident stroke, inflammation, measured through CRP at baseline, did not appear to mediate the relationship between depressive symptoms and stroke (38). Studies investigating other inflammatory markers such as ferritin, transferrin, fibrinogen and cytokines are warranted to further elucidate the relationship between CVD and comorbid MDD.
Our findings on CVD alone are in confirmation of a study by Tseke et al. (39) reporting increased levels of fibrinogen in CVD, which was interpreted as an expression of chronic inflammation in CVD. In addition, we confirmed that transferrin may be increased in coronary heart disease as previously reported (40). The involvement of transferrin in chronic inflammation is theoretically explained through prohibiting iron from participating in oxidative reactions in systemic inflammation; however, transferrin has also been found to promote free radical damage and thus enhancing systemic inflammation (11). In our analysis, MDD alone was related to lower ferritin and fibrinogen levels. A recent report by Whooley et al. (41) showed that depression was associated with lower levels of fibrinogen in outpatients with CHD, which could not be confirmed by our analysis either in men or women. Our finding on decreased ferritin is contradicting earlier studies that reported normal or increased ferritin levels in depression (9, 10). This finding might be related to milder forms of MDD included in a general population sample in our study as compared to more severe cases of depression in clinical samples. Finally, a dose-response relationship hypothesizing that recurrent MDD had stronger effects on inflammatory marker levels than single MDD as compared to no MDD was not found in this analysis.
Our study has strengths and limitations. The study in the general adult population allowed for gender-specific analyses of various types of cardiovascular diseases and single and recurrent MDD applying the same study framework. Among the limitations is the cross-sectional study design, that does not allow to draw conclusions on the time course and causative effect of inflammatory markers in the relationship between CVD and MDD. Other inflammatory markers such as cytokines are also of in interest for this research. In addition, since the cardiovascular disorders were partly based on self-report, the risk of misdiagnoses might have been introduced despite the verification of the medical diagnoses by a qualified physician.
Finally, the time gap of 2–4 weeks between the blood samples and the mental health assessment might have introduced some bias in the association between blood parameters and depression or CVDs. Since the investigated blood parameters such as ferritin and transferrin reflect longer-term

rather than acute changes in the iron metabolism, it is assumed that this potential bias is minor in our study. However, future cross-sectional studies should aim for the simultaneous assessment of blood parameters and mental health diagnoses.

In conclusion, our findings support a genderspecific role of the inflammatory markers of ferritin, transferrin and fibrinogen in the relationship between CVD and MDD. MDD reduced levels of the three inflammation markers in individuals with CVD as opposed to levels of inflammatory markers in CVD unstratified for MDD. Gender-specific analyses and stratification for CVD diagnoses and MDD status is necessary to detect the opposing patterns in inflammatory marker levels in the relationship between CVD and MDD.

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Declaration of interests

All authors declare no biomedical financial interests or potential conflicts of interest.

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Tables

Table 1. Ferritin, transferrin and fibrinogen across the sample ‡ (n = 4181)

	Ferritin Mean†; SD	Transferrin Mean†; SD	Fibrinogen Mean†; SD
Age			
18–29 (n = 895)	3.65; 0.9***	1.1; 0.2***	1.0; 0.22**
30–49 (n = 1977)	4.1; 1.1	1.05; 0.2	1.15; 0.2
50–65 (n = 1309)	4.6; 0.9	1.0; 0.1	1.1; 0.2
Gender			
Male (n = 2102)	4.7; 0.8***	1.03; 0.2***	1.01; 0.2***
Female (n = 2079)	3.6; 0.9	1.06; 0.2	1.08; 0.2
Social status			
High (n = 952)	4.2; 1.0	1.0; 0.2*	1.0; 0.2*
Middle (n = 2359)	4.2; 1.0	1.1; 0.2	1.1; 0.2
Low (n = 783)	4.3; 1.0	1.0; 0.2	1.1; 0.2
MDD			
Yes (n = 619)	4.08; 0.9***	1.03; 0.2 n.s.	1.02; 0.2***.
No (n = 3562)	4.2; 1.0	1.05; 0.2	1.05; 0.2
CVD			
Yes (n = 955)	4.2; 0.03 n.s.	1.07; 0.006***	1.6; 0.008***
No (n = 3226)	4.1; 0.02	1.03; 0.004	1.03; 0.005
Types of CVD			
CHD			
Yes (n = 183)	4.1; 0.6***	1.08; 0.1***	1.06; 0.2 n.s.
No (n = 3998)	4.2; 0.9	1.04; 0.2	1.04; 0.2
Stroke			
Yes (n = 58)	4.2; 0.9 n.s.	1.05; 0.2 n.s.	1.03; 0.3 n.s.
No (n = 4123)	4.2; 0.9	1.04; 0.2	1.04; 0.2
Hypertension			
Yes (n = 714)	4.4; 1.0***	1.07; 0.2***	1.1; 0.2***
No (n = 3467)	4.1; 0.9	1.03; 0.2	1.03; 0.2

†Geometric mean (log-transformed marker); CHD, coronary heart disease; MDD, single/recurrent major depressive disorder.
‡P-values adjusted for age, social status and gender were appropriate for the comparison of inflammatory markers among gender, age groups, social status, MDD and CVD (including subtypes of CVD): *P < 0.05/**P < 0.01/***P < 0.0005; n.s., not significant.

Table 2. Ferritin, transferrin and fibrinogen in men and women†

	Ferritin Mean*; SE; *P*-value	Transferrin Mean*; SE; *P*-value	Fibrinogen Mean*; SE; *P*-value
Men			
Cardiovascular Disorders			
CHD			
MDD (n = 13)	4.02; 0.22	1.0; 0.05	1.06; 0.02
No MDD (n = 88)	5.0; 0.08; P = 0. 0005	1.04; 0.02; P = 0.56	1.1; 0.07; P = 0.42
Stroke			
MDD (n = 5)	4.5; 0.17	0.97; 0.09	0.88; 0.11
No MDD (n = 22)	4.8; 0.45; P = 0.49	1.04; 0.04; P = 0.49	1.1; 0.04; P = 0.1
Hypertension			
MDD (n = 31)	4.3; 0.16	1.08; 0.03	0.99; 0.04
No MDD (n = 322)	5.0; 0.05; P = 0.0005	1.05; 0.009; P = 0.45	1.1; 0.01; P = 0.001
Women			
Cardiovascular Disorders			
CHD			
MDD (n = 24)	3.9; 0.2	1.06; 0.04	1.1; 0.05
No MDD (n = 58)	4.1; 0.1; P = 0.63	1.09; 0.02; P = 0.45	1.2; 0.03; P = 0.29
Stroke			
MDD (n = 11)	4.0; 0.3	1.02;0.06	1.1; 0.07
No MDD (n = 20)	4.2; 0.2; P = 0.72	1.04; 0.04; P = 0.71	1.1; 0.05; P = 0.88
Hypertension			
MDD (n = 81)	4.1; 0.09	1.01; 0.02	1.2; 0.03
No MDD (n = 280)	4.2; 0.05; P = 0.34	1.1; 0.01; P = 0.018	1.2; 0.01; P = 0.23

* Geometric mean (log-transformed marker); CHD, coronary heart disease; MDD, major depressive disorder.
† Adjusted for age, social status, body mass index, smoking status, alcohol consumption; P-values from ANOVA models for the comparison MDD yes vs. no.