

PATHWAYS LINKING EARLY LIFE STRESS, METABOLIC SYNDROME, AND THE INFLAMMATORY MARKER FIBRINOGEN IN DEPRESSED INPATIENTS

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SUMMARY

Background: Previous research has shown that metabolic syndrome as well as early life stress can account for immunoactivation (e.g. in the form of altered fibrinogen levels) in patients with major depression. This study aims at assessing the relationship between components of metabolic syndrome, early life stress and fibrinogen levels, taking the severity of depression into consideration.

Subjects and methods: Measures of early life stress and signs of metabolic syndrome were collected in 58 adult inpatients diagnosed with depression. The relationships between the factors were assessed by means of path analyses. Two main models were tested: the first model with metabolic syndrome mediating between early life stress and fibrinogen levels and the second model without the mediating effect of metabolic syndrome.

Results: The first model was not supported by our data ($\chi^2=7.02$, $df=1$, $p=0.008$, $CFI=0.00$, $NNFI=-9.44$, $RMSEA=0.50$). The second model however provided an excellent fit for the data ($\chi^2=0.02$, $df=1$, $p=0.90$, $CFI=1.00$, $NNFI=2.71$, $RMSEA=0.00$). Extending the models by introducing severity of depression into them did not yield good indices of fit.

Conclusions: The developmental trajectory between early life stress and inflammation appears not to be mediated by metabolic syndrome associated factors in our sample. Possible reasons including severity and type of early life stress, as well as potential epigenetic influences are discussed.

Key words: early life stress - metabolic syndrome – inflammatory – fibrinogen - depression

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INTRODUCTION

Depressive disorders are often preceded by a history of life adversities and commonly accompanied by various comorbidities, each of which possibly exerts its influence on the general health of the individual affected. Furthermore, a mild immunoactivation has been observed in patients with major depression (Kim et al. 2007, Sperner-Unterweger 2005). According to the 'cytokine hypothesis of depression', cytokines are involved in behavioral and neurochemical features of depression (Schiepers et al. 2005). Altered plasma cytokine levels have been reported in patients with affective disorders independent of a physical illness (Haack et al. 1999, Maes et al. 1999). E.g. associations between depression and TNF- α and its soluble receptors p55 and p75 (Himmerich et al. 2008, Piletz et al. 2009) or increased levels of IL-1 β (Piletz et al. 2009) have been found. Furthermore, more and more studies provide evidence for an autoimmune tendency in depressed patients. It has been shown that CD4⁺ and CD25⁺ Treg cells may contribute to the immune imbalance in patients with major depression, as the CD4⁺ and CD25⁺ Treg cells decrease in patients' peripheral blood (Li et al. 2009). However, the putative

causes and networks of such immuno-alterations are still not sufficiently understood.

Prenatal life, infancy, childhood, and adolescence are critical periods characterized by increased vulnerability to stressors (Chrousos 1996). The presence of unfavorable stressors, that are excessive and prolonged in nature, during these periods not only affect personality development and the behavior of those affected, but may also have adverse consequences on a physiological level, such as metabolism and immune response. This is due to the inability of the stress system to generate an appropriate response to these stressors in the long term. The body's stress response is generally meant to be of short and limited duration. The time-limited nature of this process renders its accompanying anti-growth, anti-reproductive, catabolic and immuno-suppressive effects temporarily as beneficial. However, chronic activation of the stress system, e.g. due to adverse and unfavorable rearing conditions, may entail a number of disorders following an increased and prolonged secretion of CRH and glucocorticoids. For example, individuals, who as undergraduate students rated the relationship with their parents as cold and detached had a fourfold greater risk of chronic illness including not only psychiatric diagnoses but also heart

disease and type II diabetes in midlife (Russek & Schwartz 1997).

One possible somatic consequence of a hyperactive stress system is the development of components of a metabolic syndrome (Vanitallie 2002).

In a primate study, Chrousos (Chrousos 2000) demonstrated the association between chronic stress, hypercortisolism and metabolic syndrome. Monkeys were exposed to chronic stress, which activated the HPA-axis permanently. The thus induced hypercortisolism lead to visceral obesity, insulin resistance and other biochemical manifestations of metabolic syndrome along with severe coronary atherosclerosis.

Moreover, several studies have shown that stressful emotional life experiences during childhood may lead to the development of obesity in later life (Alvarez et al. 2007, D'Argenio et al. 2009, Grilo et al. 2005), for example via a disordered eating behavior and a reduced capacity to implement nutrition and physical activity plans for the prevention of weight gain (Alvarez et al. 2007).

All relevant longitudinal studies suggest a higher incidence of metabolic syndrome and/or its components (high waist circumference, high triglyceride level, low HDL level, high blood pressure, and high glucose level) among those with depressive symptoms (Raikkonen et al. 2002, Raikkonen et al. 2007, Goldbacher et al. 2009, Pulkki-Raback et al. 2009, Vaccarino et al. 2008, Vanhala et al. 2009, Vanhala et al. 2009, Viinamaki et al. 2009). Associations between an activation of the cytokine system (e.g. TNF- α) and weight gain during psychotropic treatment of depressed patients have also been described (Kraus et al. 2002).

Recently we demonstrated that metabolic syndrome constitutes one important contributing factor for the subclinical immunoactivation in depressed inpatients (Zeugmann et al. 2010). In a further study we reported that early life stress constitutes a second factor contributing to levels of inflammatory biomarkers in a population of depressed inpatients (Zeugmann et al. Submitted). In both studies we found the hepatically synthesized acute-phase reactant fibrinogen to be affected by metabolic syndrome and by early life stress in a cohort of inpatients with major depression.

Previous research reports fibrinogen to be increased in depression and to be associated with metabolic syndrome. In recent years the role of plasma fibrinogen as an independent cardiovascular risk marker has been increasingly recognized (Mann 2002, Yan et al. 2010). Occlusive thrombi are commonly found in myocardial infarction, sudden cardiac ischemic death, or unstable angina pectoris. Thrombosis is recognized as the central mechanism underlying these atherosclerotic complications (Davies 1996). Importantly, prospective epidemiological studies have revealed an association of fibrinogen with subsequent incidence of ischemic cardiovascular events up to 20 years in the future (Kannel et al. 1996). Because fibrinogen appears to be

affected by different factors associated and co-occurring with major depression and because of its potential cardiovascular risk, it is important to gain a more profound understanding of the circuits associated with this inflammatory marker.

Metabolic syndrome and early life stress have been found to account for immunoactivation in depressed patients. Furthermore, early life stress has been reported to predispose those affected to develop a metabolic syndrome. To the authors' knowledge, there is no study, however, investigating both of the above simultaneously in major depression. Thus, in this pilot study with the aim of hypothesis generation under complex conditions, we wanted to assess the relations between early life stress, metabolic syndrome and inflammation in a sample of depressed inpatients in a real life setting.

SUBJECTS AND METHODS

Subjects

Subjects are members of the "Endophänotypisierung affektiver Erkrankungen" ("endophenotyping of affective disorders") study, part of which is presented here. Those 58 of the original study members (n=71) that agreed to participate in the current part of the study are included here. Patients were recruited when referred to the Clinic for Psychiatry and Psychotherapy at the University Hospital Berlin – Charité, Campus Benjamin Franklin between 2005 - 2007. The study was approved by the ethics committee of the Charité and all patients gave their written informed consent to participate. All patients suffered from a depressive episode when admitted to the hospital; the individual diagnosis varied within the range of the affective disorders spectrum (F31, F32, F33 for ICD-10 diagnoses and 296.XX for DSM-IV diagnoses, respectively).

Patients with acute respiratory infections within the last two weeks before assessment or during the study, an active medical illnesses that could etiologically be related to the ongoing depression, immune and autoimmune diseases, anti-inflammatory medication, a history of drug or alcohol abuse within 1 year prior to admission, a schizophrenic or schizoaffective disorder were excluded from the study.

Methods

Data were assessed within a few days after referral to the clinic. Questionnaires concerning the assessment of early life stress and parental bonding were sent to the patients after remission and after discharge from the clinic in order to avoid a negative bias when answering the questions due to severe depression. Of the 58 patients that were initially approached, 25 returned all questionnaires and these were used for further analysis. Statistical analyses were kept simple so that we could attain useful and meaningful results despite the small number of subjects.

Clinical and laboratory data were anonymous, and all ratings and interviews were performed either by a trained psychiatrist or clinical psychologist who were blind to the laboratory data.

The study followed a naturalistic design, i.e. all patients were treated according to their psychiatrist's choice with different kinds of antidepressant drugs (with the dosage adjusted according to clinical judgment and plasma levels where applicable), cognitive behavioral therapy and adjunctive methods.

Major depression

Severity of depression was quantified with the HDRS (Hamilton-Depression Rating Scale, 17-item version) (Hamilton 1969).

Metabolic syndrome

The individual components of metabolic syndrome were assessed at admission according to the criteria of the International Diabetes Federation – IDF, which state the following: central obesity defined as waist circumference =94 cm for Europid men and = 80 cm for Europid women. Furthermore, any two of the following four factors should be met: 1. raised triglycerides, i.e.=150mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality, 2. reduced HDL cholesterol, i.e. <40 mg/dL (1.03 mmol/L) in males and <50 mg/dL (1.29 mmol/L) in females or specific treatment for this lipid abnormality, 3. raised blood pressure, i.e. systolic blood pressure =130 or diastolic =85 mm/Hg or specific treatment of previously diagnosed hypertension, and 4. raised fasting plasma glucose, i.e. = 100 mg/dL (5.6 mmol/L) or previously diagnosed type 2 diabetes.

A metabolic factor was calculated for each patient. Patients received a score according to the number of signs of the metabolic cluster they displayed (running from 0 to 5). This was done to quantitatively assess the putative impact of metabolic syndrome cluster, including subclinical cases, with for example only 2 out of the 5 possible risk factors.

Early life stress

Early life stress experiences were quantified using the German version of the Childhood Trauma Questionnaire (CTQ) (Bernstein et al. 1994, Wulff 2007) which retrospectively assesses early traumatic stress during childhood and adolescence, examining five forms of maltreatment – emotional, physical and sexual abuse, and emotional and physical neglect as well as minimization/denial.

Fibrinogen

Blood was drawn through antecubital venipuncture following an overnight fast in the early morning hours. The blood was then centrifuged at 3000g for ten minutes, immediately divided into aliquots, and frozen

at –70° until analysis. Fibrinogen levels were analyzed using standard ELISA (R&D Systems).

Statistical analyses

All variables were tested for normality of distribution by means of Kolmogorov-Smirnov tests. A drop-out analysis was conducted to test for differences between those patients that returned the questionnaires concerning early life stress and those who did not. Because there were some non-normally distributed variables and in order to simplify the analysis, we used the nonparametric Mann-Whitex-Wilcoxon-Test for all variables. All statistical analyses were performed using the PASW software, version 18.0 for Macintosh. Path analysis (AMOS 18.0.2) was performed to examine the relations between early life stress, metabolic syndrome and inflammation. Two models were tested. First, a model with metabolic syndrome cluster as a mediator between early life stress and inflammation. Second, a model without the mediating effect of metabolic syndrome. Severity of depression was added to each model to account for its possible impact on inflammation.

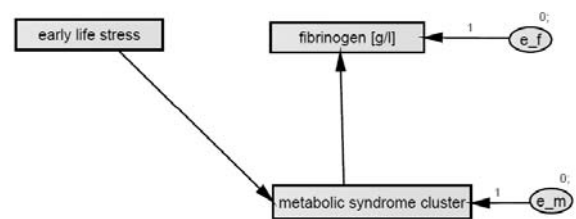


Figure 1. Model 1

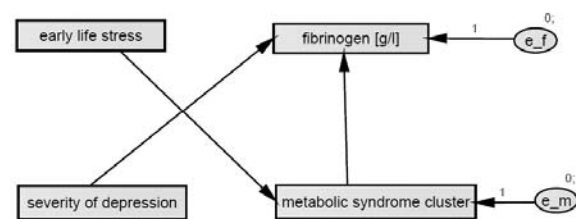


Figure 1b. Model 1b

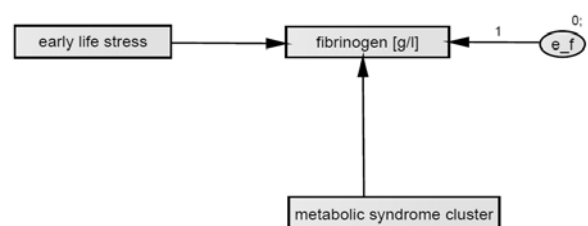


Figure 2. Model 2

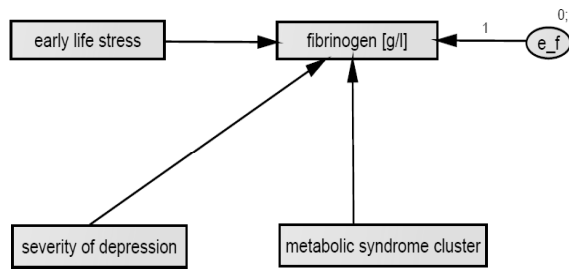


Figure 2b. Model 2b

As can be seen from the models (Figure 1) the exogenous variables were early life stress and severity of depression (the latter one only for models 1b and 2b (see Figure 1b and Figure 2b). The mediating variable was metabolic syndrome/factor. The dependent variable was inflammation (fibrinogen levels).

The overall model fits were examined using established goodness-of-fit-indices. A non-significant χ^2 statistic was used as the primary criterion of model fit (Hayduk et al. 2007). We included other recommended indicators such as the non-normed fit-index (NNFI) sometimes also called Tucker Lewis index (TLI), the comparative fit index (CFI), and the root mean-square error of approximation (RMSEA). Models were accepted as a satisfactory description of the observed data when CFI and NNFI values exceeded 0.90. For the RMSEA, values below 0.05 indicate an excellent model of fit, whereas values of 0.05 to 0.08 indicate a good fit

Table 2. Values for the components of the metabolic syndrome. Different values for males and females are given, where required according to the criteria of the IDF (see methods section)

	male male and female combined	female		min	max
waist circumference (cm)	94.75 (8.50)	83.00 (17.24)	male:	86.00	104.50
			female:	64.00	116.00
blood pressure (systolic) (mmHg)	112.29 (15.88)			90.00	150.00
blood pressure (diastolic) (mmHg)	73.40 (10.48)			60.00	90.00
HDL cholesterol (mg/dl)	62.30 (14.17)	61.94 (15.48)	male:	53.08	90.42
			female:	39.44	83.00
fasting glucose (mg/dl)	81.88 (23.72)			48.00	147.00
triglycerides (mg/dl)	127.52 (99.84)			44.00	512.00

Values are depicted as means (\pm standard deviation), unless otherwise stated

Table 3. Metabolic syndrome composite scores and their distribution.

number of factors of the metabolic syndrome cluster	n
0	9
1	6
2	5
3	2
4	3
5	0

(Bentler & Bonett 1980, Bentler 1990, Hu & Bentler 1999, Hu & Bentler 1995, Browne & Cudeck 1993).

RESULTS

Demographic variables

The demographic and clinical characteristics of the study sample are summarized in table 1 below.

Table 1. Socio-demographic and clinical variables

variable		
age (years)	47.80	(15.02)
sex (male/female) (n)	8/17	
episode (n)	4.00	(3.35)
length of episode (weeks)	33.96	(55.79)
suicide attempts in the past (n)	0.43	(0.84)
HDRS-score	21.64	(6.59)

Metabolic syndrome

Mean values for the components of metabolic syndrome are displayed in table 2.

Table 3 depicts the values of metabolic syndrome composite scores and their distribution.

Early life stress. Drop out analysis

Patients who returned their questionnaires did not differ on any of the immunological, clinical or demographic measures from the group that did not return the questionnaires concerning early life stress.

Table 4. Means \pm standard deviations (SD) of CTQ-subscales

CTQ- subscale	mean	\pm SD
emotional abuse	11.86	5.35
physical abuse	7.46	3.24
sexual abuse	6.50	4.18
emotional neglect	14.92	5.60
physical neglect	9.52	2.90
minimization/denial	0.40	0.71

Table 5. Severity of early adverse events across different subscales of the CTQ

scale	none-minimal (n)	low-moderate (n)	moderate-severe (n)	severe-extreme (n)
emotional abuse	8	7	2	8
physical abuse	17	3	3	2
sexual abuse	19	2	3	1
emotional neglect	3	10	4	8
physical neglect	7	6	6	6

Table 4 shows a summary of patients' scores on the CTQ's different subscales. Highest scores were obtained on the two subscales considering emotional maltreatment. False negative trauma reports are negligible as depicted by the minimization/denial scale.

Grouping the patients according to severity of early adverse events across subscales of the CTQ revealed that most patients of our sample had experienced early stress in the form of neglect and emotional cruelty. 8 (32%) patients were exposed to emotional neglect, 8 to emotional abuse (32%) and 6 (24%) to physical neglect, which is comparable to previous reports (Wiersma et al. 2009) who reported rates of 40.2% for regular emotional neglect and 25% for regular psychological abuse in a cohort of depressed patients. Sexual and physical abuse were not very common (Table 5).

Path analysis

Figure 3 (Model 1) displays the standardized path coefficients for a mediating model. This hypothesized model did not provide a good fit for the data: $\chi^2=7.02$, $df=1$; $p=0.008$, $CFI=0.00$; $NNFI=-9.44$; $RMSEA=0.50$.

Similarly (Figure 3b – Model 1b) the same model controlling for severity of depression seems not supported by the data: $\chi^2=9.51$; $df=3$, $p=0.023$; $CFI=0.00$; $NNFI=-4.69$; $RMSEA=0.30$.

Figure 4 (Model 2) displays the standardized path coefficients for an independent model, i.e. a model in which early life stress and metabolic syndrome both independently influence fibrinogen levels in depressed patients. This model provided an excellent fit for the data: $\chi^2=0.02$; $df=1$; $p=0.90$; $CFI=1.00$; $NNFI=2.71$; $RMSEA=0.00$.

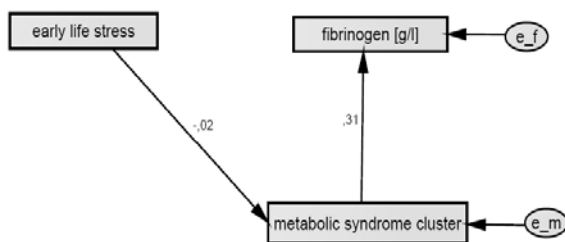


Figure 3. Model 1: numbers on arrows represent standardized regression weights

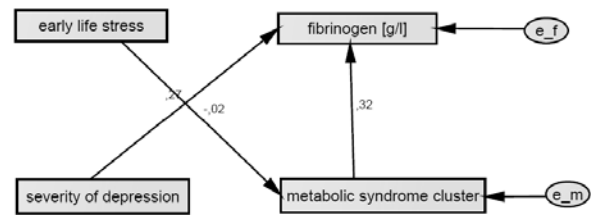


Figure 3b. Model 1b: numbers on arrows represent standardized regression weights

Extending the model by introducing severity of depression into it appears not supported by the data (see Figure 4b (Model 2b)): $\chi^2=4.18$; $df=3$; $p=0.24$.

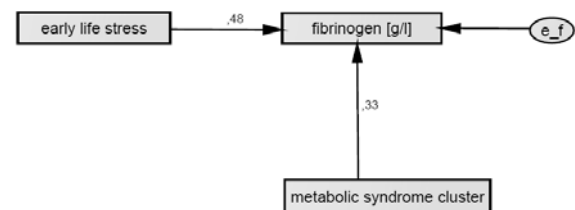


Figure 4. Model 2: numbers on arrows represent standardized regression weights

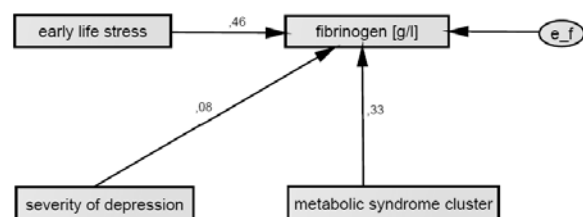


Figure 4b. Model 2b: numbers on arrows represent standardized regression weights

DISCUSSION

The results of the present study suggest that the developmental trajectory between early life stress and inflammation is not mediated by metabolic syndrome associated factors in our sample of depressed inpatients. Early life stress and metabolic syndrome associated factors each have an impact on immunity independent of each other.

The finding of early life stress's long-term impact on immune function later in life is in keeping with the current body of research. Previous investigations have demonstrated a longitudinal effect of early life-stress on adult immune functioning in rodents and primates (Laudenslager et al. 1982, Laudenslager et al. 1985, Avitsur et al. 2006). Human studies parallel these findings: Activation of maladaptive psychological schema during marital disagreements, which mirror unfavorable rearing conditions, were shown to lead to increased cytokine responses (Gouin et al. 2009). Current study also parallels findings by Pace et al. (2006) and Danese et al. (2007, 2008, 2009) which showed that early life stress, particularly in the form of neglect or emotional maltreatment affects specific immunological parameters even later on in life.

Moreover, previous studies found fibrinogen to be positively related to vital exhaustion resulting from chronic stress in school teachers (Kudielka et al. 2008) and to burnout in women (Toker et al. 2005), thereby indicating a likely association between prolonged periods of stress and increment of this acute-phase protein. According to the schema-focused model of occupational stress and work dysfunctions (Bamber 2006), it is individuals with early maladaptive schema that gravitate towards occupations with similar dynamics and structures to the toxic environments and relationships that created them. Those affected subsequently re-enact these early maladaptive schemas and their associated coping styles at the workplace (Bamber & McMahon 2008). Thus, in an indirect manner the above mentioned studies draw attention to the fact that adverse childhood experiences can affect fibrinogen levels in adulthood and our study confirmed this in a more direct manner.

The link between metabolic syndrome and fibrinogen complements research in this area. A proinflammatory and prothrombotic state (e.g. altered levels CRP, TNF- α , fibrinogen, IL-6, leptin, resistin, and adiponectin) has been linked to metabolic syndrome (Sutherland et al. 2004). Higher levels of acute-phase reactants, adhesion molecules and coagulation markers (including fibrinogen) were found in obese and overweight women (Wildman et al. 2011), and it has been suggested that waist circumference is the component of metabolic syndrome that most significantly influences the micro-inflammatory response including fibrinogen concentrations (Rogowski et al. 2010).

Fibrinogen is an important determinant of thrombogenicity and blood viscosity (Koenig 2003, Tracy 2003). As a nonspecific phase-reactant it is a downstream component of the inflammatory cascade and is implicated in the pathogenesis of atherosclerosis, myocardial injury and heart failure (Mann 2002), as well as constituting an independent risk to myocardial dysfunction (Yan et al. 2010). Since our sample consisted of patients that were not all suffering from a fully-developed metabolic syndrome, these were comparatively healthy individuals that might therefore

benefit from preventive and prophylactic interventions, such as statin therapy (Ridker 2009). Moreover, considering the early life stress - fibrinogen pathway, therapies aiming at reducing the effects of early life stress into present life (such as schema therapy (Young et al. 2006) might also be beneficial considering the micro-inflammatory state of the patients affected, at least in certain subgroups which should be investigated in follow-up research.

We did not find a direct path between early life stress and the metabolic syndrome cluster.

There are no studies assessing the effect of child abuse on metabolic syndrome in later life. Most studies concentrate on one or more symptoms out of the cluster.

There is evidence that very severe forms of childhood adversity are more likely to be associated with an increased risk of central obesity (a leading symptom of metabolic syndrome) in mid-adulthood (Thomas et al. 2008) in comparison to less severely stressful emotional environments, where the effects on body composition appear to be weaker. Since our sample was mainly exposed to emotional and physical neglect and emotional abuse, as opposed to physical or sexual abuse, the degree of severity of early life stress could account for the missing association.

Although both metabolic syndrome and immune function, result from the interplay between genetic predisposition and a circumjacent environment, inflammatory biomarkers such as fibrinogen could be determined to a lesser extent by genetic effects and be more susceptible to epigenetic influences compared to metabolic syndrome components. Heritability of fibrinogen has been estimated to be at 34% (Best et al. 2004, Pankow et al. 1998). However, the components of metabolic syndrome appear to be even more strongly inherited: Commonly reported heritability values from family and twin studies range from 40-55% for abdominal obesity, 10-75% for fasting glucose, 25-60% for triglycerides, 30-80% for HDL, 20-70% for systolic blood pressure and 10-50% for diastolic blood pressure (Teran-Garcia & Bouchard 2007). Immunological memory in general comprises of an important adaptive response to environmental challenges and adapting to them is vital for a well-functioning pathogen defense. Thus, ability to adapt is the core of a healthy immune system. Possibly, in comparison to immunological variables, metabolic syndrome related factors could be less prone to environmental influences.

Of course some limitations of this study have to be addressed. We had a return rate of approx. 50% for our questionnaires considering early life stress. Thus, we lost about half of our initial study population. However when the current literature is taken into account, we feel that our return rates for the questionnaires lies within the midrange, in comparison to other studies (e.g. Warner et al. 2004: response rate 60% for questionnaires distributed on the wards; Harrison-Woolrych & Ashton 2011: response rate of 42% for questionnaires

sent out retrospectively). Of course high drop-out rates should always be avoided. Even though we took great care to approach each patient personally via telephone when the questionnaires were sent out, 50% still did not return them. It has to be taken into account that the very nature of our questions could have contributed to the drop out rates as questions were tackling very intimate and sensitive data of the patients' pasts. Furthermore, patients were sent the questionnaires after they had been released from the clinic (in order to prevent response bias from depressive symptomatology) after which patients might not have felt comfortable to confront the topics in question, especially while not being in the intensive care of the hospital staff.

Even though the total number of cases that could be considered for analysis is relatively low, we took great care to keep the models very simple (compared to what is generally entered into structural equation models) in order to attain meaningful results, which we also did. Path analysis as a method is usually used in larger data sets, but it is justifiable to be used here, because we have only one or two equations (two equations for models 2 and 2b – see Fig. 3 and 3b, and one equation for models 1 and 1b – see Fig. 4 and 4b) and three and four variables, respectively in our model and therefore it is very simple.

Since this was a pilot study in a real-life setting under complex conditions aimed at generating hypotheses, our reported results should be replicated and verified in a larger sample. Future research should also include trials on differential treatment options adapted to the putative underlying pathways of patients' micro-inflammatory statuses.

CONCLUSIONS

In conclusion, our study is relevant for patients with metabolic syndrome who have experienced early life stress, as well as for depressed patients with a coexisting/simultaneous metabolic syndrome. The study highlights the impact of even milder forms of both, while also pointing out that metabolic syndrome does not seem to mediate the association between early life stress and fibrinogen concentrations in adulthood.

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Conflict of interest : None to declare.

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